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Synthetic Utility of *N*-Acylbenzotriazoles

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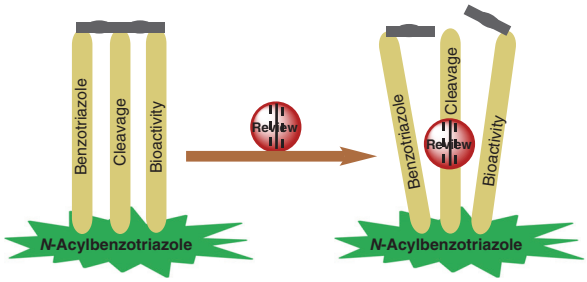

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Abstract *N*-Acylbenzotriazoles are valuable synthons in organic synthesis. They are particularly used as acylating agents and an alternative to acyl chlorides. They have been widely explored for a diverse range of applications. This review summarizes methods for the preparation of *N*-acylbenzotriazole derivatives and their diverse applications, in particular demonstrating their ability to serve as alternative acylating agents in organic transformations such as *N*-, *O*-, *C*-, and *S*-acylating agents for the convenient synthesis of a wide range of biologically important organic compounds. We also emphasize the synthesis of diverse compounds using benzotriazole ring cleavage (BtRC) methodology, including its pharmacophore study and some notable utilities as valuable starting materials, ligands, and intermediates in the field of organic synthesis.

Key words *N*-acylbenzotriazole, acylation, denitrogenative ring cleavage, acylative deacetylation, benzotriazole ring cleavage reactions

1 Introduction

N-Acylbenzotriazoles are versatile neutral acylating agents; they have been extensively used in the preparation of diverse pharmacologically important scaffolds. Because of the high stability of benzotriazole-containing intermediates, the benzotriazole methodology has been proven to be an effective method to prepare alternatives of unstable organic intermediates and hence attracted much interest in organic synthesis for a plethora of organic transformations. Benzotriazole, commonly used as a good leaving group, has been extensively used as a novel synthetic auxiliary in various organic reactions. Particularly, *N*-acylbenzotriazoles are more stable than the corresponding acid chlorides, and they can be used as acylating agents in acylation reactions without diacylation or other side reactions, unlike traditional methods. This mild, regioselective, and regiospecific reagent provides an alternative route to Friedel–Craft and Vilsmeier–Haack acylation strategies and can be used to obtain better results.[1–3] This review summarizes the emerging methods for the preparation of *N*-acylbenzotriazole derivatives, their pharmacophore study, and their utilities in the field of organic chemistry as a starting material, ligand, and intermediates involved in the important organic reactions as well functional group transformations.

2 Synthesis of *N*-Acylbenzotriazoles

N-Acylbenzotriazole motifs are, in general, prepared from acyl chlorides, aldehydes, and carboxylic acid as the starting chemicals *via* numerous synthetic pathways.

Biographical Sketches

Mangal Singh Yadav, born in Azamgarh, U.P., India (in 1992) is currently working as extended SRF under the supervision of Prof. Vinod K. Tiwari, Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, India. He completed his B.Sc. and M.Sc. (in Chemistry) from T. D. P. G. College Jaunpur. He qualified Graduate Aptitude Test in Engineering (GATE)-2017 and NET-CSIR with JRF-2017 and then, in 2018, he joined doctoral research under the supervision of Prof. Vinod K. Tiwari at Department of Chemistry, Institute of Science, Banaras Hindu University, Varanasi, India. Through his dedicated research, he significantly contributed over 15 scientific contributions in peer-reviewed journals and just submitted his doctoral thesis on the topic 'development of novel benzotriazole methodologies and their application'. His present research work is focused on the development of novel synthetic methodologies and Cu(I)-catalyzed click chemistry in glycoscience.

Abhishek Gupta, born in Bhadohi, U.P., India (in 1997), is at present Lecturer of Chemistry at the Govt. Polytechnic Mohammadpur, Bahraich, U.P. India. He obtained his B.Sc. (2017) and M.Sc. (Organic Chemistry, 2020) degrees in chemistry from the University of Allahabad, Allahabad, India. He qualified CSIR-JRF in 2020 and GATE in 2021 and completed his doctoral research under the guidance of Prof. V. K. Tiwari at the Department of Chemistry, Banaras Hindu University. His research interest is focused on the development of carbohydrate-containing molecules of chemotherapeutic potential.

Priyanka Bose, born in Kolkata, India (in 1992) has just submitted her Ph.D. thesis under the supervision of Prof. V. K. Tiwari at Department of Chemistry, Institute of Science, Banaras Hindu University and in April 2023, she joined Pharma Industry in Hyderabad as research Scientist. She earned her M.Pharma (Medicinal Chemistry as specialization) in 2017 from Dr. H. S. Gour Central University, Sagar, India and has qualified GPAT and on the same year joined the laboratory of Prof. V. K. Tiwari for her doctoral research as SERB-JRF. She was awarded the '1st Prize in SPIRIT-15', organized by the Department of Pharmaceutical Engineering, IIT-BHU. Her current research is focused on click chemistry mediated glycohybrids, computational chemistry, and molecular series synthesis having potent bioactivities including anticancer activity.

Anoop Shyam Singh was born in Varanasi, Uttar Pradesh, India (in 1986). He obtained his M.Sc. degrees in chemistry (specializing in organic chemistry, 2010) from the U. P. College Autonomous Institution, Varanasi, India and completed his Ph.D. degree in 2018 on the topic '*Development of Novel Synthetic Methodology through Benzotriazole Ring Cleavage*' under the guidance of Prof. V. K. Tiwari, at Department of Chemistry, Banaras Hindu University India. He has contributed significantly to about 30 publications and several book chapters of international repute. Currently, he is working as a Research Scientist in Jubilant Biosys Limited, Greater Noida, India.

Prabhu P. Mohapatra, born in Odisa, India (in 1967) is an adjunct Research Scientist at Augusta University, USA. He completed his M.Sc. from Sambalpur University and earned his doctoral degree in Chemistry at the Department of Chemistry, University of Delhi with Prof. S. M. S. Chauhan. He then joined Ranbaxy Pharma, Delhi, as a research scientist working on development of API. He worked as postdoctoral fellow with Prof. Alan R. Katritzky and since then has an interest in benzotriazole methodology. Dr Mohapatra has contributed to over 45 research publications in peer-reviewed journals of high repute. His research interest is focused on the development of novel synthetic methodology using benzotriazole synthon, catalysis, photochemistry, and medicinal chemistry.

Vinod K. Tiwari was born in Bihar, India (in 1976) and is associated with Banaras Hindu University (BHU) as Professor of Organic Chemistry. He earned his M.Sc. degree in Chemistry (in 1998) from BHU and Ph.D. degree from CSIR-Central Drug Research Institute, Lucknow (awarded by Jawaharlal Nehru University, New Delhi, in 2004, Mentor: Dr. R. P. Tripathi) and had postdoctoral experience at the University of Florida (Mentor: (Late) Prof. Alan R. Katritzky, in 2005), University of California-Davis (Mentor: Prof. Xi Chen, in 2007), and Guest Scientist at Universitat Konstanz, Germany (Mentor: Prof. (*em.*) Richard R. Schmidt, in 2009). He was offered the post of lecturer at Bundelkhand University (in 2004) before being appointed to BHU (in 2005). With over 25 years of research and 20 years of teaching (UG/PG) experience, Dr. Tiwari has supervised 16 Ph.D. and 25 M.Sc. dissertations, and completed 10 major projects (CSIR, DST, SERB, UGC, IoE). He significantly contributed 176 peer-reviewed publications including two *Chemical Reviews* (Citations: 7569, h-index: 42, i_{10} index: 114, Impact Factors: 650), 8 patents, 4 books, and 25 invited book chapters of high repute. Dr. Tiwari has vast editorial experience, and he is presently Guest Editor of '*SYNTHESIS*' for a thematic issue on '*Emerging Trends in Glycoscience*'. Dr. Tiwari is a highly travelled scientist (delivered 251 invited lectures in India and abroad) and holds Secretary Position, ACCT(I) (2022–2025) and council member of CRSI (2023–2026). His research is well recognized with several prestigious honors/awards/medals/invited contributions from various academic societies including ISCA, CRSI, ICS, ICC, ACCT(I), BHU, NESA, IAPS, UP-CST, Holkar Science College, ACS, RSC, Wiley, Thieme, Bentham, Springer, Elsevier Inc., etc. His current research is focused on synthetic carbohydrate chemistry, novel synthetic methodology, click chemistry in glycoscience, and carbohydrates in drug discovery and development.

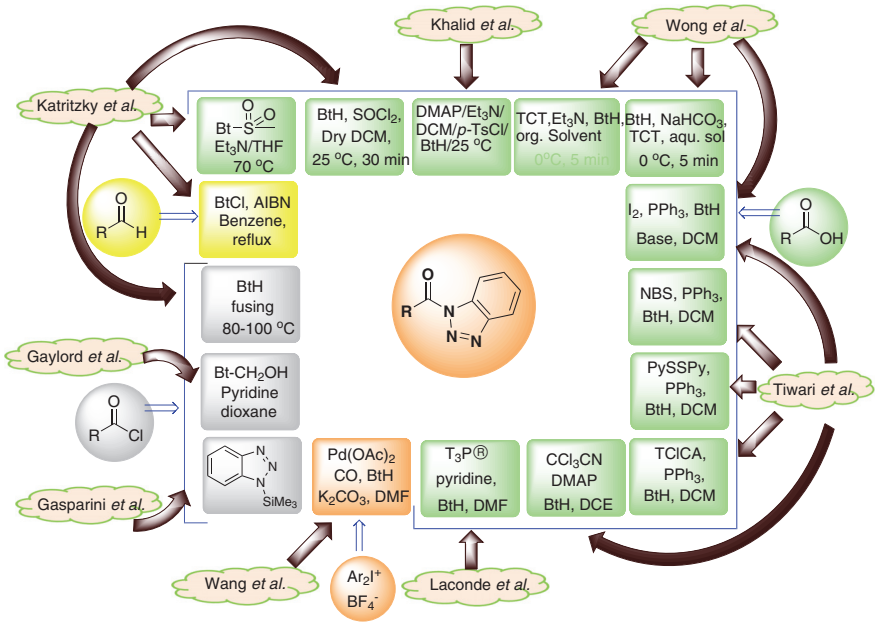
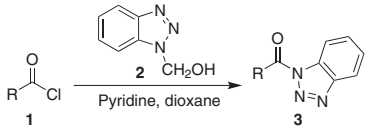


Figure 1 Some common approaches used for the synthesis of diverse *N*-acylbenzotriazoles

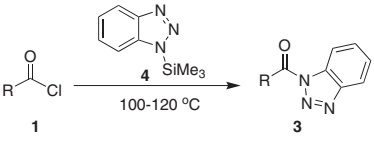
Therefore, in this section, a comprehensive summary of the methods for synthesizing a diverse range of *N*-acylbenzotriazoles is presented (Figure 1).

In 1954, Gaylord tried to reduce 1-(hydroxymethyl)benzotriazole **2** to form 1-methylbenzotriazole in the presence of acyl chloride **1** and pyridine in dioxane. However, the reaction afforded *N*-acylbenzotriazoles **3**, for example *N*-benzoylbenzotriazole as the sole product. This became the first step in the history of *N*-acylbenzotriazoles (Scheme 1).[4]



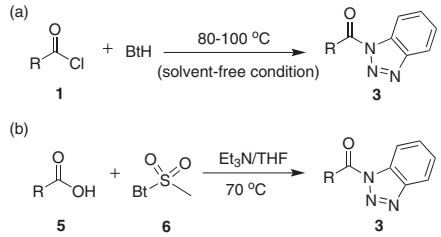
Scheme 1 Synthesis of *N*-benzoylbenzotriazole

In 1980, Gasparini *et al.* successfully synthesized various derivatives of *N*-acylbenzotriazoles through the reaction of *N*-(trimethylsilyl)benzotriazole **4** with acid chlorides **1**, thus selectively producing 1-substituted acylbenzotriazoles **3** in good yields (Scheme 2).[5]



Scheme 2 Synthesis of *N*-acylbenzotriazoles by the reaction of *N*-(trimethylsilyl)benzotriazole with acid chlorides (R = alkyl, aryl, (hetero)aryl)

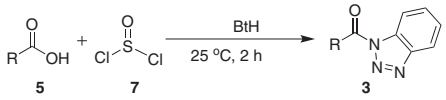
The efforts of the Katritzky group over 11 years (1992–2003) led to substantial progress in the development of methods for the synthesis of *N*-acylbenzotriazoles. In 1992, the Katritzky group reported two methods for the synthesis of a diverse range of *N*-acylbenzotriazoles. In the first method, acyl chloride **1** and 1*H*-benzotriazole (BtH) were fused together under solvent-free conditions (Scheme 3a); in the second method, carboxylic acid **5** was refluxed with *N*-(methylsulfonyl)benzotriazole **6** in basic medium to afford the final products **3** (Scheme 3b).[6] In 2002, they developed a notable method in an extension of this methodology when 1-(methylsulfonyl)benzotriazole was treated *N*-Boc-α-amino acids for the synthesis of stable *N*-(Boc-α-aminoacyl)benzotriazoles (see Scheme 14).[7]



Scheme 3 Synthesis of *N*-acylbenzotriazoles using carboxylic acid chloride or 1-(1-methylsulfonyl)benzotriazole

In 2003, the Katritzky group reported an improved and modern one-pot methodology for the synthesis of *N*-acylbenzotriazoles. The method comprised of reaction of carboxylic acids **5** with 1.0 equiv thionyl chloride (**7**) in the presence of 3.5 to 4 equiv benzotriazole in dichloromethane

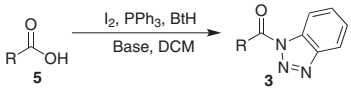
at room temperature for 2 h. This method is the most efficient, and economical, and involves an easy workup process for converting a wide range of carboxylic acids into *N*-acylbenzotriazoles **3** in excellent yields (Scheme 4).[8]



Scheme 4 Conversion of carboxylic acids into *N*-acylbenzotriazoles with thionyl chloride

In 2014, Phakhodee and co-workers introduced a new method to obtain *N*-acylbenzotriazoles **3** by utilizing I_2/PPh_3 and benzotriazole in the presence of triethylamine (Scheme 5). In this reaction, the sequence of addition of triethylamine and benzotriazole plays a key role to achieve good yields. When first triethylamine and then benzotriazole were added to a round-bottom flask containing carboxylic acid **5** and I_2/PPh_3, the acid anhydride was the sole product; whereas, addition of benzotriazole followed by triethylamine, afforded *N*-acylbenzotriazoles in good-to-excellent yields.[9a] In 2018, the Tiwari group extended this methodology and applied it to carbohydrate chemistry for the preparation of glycoconjugated *N*-acylbenzotriazoles and found the reagent to be equally effective in producing glycoconjugated *N*-acylbenzotriazoles in good-to-excellent yields with sugar acids without affecting the sugar stereochemistry.[9b]

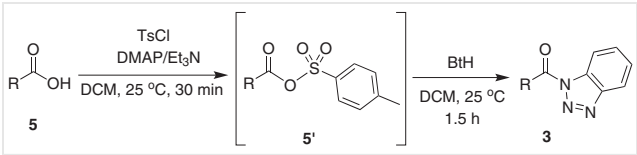
In 2015, Phakhodee and co-workers reported two eloquent *N*-acylbenzotriazole syntheses that are advantageous from economic and environmental perspectives using



Scheme 5 Conversion of carboxylic acids into *N*-acylbenzotriazoles using I_2/PPh_3

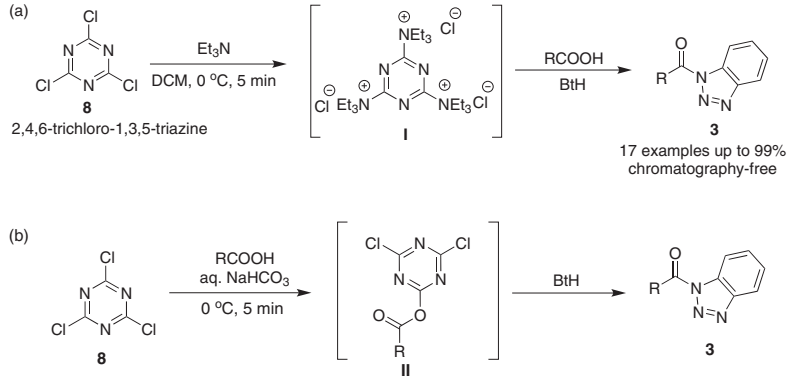
2,4,6-trichloro-1,3,5-triazine (**8**). In the first report, 0.33 equiv 2,4,6-trichloro-1,3,5-triazine was reacted with 1.0 equiv Et_3N at 0 °C followed by the addition of 1.0 equiv carboxylic acid and 1.0 equiv benzotriazole to obtain *N*-acylbenzotriazoles **3** as the final product (Scheme 6a). Extraction of the product from the crude reaction mixture using the separation technique with saturated $NaHCO_3$, 1 M HCl, and water ascertained the process to be economic and environment friendly.[10] Whereas, in another investigation, *N*-acylbenzotriazoles **3** were synthesized by the reaction of a carboxylic acid with 2,4,6-trichloro-1,3,5-triazine (**8**) in the presence of $NaHCO_3$ and benzotriazole in aqueous medium (Scheme 6b).[11]

In 2016, Abo-Dya *et al.* utilized tosyl chloride/DMAP to promote the synthesis of a diverse range of *N*-acylbenzotriazole derivatives **3**. The reaction of carboxylic acid **5** with tosyl chloride afforded the corresponding intermediate **5′**, which was subsequently attacked by 1*H*-benzotriazole to furnish the respective *N*-acylbenzotriazole derivatives **3** (Scheme 7). This method was also applied to synthesize Vorinostat (SAHA), a well-known differentiating agent for prostate and breast cancers.[12]

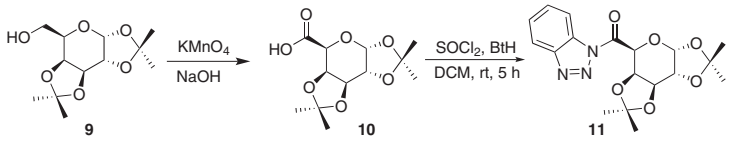


Scheme 7 Conversion of carboxylic acids into *N*-acylbenzotriazoles utilizing tosyl chloride/DMAP

The Tiwari group developed three novel methods for the synthesis of diverse range of *N*-acylbenzotriazoles besides extending two previously reported procedures for synthesizing glycoconjugated *N*-acylbenzotriazole derivatives.[13] The furanose- and pyranose-based glycoconjugated *N*-acylbenzotriazoles were used as coupling reagents for the synthesis of novel sugar amides by exploring 2003 method of the Katritzky group.[8] To achieve the target *N*-(1,2;3,4-di-*O*-



Scheme 6 Conversion of carboxylic acids into *N*-acylbenzotriazoles using 2,4,6-trichloro-1,3,5-triazine



Scheme 8 Synthesis of *N*-(1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranuronosyl)benzotriazole

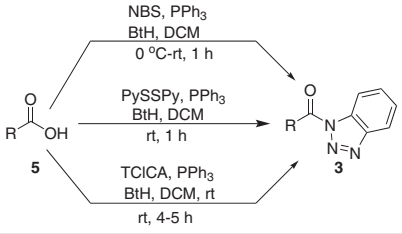
isopropylidene-α-D-galactopyranuronosyl)benzotriazole **11**, 1,2;3,4-di-*O*-isopropylidene-α-D-galacturonic acid (**10**) was first synthesized *via* the isopropylidene protection of D-(+)-galactose to yield compound **9**, followed by oxidation. When this sugar acid **10** was treated with $SOCl_2$ in the presence of benzotriazole and dichloromethane, a crystalline white solid of **11** was obtained in appreciable yield (Scheme 8).

However, for the synthesis of *N*-3-*O*-benzyl- or 3-*O*-ethyl-1,2-*O*-isopropylidene-α-D-xylofuranuronyl)benzotriazoles, a six-step reaction was performed on D-(+)-glucose. First, isopropylidene protection was carried out on D-(+)-glucose to obtain 1,2;5,6-di-*O*-isopropylidene-glucofuranose **12**, followed by 3-*O*-alkylation and selective isopropylidene deprotection to obtain compound **13**. Compound **13** on selective oxidation with $NaIO_4$ furnished the corresponding aldehyde and finally, treatment of this aldehyde with freshly prepared $AgNO_3$/KOH catalyzed oxidation afforded 3-*O*-benzyl- or 3-*O*-ethyl-1,2-*O*-isopropylidene-α-D-xylofuranuronic acids **14** as the target product. Reaction of furanuronic acids **14** with $SOCl_2$ and BtH in anhydrous DCM furnished *N*-(3-*O*-benzyl- or 3-*O*-ethyl-1,2-*O*-isopropylidene-α-D-xylofuranuronyl)benzotriazoles **15** in good yields (Scheme 9).[13]

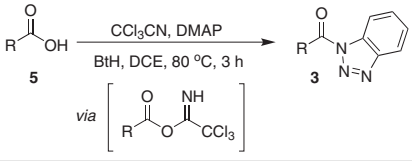
In 2018, the Tiwari group explored work of Phakhodee and co-workers[9a] and utilized it for the synthesis of glycoconjugated *N*-acylbenzotriazoles and achieved excellent results.[9b] The Tiwari group played an active role in the development of various methodologies for the synthesis of *N*-acylbenzotriazoles **3** and illustrated it by the exploration and use of various reagents such as triphenylphosphine, NBS, PySSPy, or TClCA (trichloroisocyanuric acid) with diverse carboxylic acids **5** in the presence of dichloromethane as the solvent to obtain diverse *N*-acylbenzotriazole derivatives in appreciable yields (Scheme 10).[14–16]

In 2021, the Tiwari group developed a new technique to synthesize aromatic and aliphatic derivatives of *N*-acylbenzotriazoles. The reaction was based on the activation of different carboxylic acids **5** with trichloroacetonitrile (CCl_3CN) to produce an imidate intermediate, which reacts *in situ* with benzotriazole to furnish the desired *N*-acylbenzotriazoles **3**.[17] The methodology is feasible for the synthesis of both aromatic as well as aliphatic *N*-acylbenzotriazoles (Scheme 11).

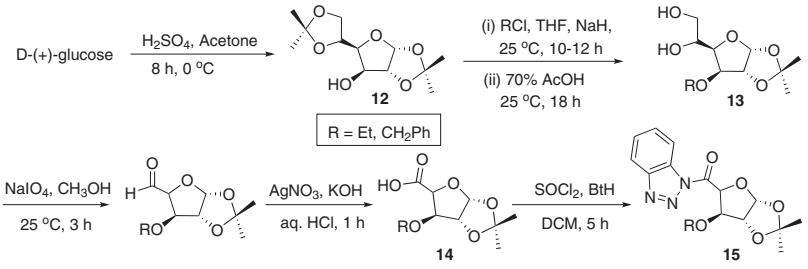
In 2019, Laconde *et al.* demonstrated propylphosphonic anhydride solution T3P as an efficient reagent for the one-pot synthesis of Bt amino acid derivatives starting from *N*-protected amino acids (Scheme 12). This method is applicable to substrates with various side-chain protecting groups including highly sensitive trityl group and can be used to



Scheme 10 Synthetic routes for *N*-acylbenzotriazoles developed by the Tiwari group

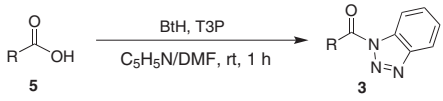


Scheme 11 Trichloroacetimidate route for the formation of *N*-acylbenzotriazoles



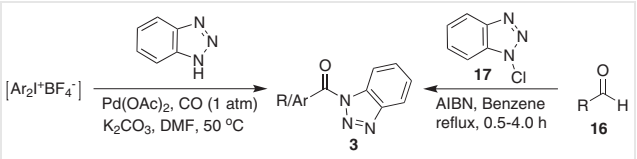
Scheme 9 Synthesis of *N*-(3-*O*-benzyl- or 3-*O*-ethyl-1,2-*O*-isopropylidene-α-D-xylofuranuronyl)benzotriazoles

avoid tedious purification and toxic reagents. In addition, T3P was used for the synthesis of biotin and *N*-Fmoc polyethylene glycol derivatives.[18]



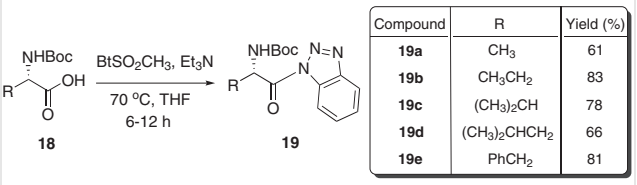
Scheme 12 Conversion of carboxylic acids into *N*-acylbenzotriazoles utilizing T3P

N-Acylbenzotriazoles are mainly synthesized from acyl derivatives, as this method is advantageous in producing a large number of *N*-acylbenzotriazoles. However, there are a few examples of critical exceptions, where acyl derivatives were not used as the starting materials. In 2001, Wang and Chen first accomplished the synthesis of *N*-acylbenzotriazoles through the $Pd(OAc)_2$-catalyzed carbonylation of several diaryliodonium salts (Scheme 13).[19] The reaction of diaryliodonium salts in the presence of BtH under one atmospheric pressure of carbon monoxide produced average-to-good yields of *N*-acylbenzotriazoles as the final product. In a simple yet classic reaction methodology developed by the Katritzky group, refluxing aldehydes **16** with *N*-chlorobenzotriazole **17** in the presence of AIBN in benzene yielded *N*-acylbenzotriazoles (in up to ~80% yield) as the major product (Scheme 13).[20]



Scheme 13 Synthesis of *N*-acylbenzotriazoles without using acyl derivatives

Acid chlorides of *N*-protected amino acids have been known for a long time.[21] Most of them cannot be stored under normal conditions because of their highly sensitive nature and reactivity;[22] they undergo racemization and decomposition on storage. The Katritzky group developed innovative methodology for the synthesis of stable *N*-(Boc-α-aminoacyl)benzotriazoles **19** from Boc-α-amino acids **18** and $BtSO_2Me$ as the benzotriazole source (Scheme 14).[7] *N*-(Boc-α-aminoacyl)benzotriazoles were found to be stable at



Compound	R	Yield (%)
19a	CH_3	61
19b	CH_3CH_2	83
19c	$(CH_3)_2CH$	78
19d	$(CH_3)_2CHCH_2$	66
19e	$PhCH_2$	81

Scheme 14 Synthesis of *N*-(Boc-α-aminoacyl)benzotriazoles from Boc-α-amino acids

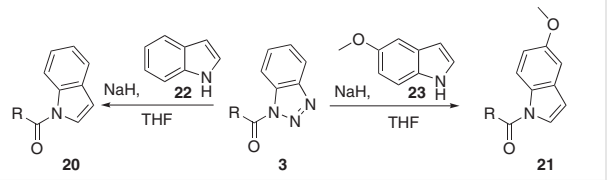
20 °C and no detectable amount of change was observed for six months. Also, the application of *N*-(Boc-α-aminoacyl)benzotriazoles was considered for the synthesis of chiral α-(*N*-protected amino acid) amides without racemization.[7]

By utilizing the methods discussed, the synthesis of a wide variety of desired *N*-acylbenzotriazoles can be achieved. Hence, we summarized all the methodology discussed and their selective starting chemical components in Figure 1 to show all the possibilities of *N*-acyl- and *N*-aroylbenzotriazole synthesis.

3 Applications of *N*-Acylbenzotriazoles in Organic Synthesis

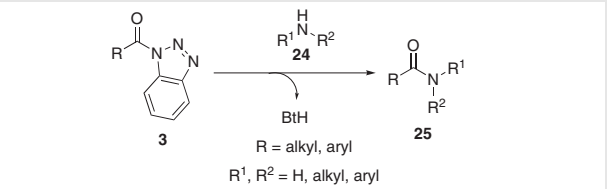
3.1 *N*-Acylation Using *N*-Acylbenzotriazoles

The Katritzky group reported a novel protocol for the synthesis of *N*-aroylindoles **20** and **21** by the application of *N*-aroylbenzotriazoles. The developed methodology was applied to the reaction of *N*-aroylbenzotriazoles with indole (**22**) and also with substituted indoles **23** in the presence of NaH to afford the desired *N*-aroylindole in moderate-to-good yields (Scheme 15).[23]



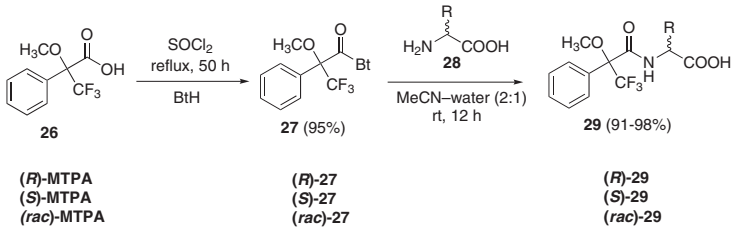
Scheme 15 Synthesis of *N*-aroylindoles using *N*-acylbenzotriazoles

N-Acylbenzotriazoles are acylating agents that react with ammonia, primary amines, and secondary amines to produce high yields of the corresponding primary, secondary, and tertiary amides, respectively, by the elimination of BtH. The procedure predominantly provides a way for solid-phase synthesis.[24] The synthetic pathway for amides **25** from amines **24** and *N*-acylbenzotriazoles is depicted in Scheme 16.



Scheme 16 Formation of primary, secondary, and tertiary amides

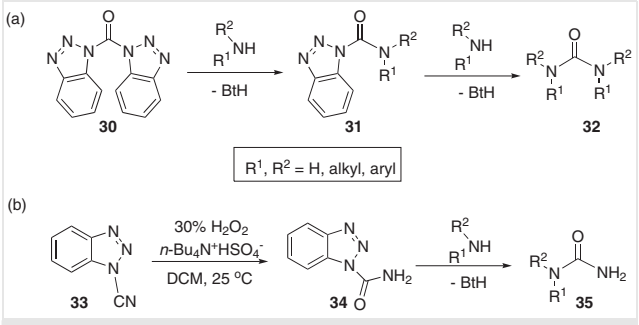
α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA, **26**), also known as Mosher's reagent, is used as a chiral derivatizing agent for defining both absolute configurations



Scheme 17 Benzotriazole-mediated synthesis of Mosher-Bt reagent and its application towards amide synthesis

and enantiomeric excess of natural and synthetic amines and alcohols by NMR spectroscopy.[25,26] MTPA chloride enantiomers used as chiral derivatizing agents are commercially available, but these are expensive, moisture sensitive, and stored at a low temperature. To overcome these limitations, the Katritzky group established a protocol for the synthesis of enantiomeric and racemic form of 1-benzotriazol-1-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-one (Mosher-Bt reagent) **27** in (*R*)-**27**, and (*S*)-**27**, *rac*-**27** forms by refluxing the MTPA **26** with BtH and thionyl chloride in acetonitrile/water (2:1) for 50 h. The prepared Mosher-Bt reagent **27** was reacted with various chiral amino acids **28** and peptides to obtain the corresponding amides **29** to prove the efficacy of the developed Mosher-Bt reagent over the sensitive MTPA chloride (Scheme 17).[27]

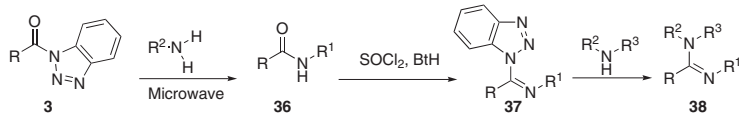
In 1997, the Katritzky group reported a versatile method for the synthesis of various substituted symmetrical and unsymmetrical urea derivatives **32** *via* the *N*-acylation of 1,1′-carbonylbisbenzotriazole **30** with primary and secondary amines. BtH was obtained as a byproduct, which can be easily removed from reaction product during workup. When secondary amines were used as the first component in the reaction, benzotriazole-1-carboxamides **31** were isolated as reaction intermediates. This method provides a useful and benign route for the synthesis of numerous urea derivatives that could not be successfully afforded by other protocols (Scheme 18a).[28] In 2003, they developed a proficient route for the synthesis of mono- and disubstituted ureas **35** by the reaction of benzotriazole-1-carboxamide **34** with primary and secondary aliphatic amines under mild reaction conditions. Benzotriazole-1-carboxamide **34** was obtained by the reaction of *N*-cyanobenzotriazole **33** with 30% H_2O_2 in the presence of *n*-$Bu_4N^+HSO_4^-$ in dichloromethane at 25 °C (Scheme 18b).[29]



Scheme 18 Preparation of substituted symmetrical and unsymmetrical urea derivatives

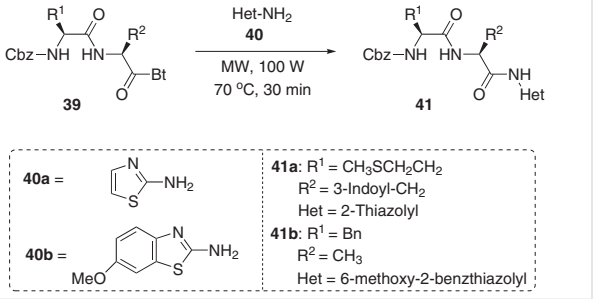
Amidines are a significant class of motifs with biological importance, and also, they are widely used in the synthesis of heterocycles. A microwave-assisted versatile route was developed for the synthesis of amidines by the reaction of various substituted primary and secondary amines with *N*-imidoylbenzotriazoles (Scheme 19). The synthesis of *N*-imidoylbenzotriazoles **37** was achieved in two steps. In the first step, amides **36** were synthesized from *N*-acylbenzotriazoles **3** under microwave (MW) conditions. In the second step, *N*-imidoylbenzotriazoles **37** were obtained in good yields by the one-pot reaction of amides **36**, thionyl chloride, and benzotriazole. The *N*-imidoylbenzotriazoles reacted with various substituted primary and secondary amines to furnish the respective amidines **38**.[30]

(α-Aminoacyl)amino-substituted heterocycles are an important class of scaffolds with substantial biological properties. A new type of derivative of *N*-substituted amide was synthesized from *N*-(protected-aminoacyl)benzotriazoles in 40–98% yields when the reaction was carried out under microwave irradiation conditions for 30 min. This method was also efficiently utilized for the synthesis of *C*-terminal *N*-protected dipeptidoyl amides in moderate-to-good yields. The *N*-protected dipeptidoyl amides **41** were synthesized from the corresponding *N*-protected peptidoylbenzotriazoles **39** under microwave irradiation conditions. Compound **41a** was obtained in 60% yield when the reac-



Scheme 19 Microwave-assisted synthesis of amidines from *N*-imidoylbenzotriazoles

tion of Cbz-L-Met-L-Trp-Bt was carried out with 2-aminothiazole **40a**, and **41b** was obtained by the coupling of Cbz-L-Phe-L-Ala-Bt with 2-amino-6-methoxybenzothiazole **40b** in anhydrous DMF (Scheme 20).[31]



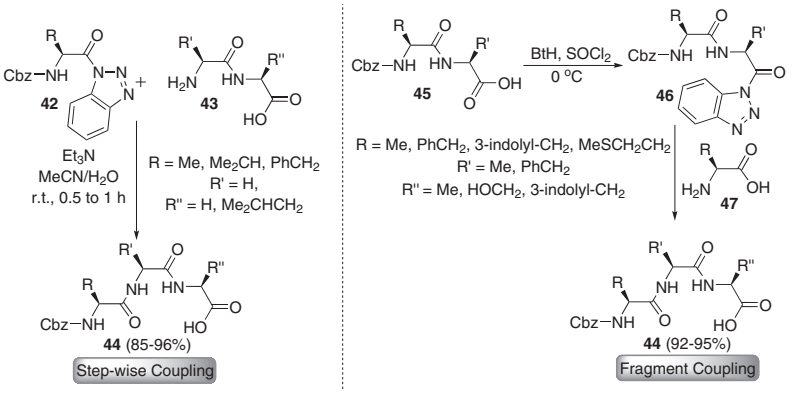
Scheme 20 Microwave-assisted synthesis of *N*-protected dipeptidoyl amides from *N*-protected peptidoylbenzotriazoles

N-Acylation was also utilized for the synthesis of dipeptides and tripeptides from *N*-(Cbz-aminoacyl)benzotriazoles. The corresponding *N*-(Cbz-aminoacyl)benzotriazoles were obtained from alanine, phenylalanine, and valine. Synthesis of tripeptide **44** was achieved in two different ways: first by the reaction of *N*-(Cbz-aminoacyl)benzotriazoles **42** with free dipeptides **43** through stepwise coupling and second by the reaction of *N*-(Cbz-aminopeptidoyl)benzotriazoles **46** obtained from acid precursors **45**. The reaction of **46** with free amino acids **47** through fragment coupling afforded tripeptides **44** (Scheme 21).[32]

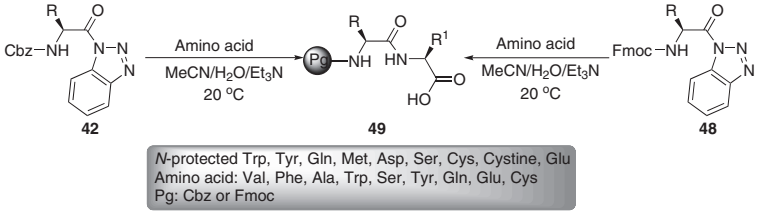
Peptide bond formation through the activation of carboxylic acid functional group of *N*-protected α-amino acids is very important and has attracted much attention recently. Therefore, various scientists have contributed towards this endeavor of peptide bond construction. In this regard, the Katritzky group demonstrated a convenient protocol for the synthesis of dipeptides **49** from the corresponding crystalline and chirally stable *N*-(Cbz- and Fmoc-α-aminoacyl)benzotriazole-activated derivatives **42** and **48** of Tyr, Trp, Cys, Met, and Gln amino acids. These benzotriazole-activated derivatives of amino acids undergo peptide coupling in aqueous acetonitrile with unprotected L-Ala-OH and L-Phe-OH to furnish the chiral dipeptides in 70–98% yield. The NMR and HPLC studies showed no racemization in the process (Scheme 22).[33]

The Katritzky group explored the utility of *N*-acylbenzotriazoles for the efficient conversion of carboxylic acids into *N*-methoxy-*N*-methylamides **52** (Weinreb amides). Weinreb amides **52** were synthesized directly from *N*-acylbenzotriazoles by the reaction with *N*,*O*-dimethylhydroxylamine hydrochloride **51** in THF.[34] They further investigated the scope of *N*-acylbenzotriazoles for the synthesis of various *O*-alkyl-, *N*-alkyl-, and *O*,*N*-dialkylhydroxamic acids **53** by using an appropriate hydroxylamine hydrochloride under similar reaction conditions (Scheme 23).[35]

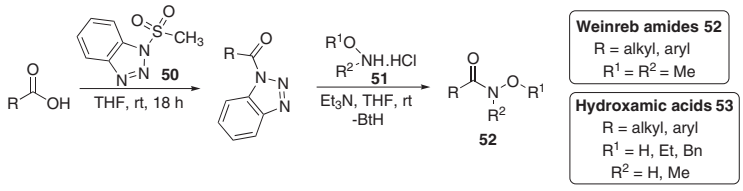
The reactivity of *N*-acylbenzotriazoles was further utilized by the Katritzky group for the *N*-acylation of sulfonamides to synthesize biologically active *N*-acylsulfonamides **54**. The reaction was carried out first by treating



Scheme 21 Synthesis of peptide using *N*-acylbenzotriazoles

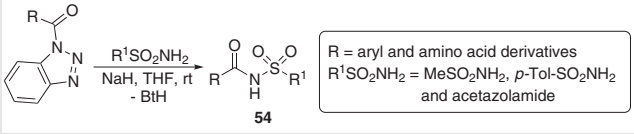


Scheme 22 Construction of dipeptides from *N*-(Cbz- and Fmoc-α-aminoacyl)benzotriazole-activated derivatives



Scheme 23 Synthesis of Weinreb amides and various substituted hydroxamic acids

various sulfonamides with NaH in THF for 1.5 h to produce the sodium salt of the sulfonamides, which then reacted with diverse *N*-acylbenzotriazoles in THF under reflux conditions followed by acidification with 2 N HCl solution to produce the desired *N*-acylsulfonamides **54** in 76–98% yields (Scheme 24).[36]

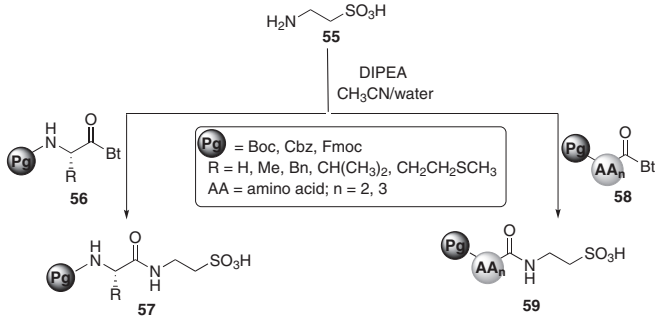


Scheme 24 Synthesis of various biologically active *N*-acylsulfonamides from *N*-acylbenzotriazoles

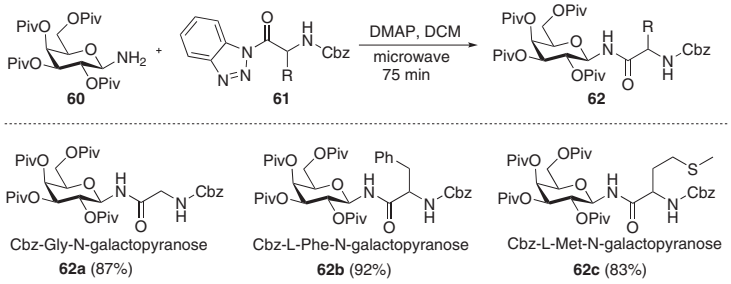
The Katritzky group developed a straightforward synthetic approach towards the preparation of taurine-containing water-soluble peptidomimetics, which are very attractive scaffolds for the application in drug delivery systems.[37] A number of taurine-containing peptides were efficiently synthesized through the acylation of *N*-terminal taurine using benzotriazole methodology. Synthesis of taurine-containing dipeptides **57** was accomplished by utilizing taurine (**55**) and benzotriazoles **56** as the starting materials in the presence of DIPEA as the base in acetonitrile solvent. A few drops of water were also added to dissolve taurine. The reaction was completed within 1–2 h to afford the desired products **57** in 76–90% yields. Similarly, the preparation of taurine-containing tri- and tetrapeptides **59** was achieved in 73–93% yields from various peptidoyl benzotriazoles **58** under similar reaction conditions (Scheme 25). The group also synthesized various taurine sulfonopeptides and taurine *N*- and *O*-conjugates using similar reaction conditions from the coupling of *N*-Cbz-taurine sulfonyl benzotriazole and several amino esters, dipeptide esters, and *N*- and *O*-nucleophilic compounds, respectively.

In another study, the Katritzky group established a protocol for the exclusive and diastereoselective synthesis of β-*N*-glycoamino acids.[38] The group utilized easily available *N*-(Cbz- or Fmoc-α-aminoacyl)benzotriazoles **61** for the acylation of tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**60**) under microwave irradiation conditions to afford the desired β-N-linked glycoamino acids **62** in excellent yields. This stereoselective glycosylation reaction was carried out in anhydrous DCM solvent in the presence of DMAP as the base at 100-W microwave irradiation for 75 min to furnish the desired glycoamino acids **62** (Scheme 26). The group also accomplished the regiospecific synthesis of β-*N*-glycodipeptides from *N*-Cbz-protected peptidoyl benzotriazoles under similar reaction conditions in 3.5 h in good-to-high yields. ^{1}D and ^{2}D NMR techniques were used to reveal the regiospecific β-*N*-linkage.

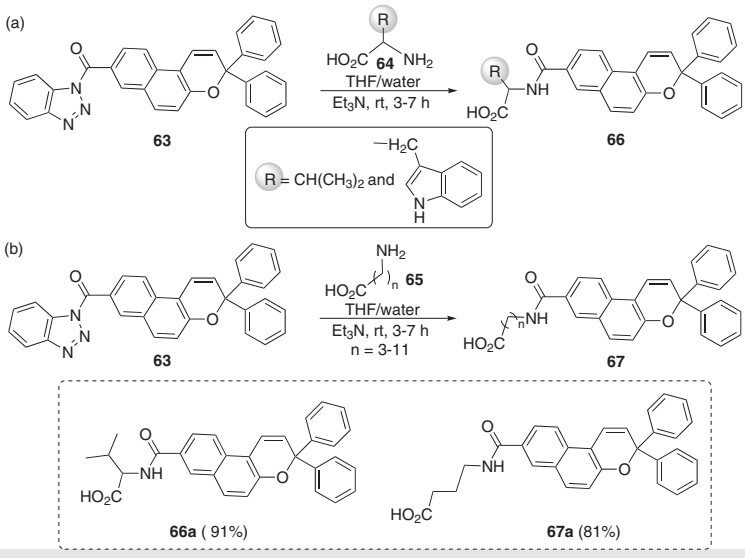
The Katritzky group further used a chromene-based *N*-acylbenzotriazole **63** for the preparation of 2*H*-chromene-based conjugates **66** and **67** of natural amino acids **64** and *N*-acyl-1,ω-amino acids **65**, respectively, at 20 °C in aqueous media (Scheme 27).[39] The group also synthesized an example of 2*H*-chromene-based conjugate of dipeptide. They also studied the variation in the gelation properties of the sodium salts of the corresponding chromene-2*H* natural and ω-amino acid conjugates in DMF and DMSO with different chain lengths.



Scheme 25 Synthesis of taurine-containing di-, tri-, and tetrapeptides using *N*-acylbenzotriazoles

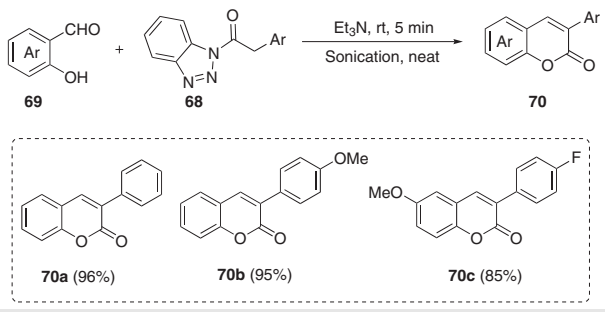


Scheme 26 Diastereoselective synthesis of β-*N*-glycoamino acids and β-*N*-glycodipeptides using benzotriazole methodology



Scheme 27 Synthesis of 2*H*-chromene amino acid conjugates using *N*-acylbenzotriazoles

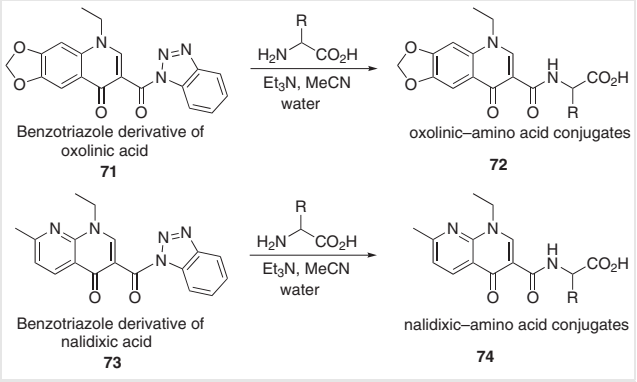
Pattarawarapan and co-workers developed a rapid, simple, and one-pot methodology for the synthesis of substituted 3-arylcoumarins **70** under ultrasound assistance. Their synthetic strategy involved a one-pot acylation/cyclization reaction between *N*-acylbenzotriazoles **68** and 2-hydroxybenzaldehydes **69** in the presence of triethylamine under neat conditions (Scheme 28).[40]



Scheme 28 Ultrasound-assisted synthesis of substituted 3-arylcoumarins using *N*-acylbenzotriazoles

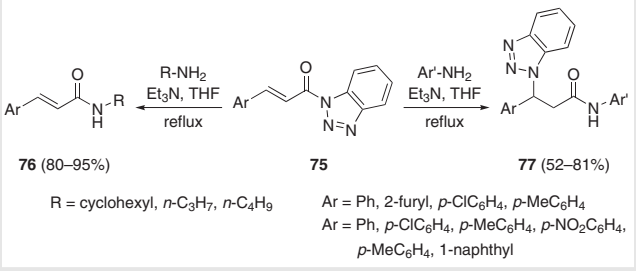
The Katritzky group also explored the chemistry of *N*-acylbenzotriazoles for the synthesis of amino acid conjugates of quinolone antibiotics, such as oxolinic acid **72** and nalidixic acid **74**, through the coupling of their respective benzotriazole-activated derivatives **71** and **73** with free amino acids under basic conditions (Scheme 29).[41] The cinoxacin- and flumequine-amino acid conjugates were also synthesized with their respective benzotriazole-activated derivatives. The coupling reaction was carried out in the presence of Et_3N base for 3 h in aqueous acetonitrile. They also prepared dipeptide conjugates of the corresponding quinolones by coupling of the dipeptide Gly–Gly with benzotriazole derivatives of quinolone antibiotics.

Wang and co-workers proposed a synthetic pathway for the preparation of 3-benzotriazolylpropanamides **77** and cinnamides **76** from aromatic and aliphatic amines, respectively. Their work showed that aromatic amines react with *N*-cinnamoylbenzotriazoles **75** to give 3-benzotriazolylpro-



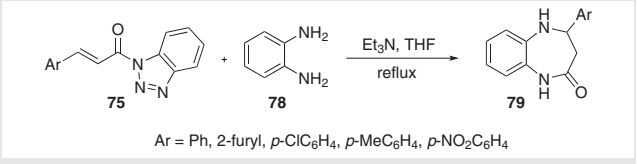
Scheme 29 Synthesis of oxolinic–amino acid and nalidixic–amino acid conjugates through *N*-acylbenzotriazole methodology

panamides **77**, and aliphatic amines react exclusively through the 1,2-addition pathway to afford good-to-high yields of cinnamides **76** (Scheme 30).[42]

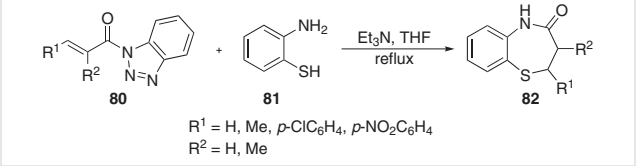


Scheme 30 *N*-Cinnamoylbenzotriazole-mediated synthesis of 3-benzotriazolylpropanamides and cinnamides

Simple synthesis of substituted 1,3,4,5-tetrahydro-1,5-benzodiazepine-2-ones **79** was also carried out *via* further acylation of the 1,4-addition product obtained from the reaction of *o*-phenylenediamine (**78**) with *N*-cinnamoylbenzotriazoles **75** (Scheme 31).[42]



Scheme 31 *N*-Cinnamoylbenzotriazole-mediated synthesis of 1,3,4,5-tetrahydro-1,5-benzodiazepin-2-ones



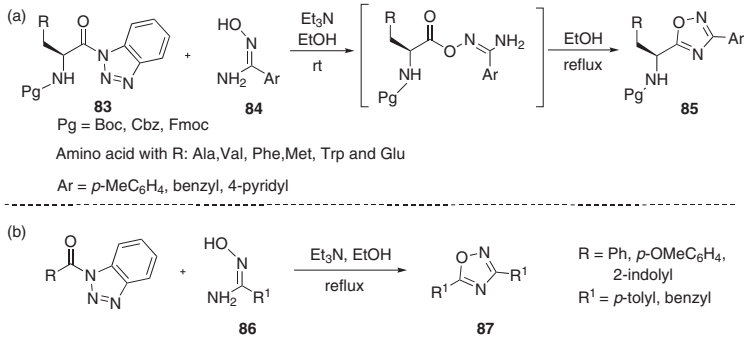
Scheme 32 α,β-Unsaturated 1-acylbenzotriazole-mediated synthesis of 2,3,4,5-tetrahydro-1,5-benzothiazepin-4-ones

Wang and co-workers extended their previous work towards the facile synthesis of 2,3,4,5-tetrahydro-1,5-benzothiazepin-4-ones **82**, analogous to 1,3,4,5-tetrahydro-1,5-benzodiazepine-2-ones, in good-to-high yields. The desired product was obtained from the reaction of α,β-unsaturated 1-acylbenzotriazoles **80** with 2-aminobenzothiol (**81**) under similar reaction conditions (Scheme 32).[43]

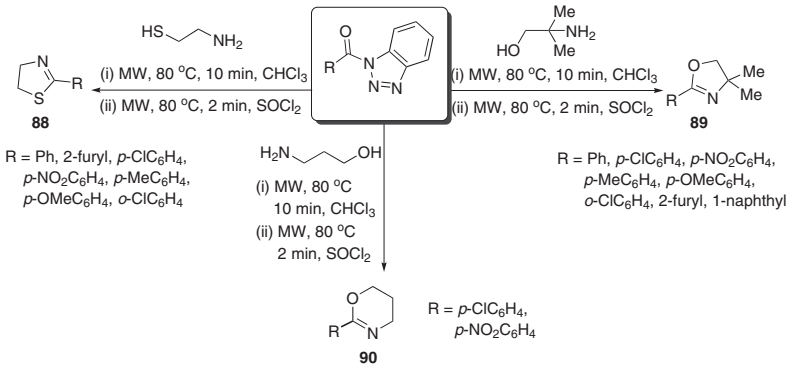
1,2,4-Oxadiazole rings are a crucial part of various biologically active synthetic heterocyclic compounds, and they are useful precursors in drug discovery processes. They are potential drug candidates in the form of hydrolysis-resisting bioisosteric replacements for ester or amide functionalities.[44] The Katritzky group developed a convenient method for the synthesis of these biologically relevant 1,2,4-oxadiazoles **85** derived from chiral α-amino acids using *N*-protected *N*-(α-aminoacyl)benzotriazoles **83** (Scheme 33a).[45] *N*-Protected *N*-(α-aminoacyl)benzotriazoles **83** reacted with *p*-tolyl-, 4-pyridinyl-, and benzylamidoximes in refluxing ethanol in the presence of catalytic Et_3N to afford good yields of 1,2,4-oxadiazoles **85**; the intermediate *O*-acylated *N*-protected amidoxime was instantly produced from the reaction of **83** with various amidoximes **84** after the addition of Et_3N in ethanol at room temperature, followed by cyclization within 5 min under reflux conditions to give 1,2,4-oxadiazoles **85** in good yields. The NMR and HPLC analysis showed that the chirality preserved in the product. The Katritzky group also demonstrated that the reaction of suitable amidoximes **86** with *N*-aroylbenzotriazoles under similar reaction conditions produced 1,2,4-oxadiazoles **87** in 73–82% yields (Scheme 33b).[45]

Similarly, the synthesis of important heterocycles, such as thiazolines **88** and oxazolines **89**, was carried out from readily available *N*-acylbenzotriazoles by the Katritzky group using a similar synthetic methodology under microwave assistance (Scheme 34).[46] In the preparation of oxazolines, the *N*-acylation of *N*-acylbenzotriazoles was performed in a sealed tube for 10 min, followed by the cyclization of intermediates in the presence of $SOCl_2$. Using a similar protocol, thiazolines **88** were synthesized using 2-aminoethanethiol hydrochloride in the presence of Et_3N. They also accomplished the synthesis of 5,6-dihydro-4*H*-1,3-oxazines **90** from the reaction of *N*-acylbenzotriazoles with 3-aminopropan-1-ol under similar reaction conditions.

N-Acylbenzotriazoles were applied for the efficient and high-yielding synthesis of biologically active 5-substituted-2-ethoxy-1,3,4-oxadiazoles **92** by Pattarawarapan and coworkers (Scheme 35).[47] Their synthetic procedure involved a one-pot *N*-acylation/dehydrative cyclization between ethyl carbazate (**91**) and *N*-acylbenzotriazoles in the presence of Ph_3P-I_2 as a dehydrating agent. A variety of 3,5-disubstituted 1,3,4-oxadiazol-2(3*H*)-ones **93** were also prepared in excellent yields from 5-substituted 2-ethoxy-1,3,4-oxadiazoles **92** by allowing them to react with a stoichiometric



Scheme 33 Synthesis of 1,2,4-oxadiazoles by utilizing *N*-protected *N*-(α-aminoacyl)benzotriazoles and *N*-acylbenzotriazole

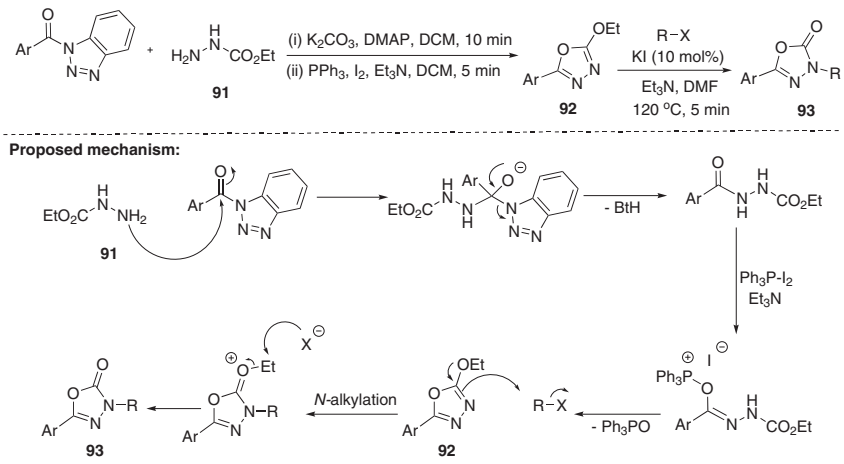


Scheme 34 Preparation of oxazolines and thiazolines under microwave irradiation

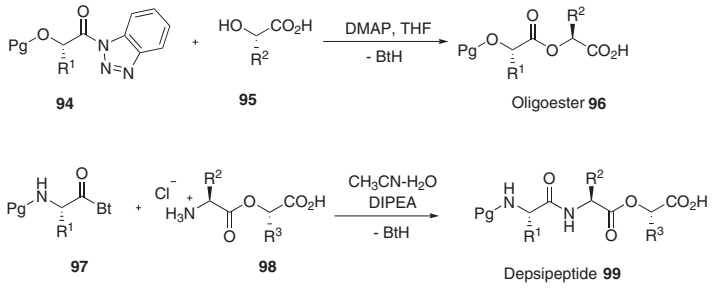
amount of alkyl halides. Electron-donating as well as electron-withdrawing group containing substrates were well tolerated in this synthetic approach.

Depsipeptides are the analogues of peptides comprising both amino acids and hydroxy acids linked by amide and ester bonds. Several natural depsipeptides display a range of biological activities such as antimicrobial, antifungal, and anti-inflammatory activities, and they are also highly valuable therapeutic agents in the form of anticancer and anti-HIV candidates.[48]

The Katritzky group developed a novel benzotriazole-mediated methodology for the efficient synthesis of chiral oligoesters **96** and depsipeptides **99** through the reaction of *O*-Pg-(α-hydroxyacyl)benzotriazoles **94** and **97**, respective-



Scheme 35 *N*-Acylbenzotriazole-mediated synthesis of 5-substituted 2-ethoxy-1,3,4-oxadiazoles and 3,5-disubstituted 1,3,4-oxadiazol-2(3*H*)-ones

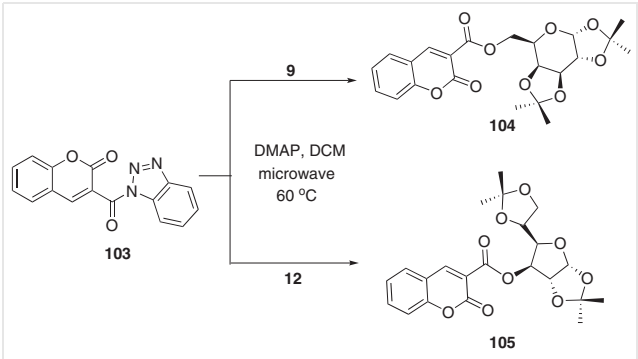


Scheme 36 Synthesis of chiral oligoesters and depsipeptides from suitable benzotriazoles

ly, by using unprotected α-hydroxycarboxylic acids **95** in the former and depsides **98** in the latter reaction (Scheme 36).[49] The methodology also elaborated for the synthesis of amide conjugates by the reaction of *O*-Pg-(α-hydroxyacyl) with amines in satisfactory outcome.

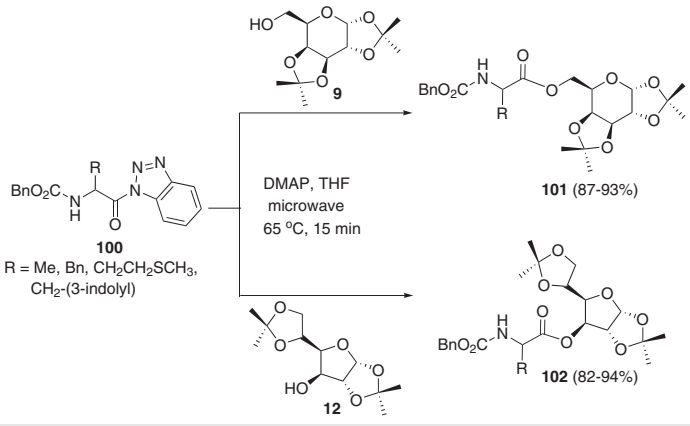
An efficient methodology for *O*-acylation of various isopropylidene-protected monosaccharides with readily available *N*-(Cbz-α-aminoacyl)benzotriazoles **100** was established by the Katritzky group (Scheme 37).[50] The reaction was performed under microwave irradiation in the presence of a catalytic amount of DMAP in THF solvent at 65 °C to afford the desired α-amino acid–sugar conjugates in good yields. Chiral *O*-(Cbz-α-aminoacyl) sugar products **101** and **102** were synthesized from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9**) and 1,2:5,6-di-*O*-isopropylidene-D-glucose (**12**), respectively.

In a similar way, the Katritzky group reported the fluorescent labeling of various monosaccharides under microwave irradiation using *N*-(coumarin-3-carbonyl)benzotriazole **103**.[51] The group achieved the convenient synthesis of various *O*-(coumarin-3-carbonyl) diisopropylidene sugars **104** and **105** through the *O*-acylation of isopropylidene-protected monosaccharides in the presence of catalytic amount of DMAP in DCM solvent at 60 °C. The preparation of *O*-(coumarin)diacetonide sugars **104** and **105** from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**9**) and 1,2:5,6-di-*O*-isopropylidene-D-glucose (**12**) is presented in Scheme 38.[51]

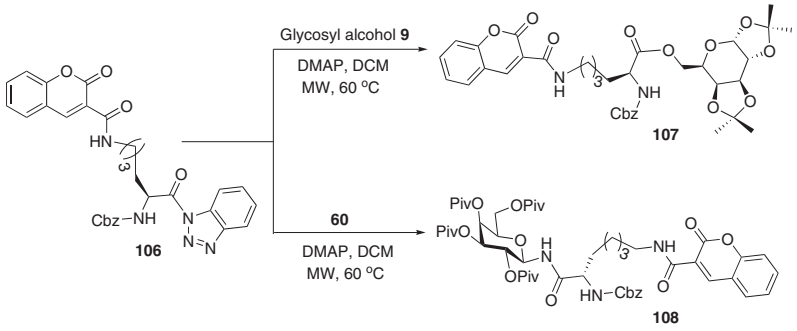


Scheme 38 Preparation of *O*-(coumarin)diacetonide sugars from isopropylidene-protected sugars

Similarly, L-lysine-scaffold based coumarin-labeled sugars were also prepared *via* *O*-and *N*-acylation using N^{ε}-coumarin-3-carbonyl-N^{α}-Cbz-L-lysine benzotriazoles **106** as the acylating agents. The synthesis of L-lysine-scaffold based coumarin-labeled monosaccharide product **107** and **108** from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose



Scheme 37 *O*-Acylation of isopropylidene-protected sugars with *N*-(Cbz-α-aminoacyl)benzotriazoles



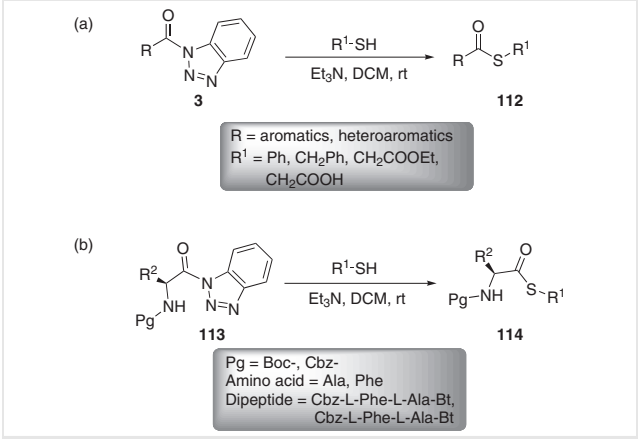
Scheme 39 Benzotriazole-mediated synthesis of L-lysine-scaffold based coumarin-labeled sugars

(**9**) and tetra-*O*-pivaloyl-β-D-galactopyranosylamine **60**, respectively (Scheme 39).[51]

Schick and co-workers devised a novel 1-acylbenzotriazole-mediated one-step synthesis of β-lactones **111** by the aldolization of carbonyl compounds (Scheme 40).[52] *N*-Acylbenzotriazoles **109** containing one hydrogen atom in the α-position to the carboxamide group were used as the substrates. These are easily deprotonated with lithium diisopropylamide to afford amide enolates that undergo condensation with carbonyl compounds at –90 to –95 °C to give *O*-lithiated β-hydroxyalkanoic acids **110**. The carboxamide derivatives **110** then underwent cyclization followed by the elimination of lithium benzotriazolide to produce the desired di- and trisubstituted β-lactones in good yields.

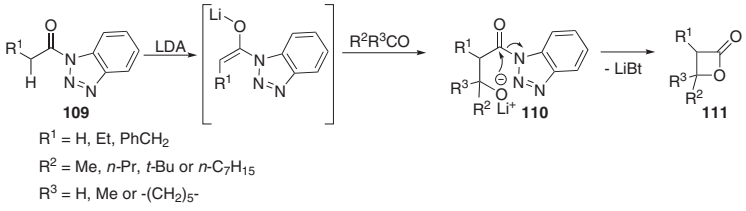
Thiolesters play a substantial role in many different syntheses, including those of heterocycles, various ketones, and biologically active substances. The majority of *S*-acylations that have been previously reported used an activated acyl derivative, such as an acyl halide with thiol sodium salts. The methods using activated acyl derivatives frequently have low yields, are constrained by the need for substrate-specific catalysts, or demand harsh conditions and lengthy workup procedures. Carbodiimides like *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) are frequently used to couple carboxylic acids with thiols in chemical reactions. The processes produce thiolesters in good yields, but because ureas are solvent-soluble, it can be challenging to remove them from the reaction mixture.[3f]

The utility of *N*-acylbenzotriazoles **3** was exploited as novel *S*-acylating agents by the Katritzky group and applied for the effective synthesis of a range of thiolesters in good-to-excellent yields (76–99%).[3f] *N*-Acylbenzotriazoles reacted with thiophenol, benzyl mercaptan, ethyl mercaptoacetate, and mercaptoacetic acid in the presence of Et_3N in DCM at room temperature to afford the corresponding thiolesters **112** (Scheme 41a). Moreover, preparation of chiral thiolesters **114** was also accomplished from *N*-Boc- or Cbz-protected amino acid and dipeptide based *N*-acylbenzotriazoles **113** under similar reaction conditions (Scheme 41b).



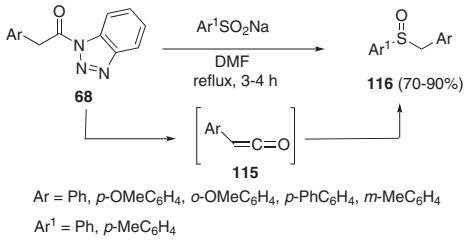
Scheme 41 Preparation of diverse thiolesters utilizing *N*-acylbenzotriazoles

The Katritzky group demonstrated a novel methodology for the synthesis of aryl benzyl sulfoxides **116** in good-to-excellent yields (70–90%) from the reaction of *N*-(arylacetyl)benzotriazoles **68** with sodium sulfinates (Scheme



Scheme 40 *N*-Acylbenzotriazole-mediated one-step synthesis of β-lactones from carbonyl compounds

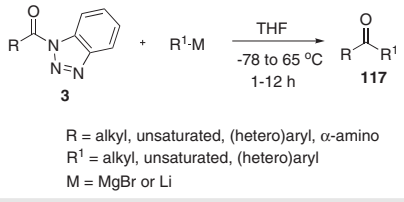
42).[53] The reaction is initiated with the elimination of benzotriazole from the *N*-(arylacetyl)benzotriazoles **68** in basic condition to generate arylketene intermediate **115**, which reacts with arenesulfinate anions to furnish aryl benzyl sulfoxides **116** after spontaneous decarboxylation.



Scheme 42 Synthesis of aryl benzyl sulfoxides from *N*-(arylacetyl)benzotriazoles

3.2 *C*-Acylation of Heterocycles Using *N*-Acylbenzotriazoles

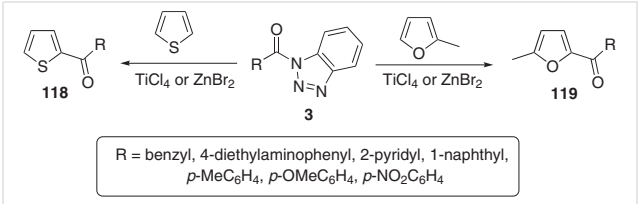
The Katritzky group further extended the application of *N*-acylbenzotriazoles to the synthesis of ketones **117** from organometallic compounds. Grignard and heteroaryllithium reagents reacted with *N*-acylbenzotriazoles **3**, derived from a range of aliphatic, unsaturated, (hetero)aromatic, and *N*-protected (*R*)-amino carboxylic acids, to furnish the corresponding ketones in good-to-excellent yields (Scheme 43).[54]



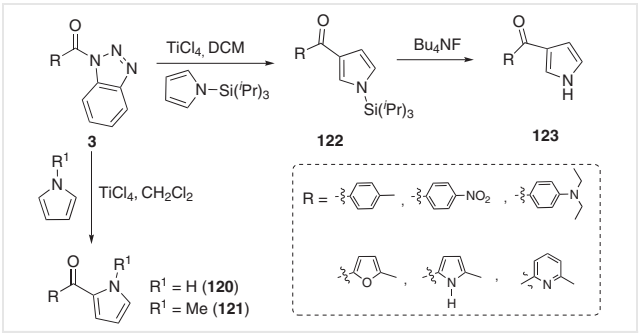
Scheme 43 *N*-Acylbenzotriazole-mediated synthesis of ketones from organometallic compounds

C-Acylation of heterocyclic compounds, such as furans, thiophenes, pyrroles, and indoles, with *N*-acylbenzotriazoles under Friedel–Crafts reaction condition was demonstrated by the Katritzky group (Scheme 44).[55] Their synthetic protocol furnished *C*-acylated heterocycles in excellent yields with high regioselectivity. *C*-Acylation reactions of thiophene and 2-methylfuran were performed in the presence of $TiCl_4$ (at 23 °C) or $ZnBr_2$ (at 110 °C) to provide comparable yields of 2-acylated products **118** and **119**, respectively.

Acylpyrroles are important motifs with biological significance and also play the role of intermediates in the multistep synthesis of various drug candidates.[56] Synthesis of acylpyrroles can be easily achieved through the acylation of pyrroles. The Katritzky group performed the reaction of unsubstituted/1-substituted pyrroles with *N*-acylbenzotriazoles **3** in the presence of $TiCl_4$, which resulted in an easy replacement of the benzotriazolyl group by the pyrrole, leading to the formation of 2-acylpyrroles **120** and **121**. *N*-Protection of pyrroles with a bulky group like triisopropylsilyl group directs the acylation to C-3 and affords *N*-triisopropylsilyl-3-acylpyrroles **122**. Subsequent deprotection using tetrabutylammonium fluoride gives 3-acylpyrrole **123** in 98% yield (Scheme 45).[3b]

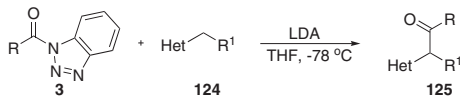


Scheme 44 Direct access to 2-acyl-5-methylfurans and 2-acylthiophenes through *N*-acylbenzotriazoles

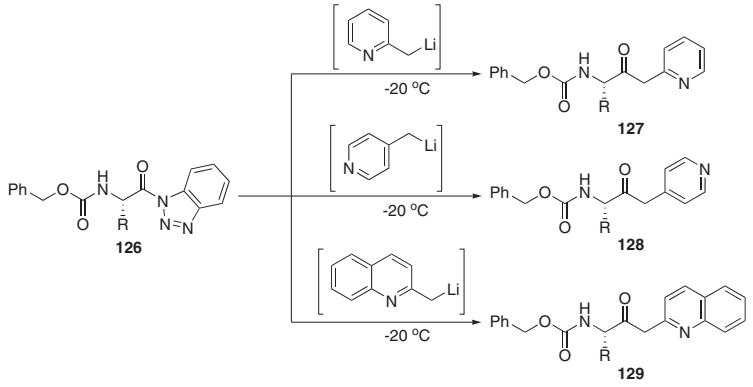


Scheme 45 Synthesis of 2-acylpyrroles *via* substitution of the benzotriazole moiety

A convenient route for the synthesis of 1-substituted 2-azinylethanones **125** was reported by the Katritzky group through the acylation of alkylated azines **124** with *N*-acylbenzotriazoles. Various alkylazines (2-methylpyridine, 2-benzylpyridine, 4-benzylpyridine, 2-methylquinoline, 4-methylquinoline, or 4-methylpyrimidine) reacted with readily available *N*-acylbenzotriazoles in THF at –78 °C with LDA to furnish acylated products **125** in 50–95% yields (Scheme 46).[57]



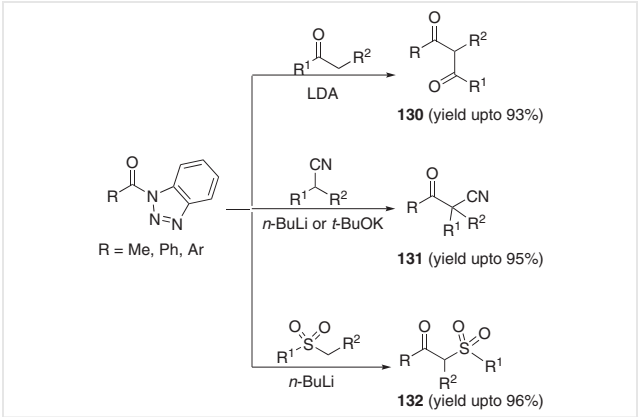
Scheme 46 Use of *N*-acylbenzotriazoles as acylating agents of various alkylated azines



Scheme 47 Benzotriazole-mediated one-step synthesis of optically pure aminoacyl conjugates of pyridine and quinoline

The Katritzky group further applied the benzotriazole methodology for the efficient synthesis of amino acyl conjugates of nitrogen heterocycles such as pyridine and quinoline, which act as potential pharmacophores in drug discovery and development. Lithiated substrates 2-methylpyridine, 4-methylpyridine, and 2-methylquinoline reacted with *N*-(Cbz-α-aminoacyl)benzotriazoles **126** and afforded *N*-(α-Cbz-aminoacyl)methylene heterocycles **127**, **128**, and **129**, respectively (Scheme 47).[58]

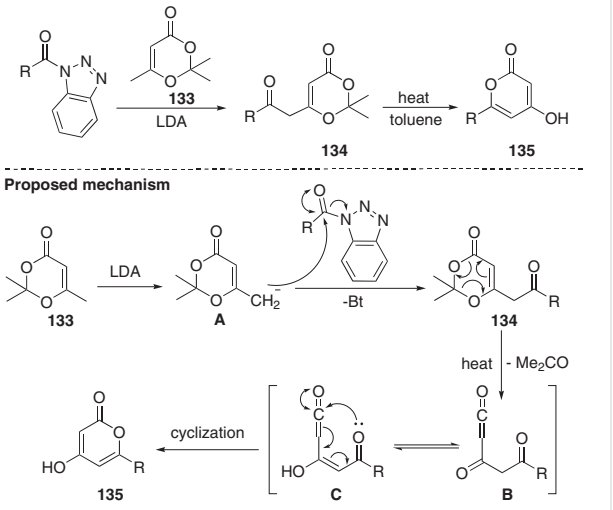
C-Acylations have been widely considered as a valuable technique in C–C bond formation and therefore are synthetically important.[59–61] Carbon acylation of simple ketone enolates has been explored for the synthesis of 1,3-keto esters and 1,3-diketones using different acylating reagents such as acid chlorides,[62] acyl cyanides,[63,64] *N*-acylimidazoles,[65] methyl methoxymagnesium carbonate,[66] formates, and oxalates.[60] The Katritzky group synthesized β-diketones **130** from *N*-acylbenzotriazoles in a regioselective manner *via* *C*-acylation. The *C*-acylated products were formed in excellent yields by the reaction of alkyl and aryl *N*-acylbenzotriazoles derivatives with aliphatic ketones, saturated cyclic ketones, and unsaturated cyclic ketones in the presence of lithium diisopropylamide in THF at –78 °C (Scheme 48).[67] The synthesis of β-ketonitriles and α-mono- and α,α-disubstituted β-ketonitriles **131** was also achieved by the acylation of both primary and secondary alkyl cyanides as depicted in Scheme 48. The reactions were performed using a strong base at different temperatures, either by potassium *tert*-butoxide at 23 °C or *n*-butyllithium at –78 °C.[3d] In addition, sulfones were also converted into β-keto sulfones **132** (Scheme 48). Aliphatic, aromatic, and heteroaromatic β-keto sulfones were prepared in 70–96% yields using *n*-butyllithium. β-Keto sulfones are useful intermediates and have substantial synthetic applications in the synthesis of different moieties such as disubstituted acetylenes, vinyl sulfones, allenes, olefins, and polyfunctionalized 4*H*-pyrans.[68] A few β-keto sulfones show evidence of fungicidal activity,[69] and some are used as precursors for synthesis of optically active β-hydroxy sulfones.[70]



Scheme 48 *N*-Acylbenzotriazole-mediated regioselective *C*-acylation for the synthesis of β-diketones, β-ketonitriles, and β-keto sulfones

Furthermore, pyrones are a significant class of lactone derivatives and are important functionality present in many natural products with diverse range of biological applications. The Katritzky group formulated a two-step synthetic strategy for the preparation of functionalized pyrones (Scheme 49).[71] The first step involves the synthesis of 6-(acylmethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-ones **134** by reacting 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**133**) with *N*-acylbenzotriazoles using LDA in 37–66% yields. Compounds **134** rapidly undergo cyclization under heating conditions in toluene to afford 6-substituted 4-hydroxy-2-pyrones **135** in up to 86% yield. In the proposed reaction pathway, initially LDA abstracts a proton from compound **133** to afford the corresponding anion **A** which subsequently attacks the *N*-acylbenzotriazole to give 6-(acylmethyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-ones **134**. Under heating, elimination of acetone results in *in situ* generation of intermediate **B**, which tautomerizes to enolic form **C**, followed by cyclization to obtain the desired pyrone derivatives **135**.

β- and γ-Amino acid derivatives are the key motifs for several biologically relevant compounds as well as in natural products.[72] A versatile approach was developed for the

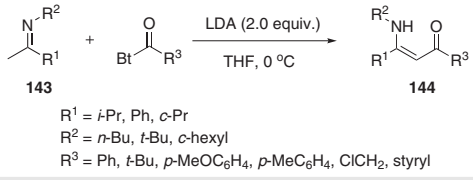


Scheme 49 Synthesis of biologically relevant pyrone derivatives using *N*-acylbenzotriazoles

synthesis of ω-aryl-substituted β- and γ-amino acid derivatives (Scheme 50).[73] The treatment of *N*-Tfa-amino acid monoesters **136** (Tfa = trifluoroacetyl) with thionyl chloride and benzotriazole in dichloromethane afforded 1-(*N*-Tfa-α-aminoacyl)benzotriazoles **137**, which on Friedel–Crafts reaction with aromatic compounds provided α-amino ketones **138**. The reduction of α-amino ketones with sodium borohydride or with triethylsilane afforded the corresponding ω-aryl-substituted β- and γ-amino acid derivatives **139**. The result obtained from chiral HPLC confirms that the chirality was maintained throughout the reaction.

The existence of the nitro group at the α-position with respect to the carbonyl carbon provides specificity this type of molecule. Their existence offers viable reactivity patterns to compounds like α-nitro ketones. α-Nitro ketones are important precursors used in the synthesis of compounds with chemotherapeutic applications. The Katritzky group established a method for the synthesis of α-nitro ketones by the application of *N*-acylbenzotriazoles (Scheme 51).[3h] The reaction of nitro alkanes **140** with 2.0 equiv potassium *tert*-butoxide resulted in the generation of a doubly metalated complex **141** that reacted with various substituted *N*-acylbenzotriazoles to furnish functionalized α-nitro ketones **142** in up to 86% yields.

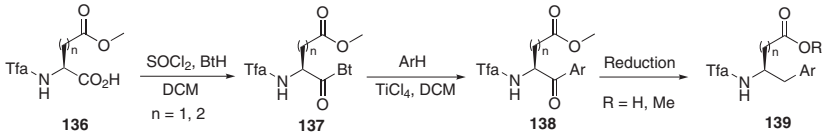
Other intermediates involving *C*-acylation were explored with *N*-acylbenzotriazole derivatives such as the acylation of metalated ketimines **143** (1.0 equiv) was accomplished in the presence of LDA (2.0 equiv) in anhydrous THF at 0 °C using *N*-acylbenzotriazoles as acylating agents, producing enaminones **144** (Scheme 52).[74] Enaminones are very important compounds and used as synthetic intermediates in various heterocyclic moieties, e.g., carbazolequinone alkaloids[75] pyrroles,[76] isoxazoles,[77] tricyclic benzo[*a*]quinolizines,[78] and benzodiazepines.[79]



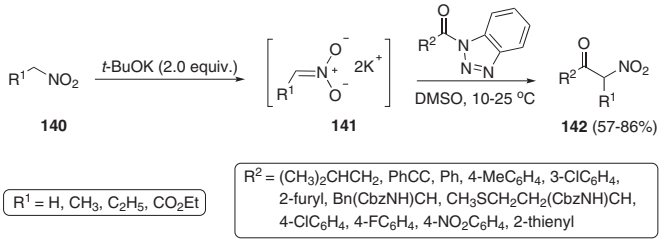
Scheme 52 *N*-Acylbenzotriazole-assisted synthesis of enaminones

3.3 Preparation of β-Keto Esters and β-Diketones by Acylative Deacetylation

In 2004 in extension of the reactions of *N*-acylbenzotriazoles, the Katritzky group showed that aromatic *N*-acylbenzotriazoles react with ethyl acetoacetate to afford β-keto esters in high yields (Scheme 53).[80] This one-pot, two-step reaction was used to demonstrate the *C*-acylative deacetylation reaction. In the first step, *N*-acylbenzotriazole **3** and acetoacetic ester were treated with NaH followed by

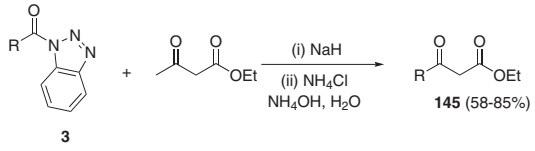


Scheme 50 Synthesis of chiral β- and γ-amino acid derivatives by the application of *N*-protected *N*-(aminoacyl)benzotriazoles

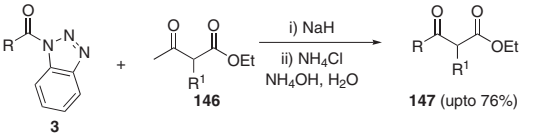


Scheme 51 *N*-Acylbenzotriazole-mediated synthesis of α-nitro ketones

the reaction with NH_4Cl in the second step. The crude product was then exposed to silica gel column chromatography, and β-keto esters **145** were obtained in 58–85% yields with a keto/enol ratio 80:20; the exception was R = 4-pyridyl where a keto/enol ratio of 39:61 was found. When 2-benzyl- or 2-methyl-substituted acetoacetates **146** were used under similar reaction conditions, the corresponding α-substituted β-keto esters **147** were obtained in 51–76% yields (Scheme 54). The conversions are of specific importance as the direct acylation of esters with *N*-acylbenzotriazoles to produce β-keto esters is not available proficiently in previous reports.



Scheme 53 Synthesis of β-keto esters *via* *C*-acylative deacetylation

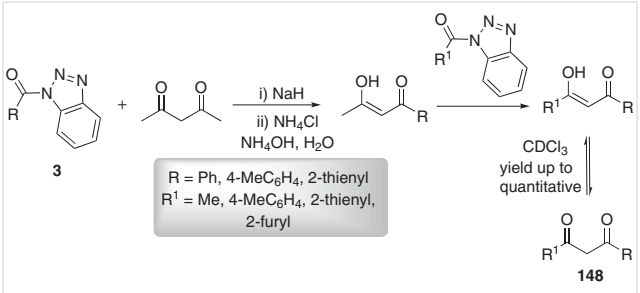


Scheme 54 Synthesis of 2-substituted β-keto esters *via* *C*-acylative deacetylation

Similarly, by acylative deacetylation, α-acetyl ketones were transformed into more complex β-diketones **148** (Scheme 55).[80] In this type of reaction, triketones are the expected intermediates, which subsequently undergo reaction by Japp–Klingemann mechanism with loss of the acetyl group.[81] In this case, acetylacetone undergoes a double *C*-acylative deacetylation *via* repeated reactions with 2.0 mol of the same or different *N*-acylbenzotriazoles, resulting in a β-diketone in which only the central carbon atom of acetylacetone is preserved. Symmetrical β-diketones (2 examples) were formed in 97% and 100% yields when 2.0 mol of the *N*-acylbenzotriazoles were utilized. Using this approach, even the unsymmetrical diketones were obtained in good yields.

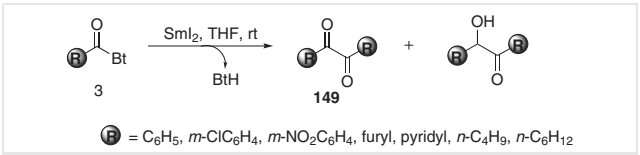
3.4 *N*-Acylbenzotriazoles Used for the Preparation of Other Valuable Intermediates

N-Acylbenzotriazoles **3** are used as excellent acylating reagents as well as key synthons for synthesizing important intermediates. Baruah *et al.* synthesized 1,2-diketones through the coupling of keto cyanides catalyzed by samarium diiodide.[82] Preparation of keto cyanides required toxic cyanides and high temperatures. Wang and Zhang reported



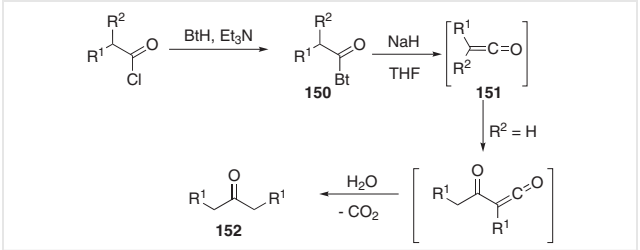
Scheme 55 Synthesis of β-diketones *via* *C*-acylative deacetylation

a modified synthesis of 1,2-diketones **149** by coupling two molecules of *N*-acylbenzotriazole catalyzed by samarium diiodide in THF; the products are stable, crystalline solids (Scheme 56).[83] Thus, by using benzotriazole and easily available starting materials, auxiliary 1,2-diketones **149** were synthesized under mild reaction conditions.



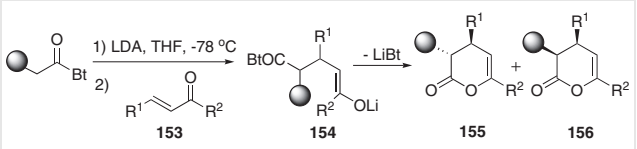
Scheme 56 Synthesis of 1,2-diketones form *N*-acylbenzotriazole

The Katritzky group synthesized arylketenes **151**, which can be further used to access other important organic intermediates, from *N*-(arylacetyl)benzotriazole **150** under basic conditions facilitated by the elimination of benzotriazole. Symmetrical ketones **152** were achieved in good yields from *N*-(arylacetyl)benzotriazoles *via* reaction with NaH in THF followed by hydrolysis (Scheme 57).[84]



Scheme 57 Synthesis of 1,3-diarylacetones from *N*-(arylacetyl)benzotriazole

Further, the Katritzky group reported synthesis of predominantly *trans*-isomers **155** of 3-alkyl-4,6-diaryl-3,4-dihydropyran-2-ones in good yields (Scheme 58).[85] In this reaction, lithiated aliphatic unbranched *N*-acylbenzotriazoles undergo 1,4-addition with α,β-unsaturated aromatic ketones **153** to produce **154**, which afforded the diastereomeric mixture of 3,4-dihydropyran-2-ones **155** and **156** with predominance of *trans*-isomer **155** in 70% yield.

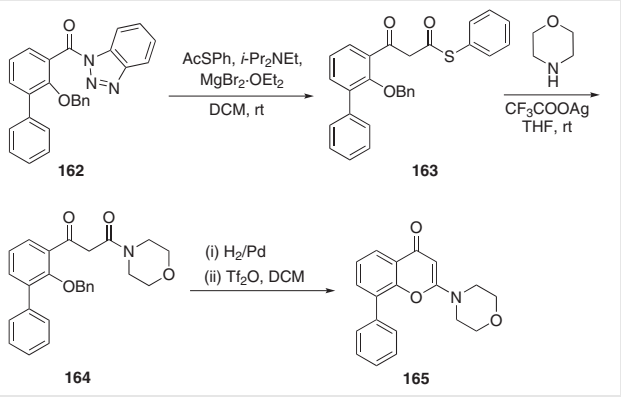


Scheme 58 Ring synthesis of 3-alkyl-4,6-diaryl-3,4-dihydropyran-2-ones

Coltart and co-workers further explored *N*-acylbenzotriazoles in the acylation of enolizable thioesters to give β-keto thiolesters **158** (Scheme 59).[86] In the presence of $MgBr_2$·OEt_2 and *i*-Pr_2NEt, the thiolesters **157** undergo chemoselective soft enolization followed by acylation by *N*-acylbenzotriazoles in DCM in air to afford β-keto thiolesters **158**. The obtained β-keto thiolesters **158** are very stable and also these are synthetic equivalents of β-keto acids and can be transformed directly into β-keto esters **159** and β-keto amides **160** after treatment with an alcohol or an amine, respectively, in the presence of silver trifluoroacetate in THF. The β-keto thiolesters **158** also reacted with ethylzinc iodide and a palladium complex to give 1,3-diketo derivatives **161**.

Coltart and co-workers also reported the synthesis of 2-morpholino-8-phenyl-4*H*-chromen-4-one (**165**), an important PI3-K inhibitor, by utilizing the C–C bond forming protocol. First, the β-keto thiolester **163** was produced by the crossed-Claisen coupling of **162** with *S*-phenyl thioacetate. Treatment of **163** with morpholine in the presence of silver trifluoroacetate in THF resulted in the replacement of the phenylthio group by a morpholino group to produce amide **164**. The derivative **164** undergoes deprotection of the benzyloxy group followed by cyclization of the obtained phenol derivative catalyzed by triflic anhydride to furnish smoothly chromen-4-one **165** (Scheme 60).[86]

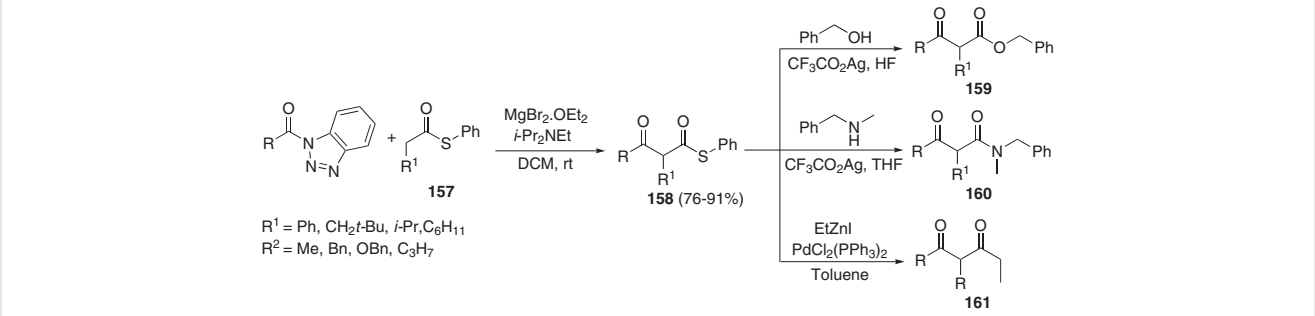
Chafuroside A and its regioisomer chafuroside B are flavone *C*-glycosides, possessing remarkable biological activities against various frontline diseases. Due to their importance in drug discovery and development, continuous efforts have been made for their total synthesis by various scientific communities. In this direction, Kan, Wakimoto,



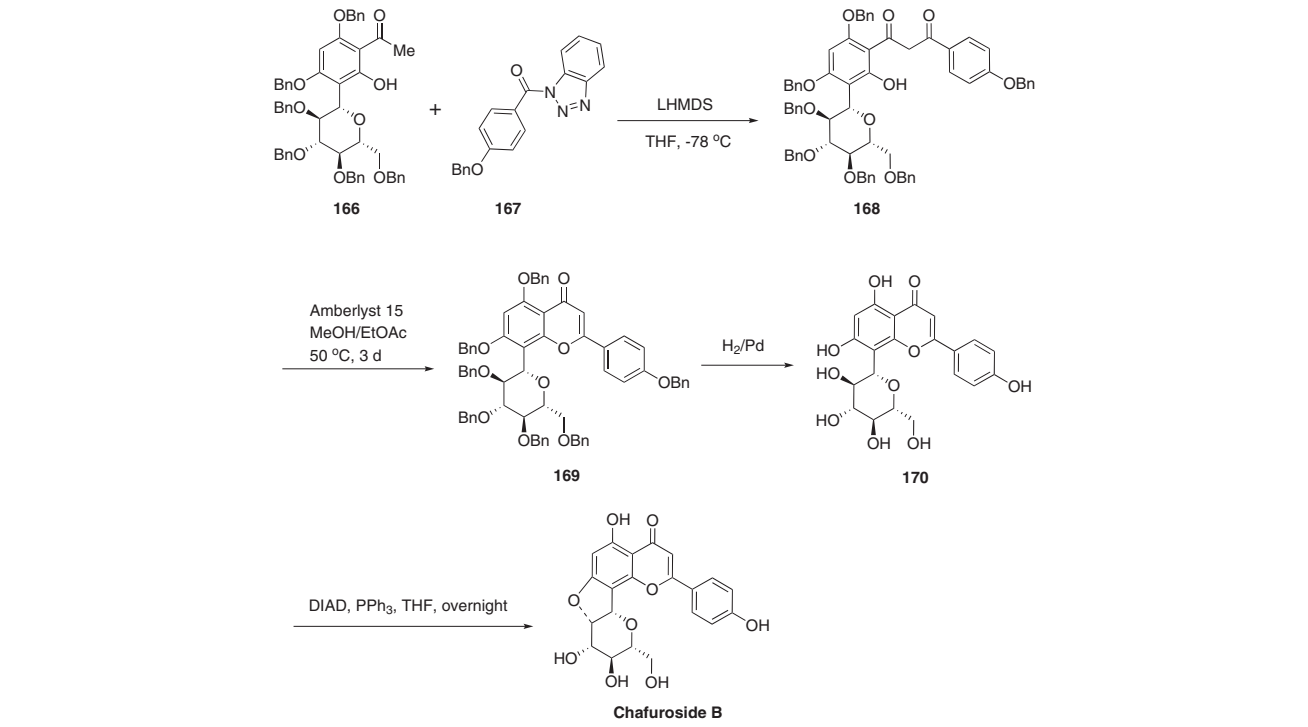
Scheme 60 *N*-Acylbenzotriazole-assisted synthesis of 2-morpholino-8-phenyl-4*H*-chromen-4-one

and co-workers developed a novel synthetic strategy for the total synthesis of chafuroside A and B through the assistance of benzotriazole chemistry. A segment of the total synthesis of chafuroside B is shown in Scheme 61; here the crucial step is the acylation of 2-hydroxyacetophenone derivative **166** using 1-(4-benzyloxybenzoyl)benzotriazole (**167**) in the presence of LHMDS to afford the β-diketone intermediate **168** in 95% yield. Under acidic conditions, using the Amberlyst 15 catalyst, derivative **168** undergoes a ring-closing reaction to produce 4*H*-chromen-4-one **169**, which on deprotection of the benzyloxy groups, furnish a naturally occurring flavonoid vitexin (**170**), which under Mitsunobu conditions furnishes the desired chafuroside B in 63% yield.[87]

In another investigation, a group from Roche used an *N*-acylbenzotriazole for the construction of the 1*H*-pyrido[2,3-*d*]pyrimidine system (Scheme 62).[88] Efficient synthesis of 8-cyclopentyl-5-hydroxy-2-(methylsulfanyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**174**) was carried out using benzotriazole chemistry in 97% yield. First, treatment of *o*-(cyclopentylamino) acid **171** with benzotriazole in the presence of EDCI as dehydrating agent in DCM results in the formation of the 1-acylbenzotriazole derivative **172**. Reaction of **172** with lithiated ethyl acetate in THF provides β-

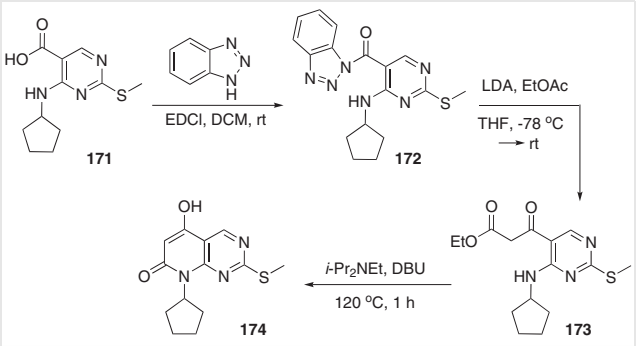


Scheme 59 Synthesis of β-keto thiolesters and their transformation into β-keto esters, β-keto amides, and β-diketones



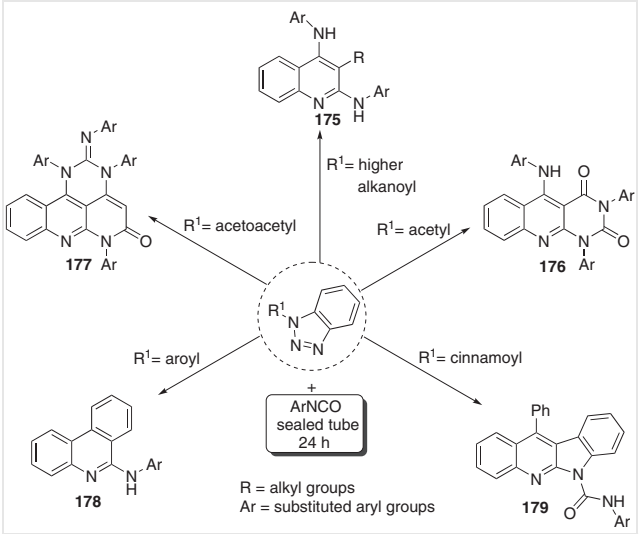
Scheme 61 Total synthesis of chafuroside B through the application of an *N*-acylbenzotriazole

keto ester **173**, which undergoes cyclocondensation reaction on treatment with DBU and *N*,*N*-diisopropylethylamine at 120 °C to furnish **174** in 97% yield.

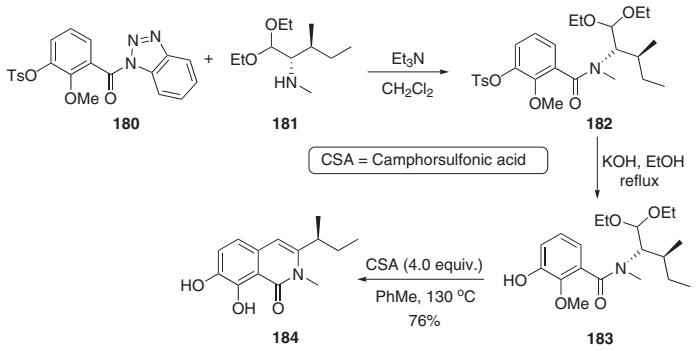


Scheme 62 *N*-Acylbenzotriazole-mediated synthesis of 8-cyclopentyl-5-hydroxy-2-(methylsulfanyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

The synthesis of a variety of heterocyclic compounds has frequently utilized aryl isocyanates.[89,90] The Katritzky group further demonstrated the versatility of benzotriazoles by establishing a protocol for *N*-acylbenzotriazole-mediated synthesis of various polycyclic heteroaromatic compounds (Scheme 63).[91] In their synthetic strategy, several distinct type of *N*-acylbenzotriazoles reacted with various aryl isocyanates in a sealed tube for 24 h to furnish five different categories of polycyclic heteroaromatic molecules. Derivatives of quinoline **175**, pyrimidino[5,4-*c*]quinoline **176**, benzo[*b*][1,8]naphthyridine **177**, phenanthridine **178**, and indolo[2,3-*b*]quinoline **179** were synthesized in good yield from the reaction of alkanoyl-, acetyl-, acetoacetyl-, aroyl-, and cinnamoylbenzotriazoles, respectively, with various aryl isocyanates (Scheme 63).[91] These products **175**–**179** were constructed through the incorporation of 3, 3, 4, 2, and 2 molecules, respectively, of aryl isocyanate per *N*-acylbenzotriazole molecule.



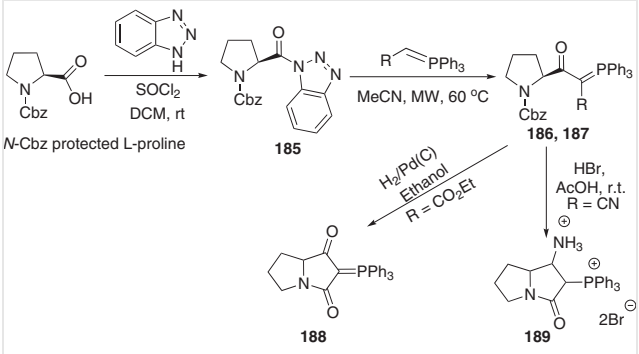
Scheme 63 *N*-Acylbenzotriazole-mediated efficient synthesis of various polycyclic heteroaromatics



Scheme 64 *N*-Acylbenzotriazole-mediated synthesis of isoquinolones through modified Pomeranz–Fritsch mechanism

Barrett and co-workers reported a *N*-acylbenzotriazole-mediated synthesis of an isoquinolone **184**, a part of the antifungal agent Sch 56036 (Scheme 64).[93] Acetal **181**, obtained from readily available L-isoleucine, was acylated with *N*-acylbenzotriazole **180** to give amide **182** in 68% yield. Reaction of amide **182** with KOH under refluxing conditions gave detosylation to give phenol **183**. Subsequent reaction of phenol **183** with 4.0 equiv of camphorsulfonic acid in refluxing toluene resulted in cyclization (*via* Pomeranz–Fritsch mechanism), followed by demethylation to give isoquinolone **184** in a satisfactory outcome.

Bicyclic pyrrolizines were synthesized by the Katritzky group starting from *N*-acylbenzotriazole **185**, obtained through the reaction of *N*-Cbz-L-proline with benzotriazole and thionyl chloride (Scheme 65).[94] The reaction of *N*-acylbenzotriazole **185** with ethyl (triphenylphosphoranylidene)acetate afforded (2*S*)-1-Cbz-2-[(ethoxycarbonyl)(triphenylphosphoranylidene)acetyl]pyrrolidine **186** in 66% yield. Deprotection of pyrrolidine **186** by H_2/Pd(C) followed by ring closure resulted in formation of pyrrolizine-1,3-dione **188**. In a similar way, reaction of *N*-acylbenzotriazole **185** with (triphenylphosphoranylidene)acetonitrile gave (2*S*)-1-Cbz-2-[cyano(triphenylphosphoranylidene)-acetyl]pyrrolidine **187**. Deprotection of pyrrolidine **187** with 33% HBr in acetic acid followed by cyclization afforded 3*H*-1-ammonio-2-(triphenylphosphonio)-5,6,7,7a-tetrahydropyrrolizin-3-one dibromide **189** in 66% yield.

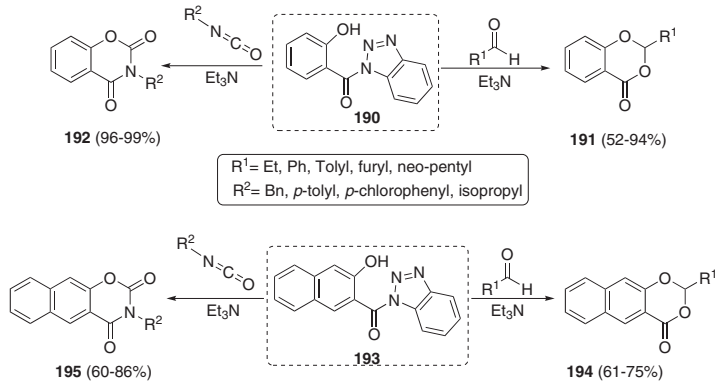


Scheme 65 Synthesis of pyrrolizine-1,3-dione and pyrrolizin-3-one using benzotriazole methodology

The Katritzky group exploited a practical route using benzotriazole-mediated methodology for an efficient and high yielding synthesis of 1,3-benzodioxin-4-ones **191**, 1,3-benzoxazine-2,4-diones **192**, naphtho-1,3-dioxinones **194**, and naphthoxazine-1,3-diones **195** (Scheme 66).[95] The reaction of *N*-(*o*-hydroxyarylcarbonyl)benzotriazoles **190** and **193** with various aldehydes in anhydrous THF as solvent in the presence of base furnished 1,3-benzodioxin-4-ones **191** and naphtho-1,3-dioxinones **194**, respectively at room temperature, whereas, under the similar reaction conditions, their reaction with suitable isocyanates produced 1,3-benzoxazine-2,4-diones **192** and naphthoxazine-1,3-diones **195**, respectively, in excellent yields. Both aromatic and aliphatic aldehydes and isocyanates were well tolerated as substrates in this methodology.

The fascinating chemistry of benzotriazoles was further extended by the Katritzky group for the synthesis of a diverse range of biologically active heterocyclic compounds. Towards this effort, the group applied the benzotriazole methodology to synthesize fused ring systems of pyrido[1,2-*a*]pyrimidin-2-ones **200** and 2*H*-quinolizin-2-ones **201**. Pyrido[1,2-*a*]pyrimidines are biologically potent heterocycles, and they are structural features of several chemotherapeutic drugs such as the tranquilizer pirenperone (**196**),[96] the antiallergic agent ramastine (**197**),[97]an antiulcerative agent **198**,[98] and an anti-asthmatic agent TBX **199**,[99] contain the pyrido[1,2-*a*]pyrimidine moiety in their structures (Figure 2).

The reaction was carried out between *N*-(phenylpropynoyl)benzotriazole **202** and substituted 2-aminopyridines in acetonitrile solvent in a sealed tube at 120 °C for 12 h which furnished the pyrido[1,2-*a*]pyrimidin-2-ones **200** in good yields (71–73%) (Scheme 67).[100] Similarly, the reaction of *N*-(phenylpropynoyl)benzotriazole **202** with substituted 2-picolines under same reaction conditions afforded 2*H*-quinolizin-2-ones **201** in moderate-to-good yields (39–81%).



Scheme 66 Acylbenzotriazole-mediated synthesis of 1,3-benzodioxin-4-ones, naphtho-1,3-dioxinones, 1,3-benzoxazine-2,4-diones, and naphthoxazine-1,3-diones

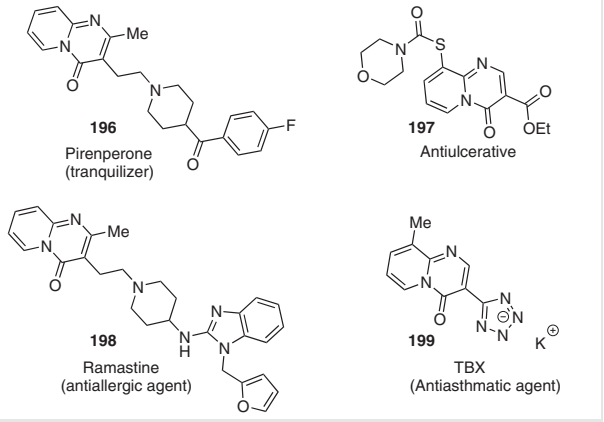
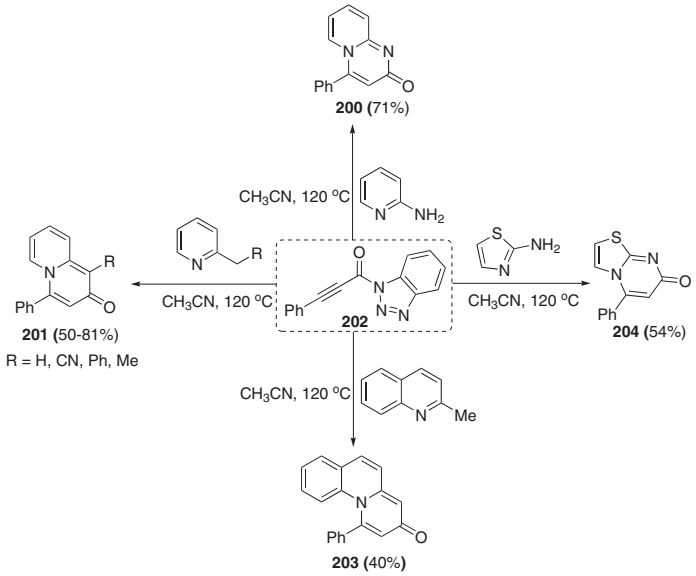


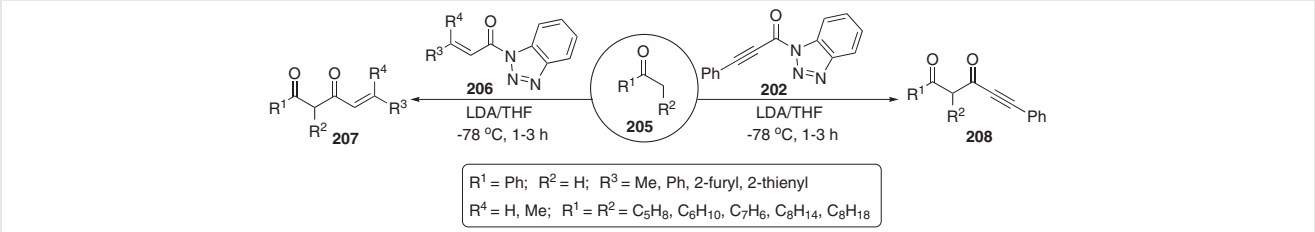
Figure 2 Drugs containing the pyrido[1,2-*a*]pyrimidine moiety in their structures

The group also applied this methodology to the preparation of fused ring systems of pyrido[1,2-*a*]quinolin-3-one **203** and thiazolo[3,2-*a*]pyrimidin-7-one **204**. The reaction of 2-methylquinoline with *N*-(phenylpropynoyl)benzotriazole **202** in acetonitrile in a sealed tube at 120 °C afforded pyrido[1,2-*a*]quinolin-3-one **203** in 40% yield. Likewise, the 5-phenyl-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one (**204**) was obtained in 54% yield from the reaction of 2-aminothiazole with *N*-(phenylpropynoyl)benzotriazole **202** under similar reaction conditions (Scheme 67).[100]

In their next investigation, the Katritzky group utilized *N*-acylbenzotriazoles of various aliphatic and aromatic α,β-unsaturated carboxylic acids as stable and easily accessible acylating agents for the regioselective *C*-acylation of various ketones **205** in order to synthesize medicinally active γ,δ-unsaturated β-diketones (Scheme 68).[101] The desired γ,δ-



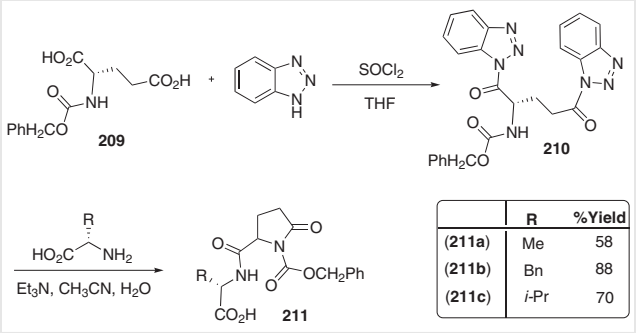
Scheme 67 Synthesis of various biologically active heterocycles using benzotriazole strategy



Scheme 68 Synthesis of γ,δ-unsaturated β-diketones through *C*-acylation of various ketones

unsaturated β-diketones **207** and **208** were prepared from the reaction *N*-(α,β-unsaturated acyl)benzotriazoles **206** and **202** and ketones in the presence of a LDA as base at –78 °C in 3 h. First, the reaction of ketones with LDA produced the corresponding lithium enolate which on reaction with *N*-acylbenzotriazoles furnished the diketones in good yields.

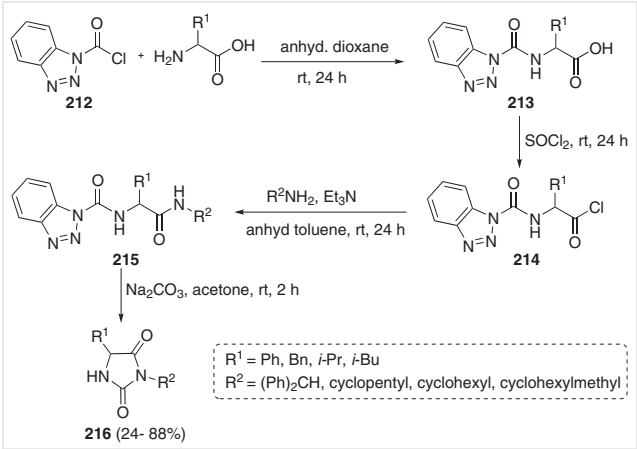
The Katritzky group demonstrated a convenient synthesis of *N*-protected-pyroglutamyl pseudopeptides **211a–c** from glutamyl-bis-benzotriazole **210** through cyclization of an *N*-terminal glutamic acid residue (Scheme 69).[102] *N*-Protected L-glutamic acid **209** was used for the acylation of 1*H*-benzotriazole in the presence of thionyl chloride in THF to generate glutamyl-bis-benzotriazole **165**, which underwent condensation with an L-amino acid in the presence of triethylamine as base in aqueous acetonitrile to furnish pyrrolidin-2-ones **211**. The crude products were washed with 4 N HCl to afford pure products **211a–c** in 58–88% yields.



	R	%Yield
(211a)	Me	58
(211b)	Bn	88
(211c)	*i*-Pr	70

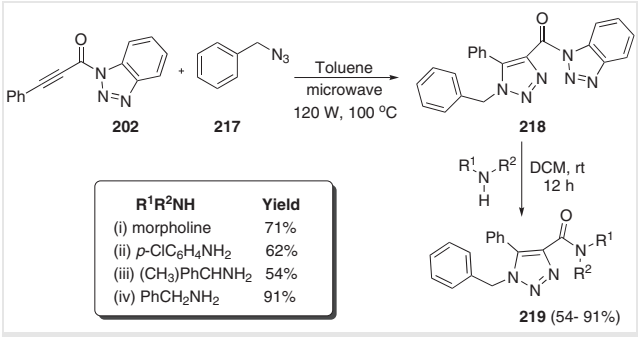
Scheme 69 Benzotriazole-mediated synthesis of *N*-protected-pyroglutamyl pseudopeptides

Mintas, Zorc, and co-workers reported a benzotriazole-mediated methodology for synthesis of 3,5-disubstituted hydantoin (imidazolidine-2,4-dione) derivatives **216** through cyclization of the corresponding *N*-(benzotriazol-1-ylcarbonyl)-L- and D-amino acid amides **215** in the presence of a base (Scheme 70).[103] 1-(Chloroformyl)benzotriazoles **212** were prepared from benzotriazole using a previously reported method.[104] The reaction of **212** with amino acids in anhydrous dioxane produced **213** that on treatment with thionyl chloride was converted into acid chlorides **214** which were subsequently reacted with amines to afford amides **215**. The cyclocondensation of these amides in the presence of sodium carbonate as base followed by elimination of the benzotriazole moiety furnished hydantoins **216** in 24–88% yields.



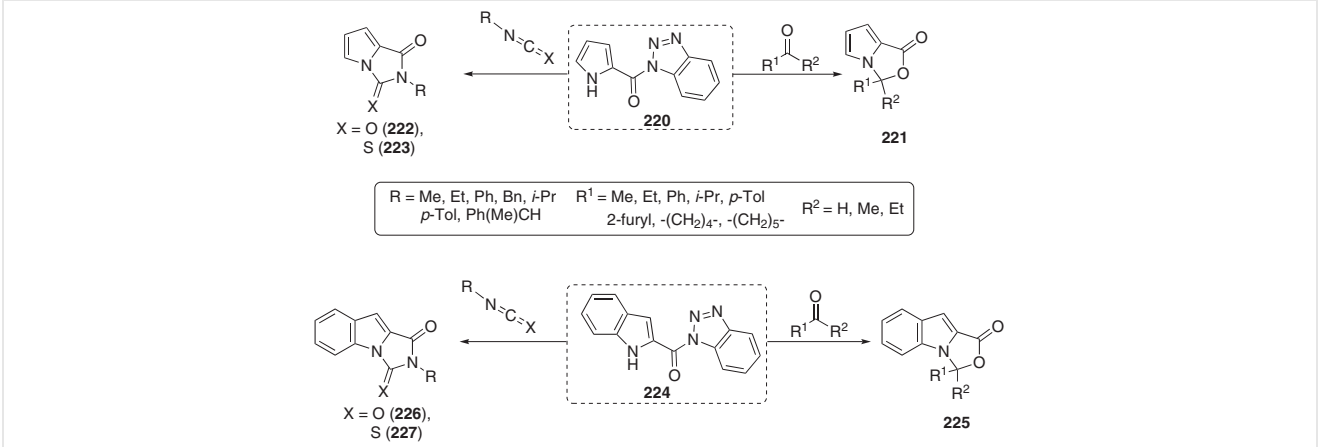
Scheme 70 Benzotriazole-facilitated synthesis of 3,5-disubstituted hydantoins

A general and convenient method for the synthesis of 4-carbamoyl-1,2,3-triazoles **219** from *N*-(phenylpropynoyl)benzotriazole **202** under microwave irradiation has been reported by the Katritzky group (Scheme 71).[105] First, the condensation of phenylpropynoic acid with 1-(methylsulfonyl)benzotriazole produced *N*-(phenylpropynoyl)ben-



R^1R^2NH	Yield
(i) morpholine	71%
(ii) *p*-$ClC_6H_4NH_2$	62%
(iii) $(CH_3)PhCHNH_2$	54%
(iv) $PhCH_2NH_2$	91%

Scheme 71 Benzotriazole-mediated synthesis of 4-carbamoyl-1,2,3-triazoles under microwave irradiation



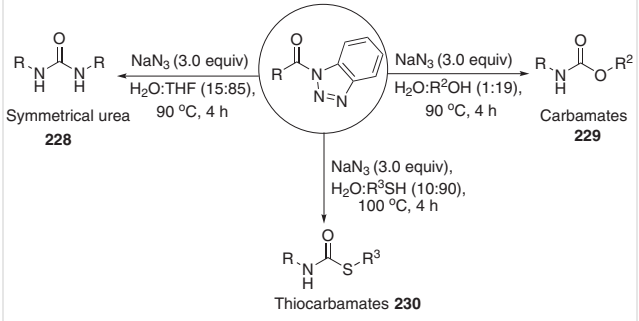
Scheme 72 One-step synthesis of pyrrolo[1,2-*c*]oxazol-1-ones, pyrrolo[1,2-*c*]imidazoles, oxazolo[3,4-*a*]indol-1-ones, and imidazo[1,5-*a*]indoles

zotriazole **202**, which on [3+2] cycloaddition reaction with benzyl azide (**217**) in toluene under microwave irradiation furnished substituted 4-(benzotriazol-1-ylcarbonyl)-1,2,3-triazole **218**. The treatment of **218** with various amines in DCM at room temperature provided corresponding 4-carbamoyl-1,2,3-triazoles **219** in 54–91% yields after elimination of the benzotriazole moiety.

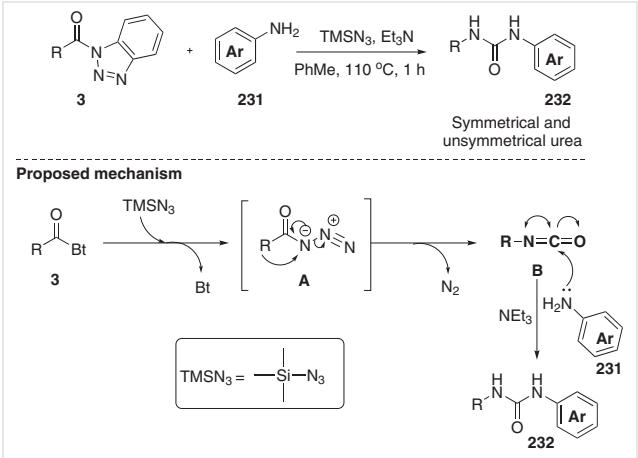
A novel protocol was devised by the Katritzky group for one-step synthesis of various important bicyclic compounds with fused pyrrole, indole, oxazole, and imidazole rings (Scheme 72).[106] Easily available and stable benzotriazol-1-yl(1*H*-pyrrol-2-yl)methanone **220** reacted with various ketones, isocyanates, and isothiocyanates in the presence of a strong, non-nucleophilic base such as DBU in THF to give pyrrolo[1,2-*c*]oxazol-1-ones **221** and pyrrolo[1,2-*c*]imidazoles **222** and **223**, respectively, in a simple one-step method. This protocol was also utilized for the synthesis of oxazolo[3,4-*a*]indol-1-ones **225** and related imidazo[1,5-*a*]indoles **226** and **227** from benzotriazol-1-yl(1*H*-indol-2-yl)methanone **224** in one-step.

In 2016, the Tiwari group implemented a plan for the synthesis of diverse urea, carbamates and thiocarbamates *via* the Curtius rearrangement in different solvent compositions at elevated temperatures (Scheme 73).[107] Readily available *N*-acylbenzotriazoles reacted with NaN_3 in THF/water (85:15) at 90 °C, H_2O/alcohol (1:19) at 90 °C for 4 h, and thiol/water (90:10) at 100 °C to afford the symmetrical ureas **228**, carbamates **229**, and thiocarbamates **230**, respectively.

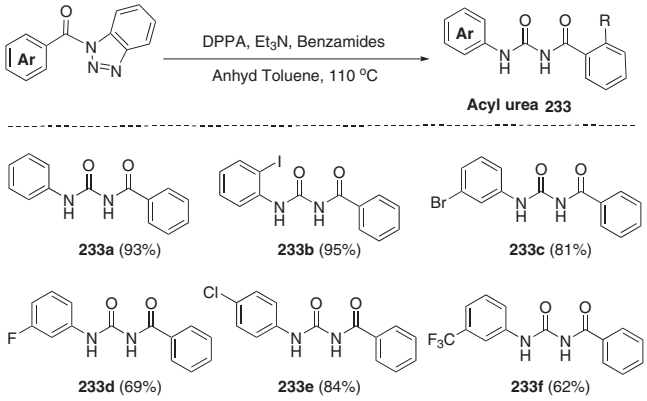
In 2019, the Tiwari group devised a new methodology for the synthesis of symmetrical and unsymmetrical ureas from *N*-acylbenzotriazole **3** (Scheme 74);[108] the route in Scheme 73 was limited to symmetrical ureas. The ureas **232** were obtained in a one-pot reaction when *N*-acylbenzotriazole **3** was treated with $TMSN_3$ followed by the addition of amines **231** in toluene at 110 °C for 60 min. Mechanistically, compound **3** reacts with trimethylsilyl azide (as azide source) to give acyl azide **A** by elimination of benzotriazole. The acyl azide **A** undergo subsequent rearrangement (Curtius rearrangement) and furnishes isocyanate intermediate **B** by the evolution of molecular nitrogen. The isocyanate is



Scheme 73 Synthesis of urea, carbamates, and thiocarbamates using *N*-acylbenzotriazoles



Scheme 74 *N*-Acylbenzotriazole-mediated synthesis of symmetrical and unsymmetrical ureas

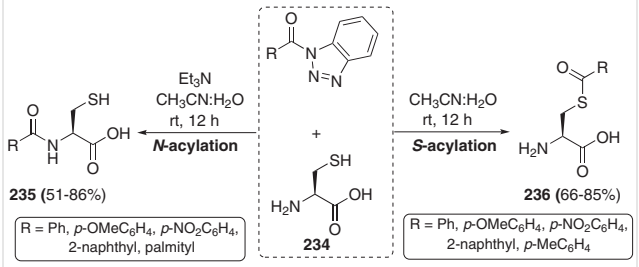


Scheme 75 Synthesis of substituted *N*-acylureas from *N*-acylbenzotriazoles

subsequently trapped by the amine nucleophile to afford ureas **232** (25 examples, up to 99% yield). *N*-Acylureas were also obtained in reasonable yields when 1-(1*H*-benzotriazol-1-yl)-2-phenylethane-1,2-dione was reacted with various amines under the optimized reaction condition.[108]

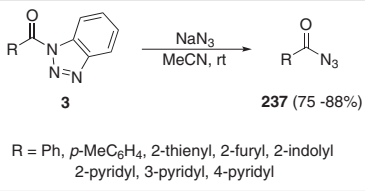
Furthermore in 2021, the Tiwari group devised an efficient, one-pot method for the synthesis of *N*-acylureas, ureas, carbamates, and thiocarbamates using diphenylphosphoryl azide (DPPA) as an azide transfer reagent.[109] The synthesis of *N*-acylurea **233** is depicted in Scheme 75. Initially, *N*-acylbenzotriazole **3** reacted with DPPA to give an acyl azide that underwent rearrangement under heating to furnish an isocyanate intermediate after the elimination of molecular nitrogen. The reaction of the isocyanate with amides, amines, phenols, and thiophenols resulted in the formation of *N*-acylureas, ureas, carbamates, and thiocarbamates, respectively. In most of the cases, column chromatography was avoided, and compounds were purified by sequential washing with appropriate solvents.

In their next investigation, the Katritzky group developed a protocol for selective synthesis of *S*-acylcysteines and *N*-acylcysteines utilizing *N*-acylbenzotriazole chemistry under mild reaction conditions (Scheme 76).[3n] The reaction of *N*-acylbenzotriazoles with L-cysteine (**234**) in the presence of triethylamine as base in MeCN/H_2O (3:1) at room temperature afforded *N*-acylcysteines **235** exclusively in 51–86% yields, whereas, *S*-acylcysteines **236** were obtained as the sole product in 66–85% yields under similar reaction condition but in the absence of basic medium. The structures of the synthesized compounds were confirmed by using various spectroscopic characterizations and also single-crystal X-ray diffraction techniques.



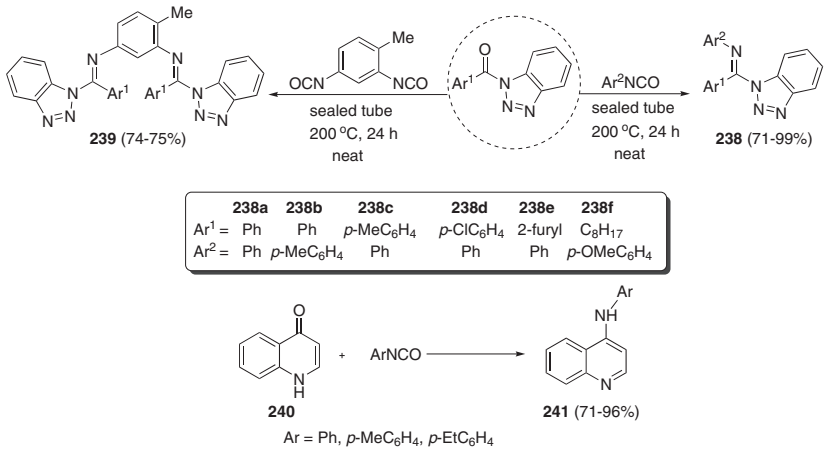
Scheme 76 Selective synthesis of *S*-acyl- and *N*-acylcysteines

The Katritzky group reported a general route for preparation of acyl azides **237** by the reaction of *N*-acylbenzotriazoles with sodium azide in acetonitrile solvent at room temperature (Scheme 77).[3i] The beauty and advantage of this developed protocol is that along with good yields, it avoids the use of acid activators and NO^+ equivalents typically employed to synthesize these compounds from acid chlorides and hydrazides, respectively. Also, there is least chance of isomerization of α,β-unsaturated derivatives, side reactions such as Curtius rearrangements and racemization of the chiral center in case of amino acid derivatives.



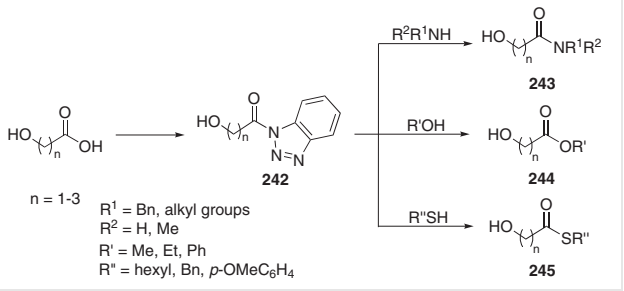
Scheme 77 Synthesis of acyl azides from *N*-acylbenzotriazoles

The Katritzky group utilized the fascinating chemistry of *N*-acylbenzotriazoles for the preparation of amidines from the condensation reaction of readily available mono- and diisocyanates and *N*-acylbenzotriazoles (Scheme 78).[110] The one-pot reaction was performed at 200 °C in a sealed tube under neat conditions for 24 h to afford various aryl **238a–d**, heteroaryl **238e**, bulky aliphatic **238f**, and difunctionalized 1-imidoylbenzotriazoles **239** in 71–99% yields. This protocol was also efficiently utilized for the direct synthesis of (arylamino)heterocycles, such as 4-(arylamino)quinoline **241** from quinolin-4(1*H*)-one (**240**), in 71–96% yields



Scheme 78 Preparation of amidines from isocyanates and *N*-acylbenzotriazoles

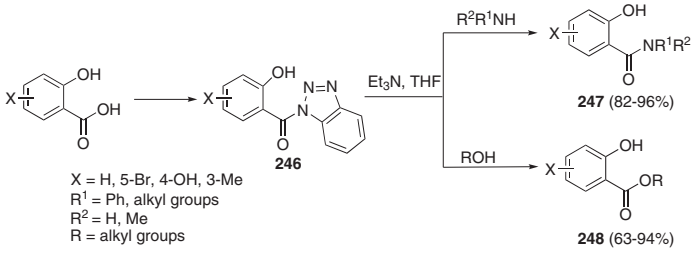
In their next effort, the Katritzky group presented a facile and economically viable route for the high-yielding synthesis of aliphatic hydroxy carboxamides 243, hydroxy esters 244, and hydroxy thiolesters 245 from aliphatic hydroxy-substituted *N*-acylbenzotriazole intermediates 242 on treatment with amines, alcohols, and thiols, respectively (Scheme 79), along with the synthesis of aromatic hydroxy carboxamides 247 and aromatic hydroxy esters 248 from *N*-(*o*-hydroxybenzoyl)benzotriazoles 246 and amines or alcohols, respectively (Scheme 80). The hydroxy *N*-acylbenzotriazole intermediates were obtained by the activation of hydroxy carboxylic acids without prior protection of the hydroxy substituent.[111]



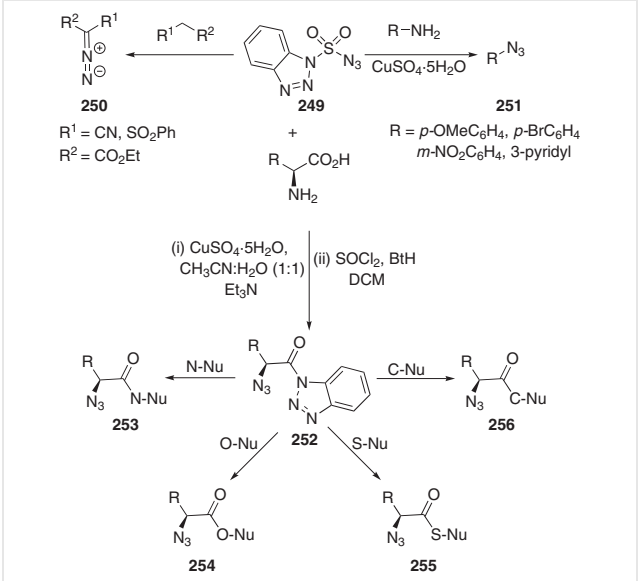
Scheme 79 Benzotriazole-mediated synthesis of aliphatic hydroxy carboxamides and aromatic hydroxy esters from hydroxy-substituted carboxylic acids

Furthermore, the Katritzky group synthesized novel benzotriazol-1-ylsulfonyl azide **249**, a crystalline, stable, and easily available compound, and reacted it with active methylene compounds and amines to give a broad range of diazo compounds **250** and azides **251**, respectively, in good yields (Scheme 81).[112] They also utilized sulfonyl azide **249** as an efficient diazo transfer reagent for the convenient preparation of *N*-(α-azidoacyl)benzotriazoles **252** which are very suitable candidates for *N*-, *O*-, *S*-, and *C*-acylation reactions and afforded various amides **253**, esters **254**, thiolesters **255**, and ketones **256**, respectively

The Katritzky group also proposed a plausible mechanistic pathway for formation of diazo compound **250** from an active methylene compounds. The reaction proceeds through a diazo transfer reaction in which the first step is the nucleophilic attack of the generated enolate intermediate **A** onto the benzotriazol-1-ylsulfonyl azide **249** followed by proton transfer to furnish intermediate **B**. Further, intermediate **B** is converted into intermediate **C** in the presence of base, which undergoes an elimination reaction to afford the desired diazo compound **250** (Scheme 82).



Scheme 80 Benzotriazole-mediated synthesis of *o*-hydroxybenzamides and -benzoates from *o*-hydroxybenzoic acids

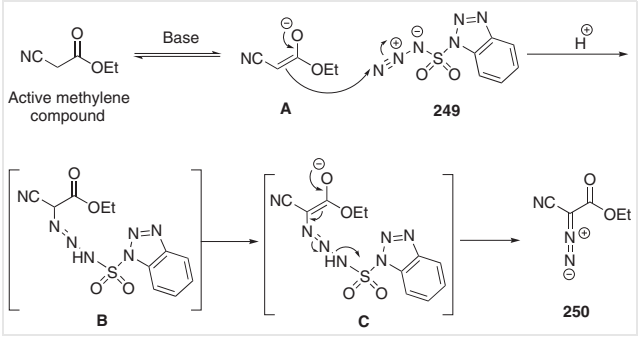


Scheme 81 Synthesis of *N*-(α-azidoacyl)benzotriazoles and their application towards *N*-, *O*-, *C*-, and *S*-acylation reactions

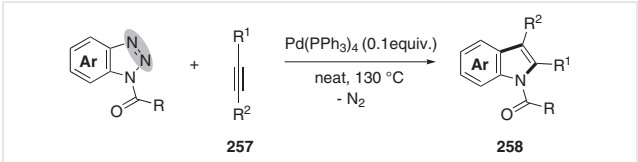
3.5 Benzotriazole Ring Cleavage (BtRC) Reactions

Natural products and pharmaceuticals both frequently contain fused heterocycles that contain nitrogen.[113–115] Because of their significant biological and physiological activities, considerable effort has been put into developing new synthetic methods for their preparation. It has been determined that the most helpful transformations among these are cyclization and cycloaddition reactions.[116] Nowadays, benzotriazole ring cleavage (BtRC) reaction have become an indispensable tool for the synthesis of various types of heterocyclic and amides derivatives.[117]

In 2009, Nakamura and co-workers reported a benzotriazole ring cleavage methodology for the synthesis of biologically relevant indole derivatives **258** (Scheme 83).[117a] The developed strategy included a denitrogenative cycloaddition reaction of *N*-aroylbenzotriazoles and alkynes **257** in the presence of a Pd catalyst. This methodology does not work with terminal alkynes but despite this it is of great utility in organic synthesis due to its tolerance of a wide variety of benzotriazoles. Also, this reaction displays some excellent features like satisfactory yields, simple purification of indole derivatives, and a solvent- and base-free experimental procedure. It also exhibits good regioselectivity for the asymmetric alkynes by placing the bulkier substituent of asymmetric alkynes at C-2 of the indole ring. This work showed that benzotriazoles could be utilized as the synthetic equivalents of *ortho*-aminoarenediazoniums or 2-haloanilides in metal-catalyzed coupling reactions.[117a]

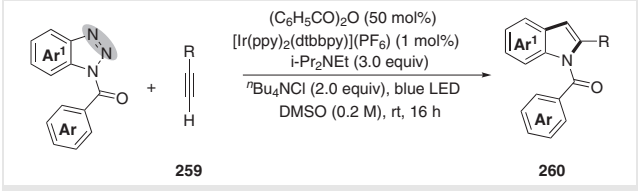


Scheme 82 Mechanism for the formation of diazo compounds from active methylene compounds by a diazo transfer reaction

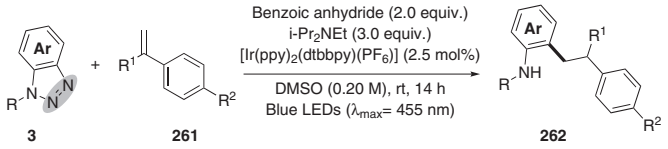


Scheme 83 Pd-catalyzed synthesis of biologically relevant indole derivatives from *N*-aroylbenzotriazoles and alkynes

The Glorius group also synthesized 2-aryl-substituted indole derivatives **260** by the reaction of *N*-aroylbenzotriazoles with terminal alkynes **259** in the presence of an Ir catalyst under blue light irradiation (Scheme 84).[117b] This method also exhibits good-to-excellent regioselectivity for the synthesis of 2-substituted indoles, as well as excellent functional group tolerance and a wide substrate range. Various *p*-substituted arylacetylenes were utilized and gave the corresponding products in 48–92% yields. In contrast to Nakamura's methodology[117a] this reaction is incompatible with internal alkynes and no products were formed. They also investigated the effects of substitution on the benzotriazole ring on the reaction using 5-methyl- or 5-chloro-substituted *N*-aroylbenzotriazoles and obtained 2-arylated indoles in 52% and 85% yield, respectively. The deprotected indoles could be obtained from substrates containing strong electron-withdrawing groups, such as 4-(trifluoromethyl)benzoyl-substituted benzotriazoles, which delivers a significant route for the synthesis of 2-aryl-substituted indoles without the extra deprotection steps. Stern–Volmer studies and reaction quantum yield determination confirm the proposed photoinduced radical chain pathway.



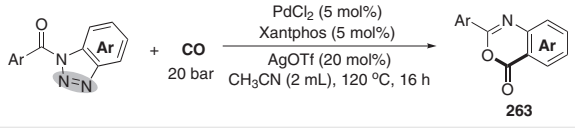
Scheme 84 Ir-catalyzed synthesis of 2-aryl-substituted indole derivatives from *N*-aroylbenzotriazoles and alkynes under blue light irradiation



Scheme 85 Blue LED induced Ir-catalyzed denitrogenative alkylation of benzotriazoles with styrene derivatives

A similar but modified approach came from the Glorius group for the efficient preparation of *ortho*-alkylated *N*-arylbenzamides **262** (R = aroyl) (Scheme 85).[118] They used styrenes **261**, in place of terminal alkynes, and employed Ir as the catalyst in the presence of blue LEDs. The reaction proceeds through the denitrogenative alkylation of benzotriazoles and displays compatibility with various substitutions on benzotriazoles and gives moderate-to-good yields in the case of both electron-withdrawing and electron-donating group bearing styrenes. Since aliphatic alkenes are poor radical acceptors in comparison to styrenes, therefore, they do not undergo this reaction, which is the only limitation of this developed protocol.

A novel protocol for the synthesis of 3,1-benzoxazinones **263** was devised by Wu and co-workers in 2017 (Scheme 86).[117f] The target molecules were synthesized by carbonylative activation of *N*-acylbenzotriazoles under silver and palladium bimetallic catalysis. This reaction methodology is very beneficial in constructing a series of biologically important 3,1-benzoxazinones **263** in satisfactory yields and also performs well with various substituted benzotriazoles.

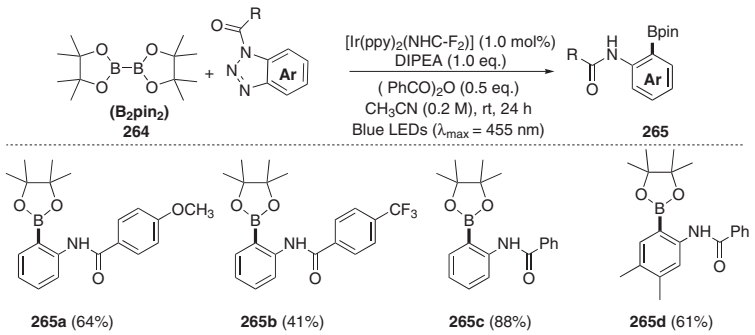


Scheme 86 Synthesis of 3,1-benzoxazinones through Pd-catalyzed carbonylative cyclization of benzotriazoles with carbon monoxide

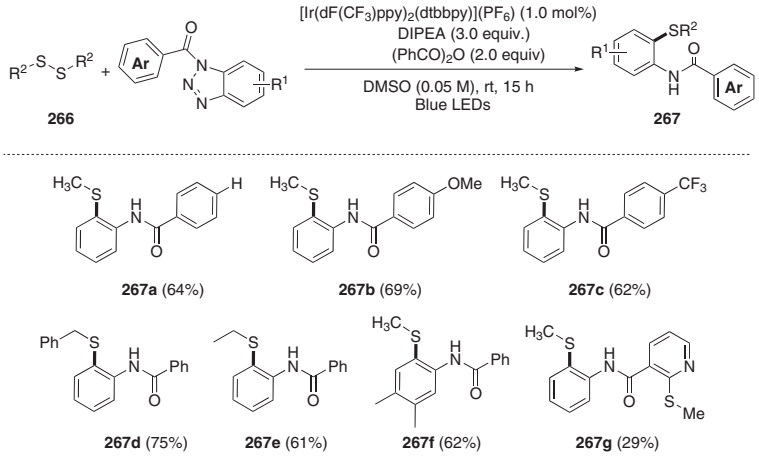
In organic synthesis, one of the transformations of enormous importance is the construction of carbon–heteroatom bonds. Therefore, many scientific groups across the world have developed and reported methods for the construction of carbon–heteroatom bonds, in which one of the important conventional methods is the transition-metal-catalyzed cross coupling reaction.[119] Various developments have been made in this field, one of which is the radical oxidative coupling strategy for carbon–heteroatom bond formation. This field of work has gained tremendous attraction in recent years and has become a hot spot in the field of carbon–heteroatom bond construction.[120]

By using a denitrogenative process, the Glorius group reported a novel visible-light-promoted borylation and thiolation of benzotriazoles using B_2pin_2 **264** and alkyl disulfides **266**, respectively, to produce *ortho*-functionalized *N*-arylbenzamide derivatives **265** (Scheme 87) and **267** (Scheme 88).[118] On either the benzotriazole core or the benzoyl fragment, the reaction could tolerate both electron-donating and electron-deficient substituents. Aryl disulfides were unable to provide the thiolation products, whereas a variety of alkyl disulfides **266** were compatible with this transformation.

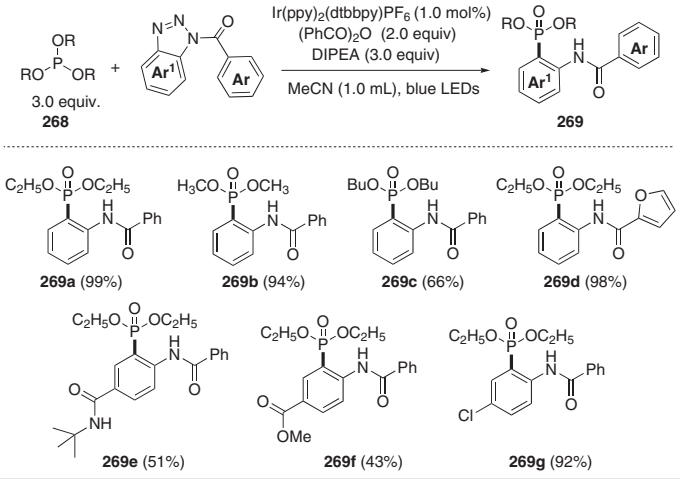
Yang, Xia, and co-workers established the visible-light-induced denitrogenative phosphorylation of *N*-aroylbenzotriazoles with phosphites under mild conditions (Scheme 89).[121] *N*-Aroylbenzotriazoles were treated with 3.0 equiv of phosphite **268**, Ir photocatalyst, and 15-W LEDs as light source to give a series of *ortho*-phosphorylated *N*-arylbenzamide derivatives **269** in up to 99% yield. Furthermore, this reaction demonstrated perfect functional group tolerance. Several trialkyl phosphites were suitable for the reaction, and the steric hindrance of the phosphite had a significant effect on product yield; the reaction was unsuccessful with triphenyl phosphite as the phosphorylation agent. Furthermore, a gram-scale reaction under standard conditions fur-



Scheme 87 Synthesis of *ortho*-functionalized *N*-arylbenzamide derivatives *via* visible-light-promoted borylation of benzotriazoles



Scheme 88 Synthesis of *ortho*-functionalized *N*-arylbenzamide derivatives *via* visible-light-promoted thiolation of benzotriazoles with disulfides



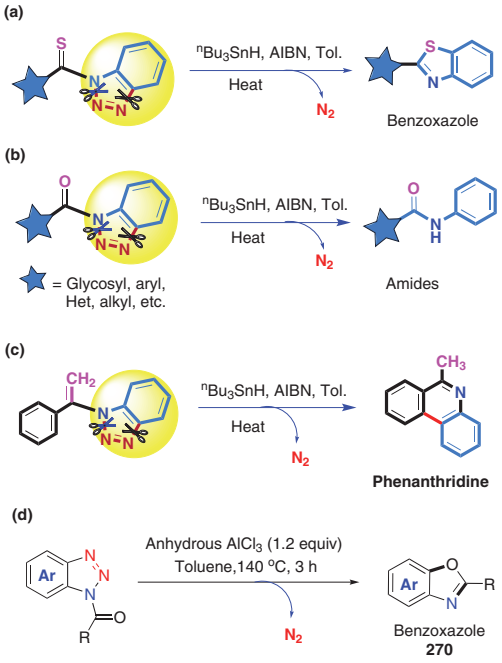
Scheme 89 Visible-light-induced phosphorylation of *N*-acylbenzotriazoles with phosphites

nished good-to-excellent yield of products, demonstrating the synthetic utility of this new protocol.

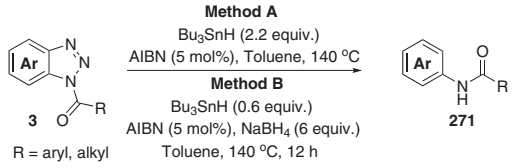
Significant contributions were made by the Tiwari group towards the development of benzotriazole ring cleavage (BtRC) methodology.[117i–o] In their first work, they accomplished the synthesis of benzoxazoles **270** from *N*-acylbenzotriazoles under heating condition in the presence of a Lewis acid using toluene as solvent.; the reaction goes through a denitrogenative ring-opening process followed by cyclization (Scheme 90d).[117m] This protocol has several advantages such as an excellent tolerance to substitution on the aromatic ring, moderate-to-good yields, use of easily available and economical catalyst, and milligram to gram scale conversion. They also investigated this protocol with aliphatic *N*-acylbenzotriazoles and found that the reaction undergoes Friedel–Crafts acylation reaction to furnish an excellent yield of ketones.

The Tiwari group also developed a methodology for synthesis of substituted amides **271** from *N*-aroyl- and *N*-alkanoylbenzotriazoles *via* free radical benzotriazole ring-opening process in the presence of *n*-Bu_3SnH/AIBN.[117o] In addition, the byproduct tin dimer was reduced by using $NaBH_4$ to regenerate the *n*-Bu_3SnH reagent. This reduces the consumption of *n*-Bu_3SnH reagent in this reaction and makes this protocol economic (Scheme 91).

Wang and Zhang reported an interesting methodology for the synthesis of heterocyclic compounds from benzotriazoles without the loss of a nitrogen molecule.[122] The synthesis of the benzimidazole system goes through ring cleavage of benzotriazoles followed by successive ring closure. 1-Acylamido-2-alkyl/aryl-substituted benzimidazoles **272**

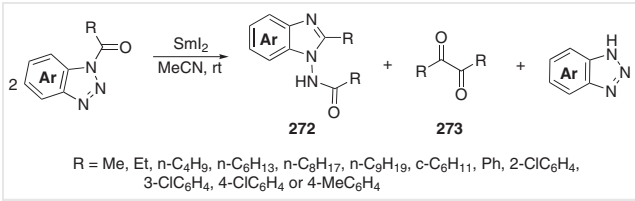


Scheme 90 *N*-Acylbenzotriazoles for the synthesis of diverse biologically relevant molecules including benzothiazoles, benzoxazoles, amides, etc.



Scheme 91 Benzotriazole ring-opening strategy for synthesis of amides using *n*-Bu_3SnH/AIBN combination

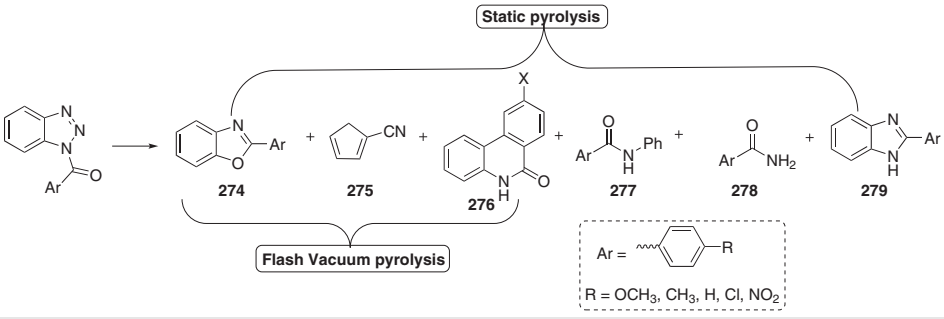
were synthesized by the reduction of 1-acylbenzotriazoles **3** using samarium(II) iodide (2 equiv) in 43% (R = 4-ClC_6H_4) to 82% (R = *c*-C_6H_{11}) yields (Scheme 92). Different results were obtained by varying substitution in substrate and solvents, for instance, in case of R = 4-$MeOC_6H_4$, the diketone **273** was obtained as the sole product in 72% isolated yield whereas in other reactions diketones **273** were isolated as side products. Also, using THF as the solvent in place of acetonitrile gave diketones **273** as the sole product. Therefore, it was concluded that acetonitrile solvent is crucial for exclusive production of 1-acylamido-2-alkyl/aryl-substituted benzimidazoles **222** through reduction of *N*-acylbenzotriazoles with SmI_2. However, there is not any certain clear mechanism regarding the transformation.



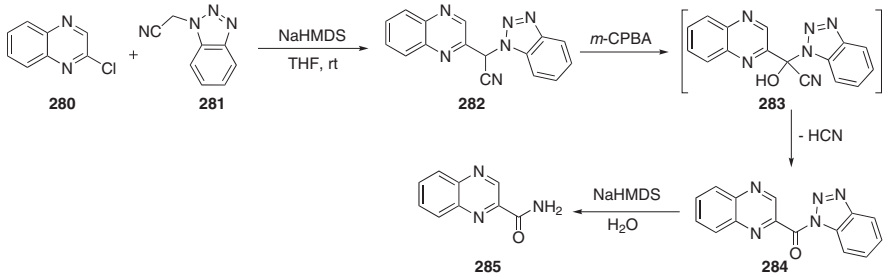
Scheme 92 Samarium(II) iodide induced ring opening of *N*-acylbenzotriazoles

A gas-phase pyrolysis (static pyrolysis) technique was devised by Al-Awadi and co-workers to access benzoxazole **274**, 1-cyanocyclopentadiene **275**, phenanthridin-6(5*H*)-ones **276**, substituted *N*-phenylbenzamide **277**, benzamide **278**, and benzimidazole **279** from 1-aroylbenzotriazoles at 300–340 °C temperature and 6 × 10^{-2} mbar pressure (Scheme 93).[123] They also investigated a different pyrolysis technique and found that when pyrolysis of 1-aroylbenzotriazole was carried out by flash vacuum pyrolysis at 600 °C and 0.2 Torr, only the benzoxazole, 1-cyanocyclopentadiene, and phenanthridin-6(5*H*)-one were obtained. The group also carried out kinetic and mechanistic studies and revealed that biradical or carbene reactive intermediates were involved in the reaction pathway of gas-phase pyrolysis of benzotriazole in the reaction course.

The synthesis of N-containing heteroaryl amides can be achieved by utilizing azole-*N*-acetonitrile derivatives as substrates through a strategy where they act as synthons for an ambident carbonyl moiety and the course of reaction involves sequential base-mediated S_NAr substitution of a 2-haloheterocycle, *in situ* oxidation, and amine displacement. N-Containing heteroaryl amides can be synthesized efficiently from the corresponding halides in a prompt one-pot



Scheme 93 Gas-phase pyrolysis of 1-aroylbenzotriazoles at 340 °C and 6 × 10^{-2} mbar



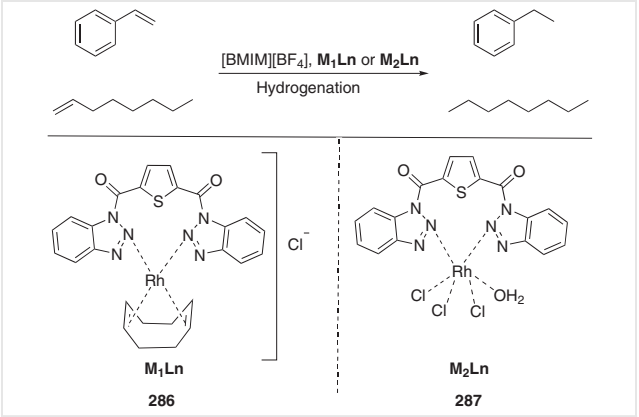
Scheme 94 One-pot synthesis of heteroaryl amide

fashion by utilizing this approach. A similar protocol was developed by Wang and co-workers who accomplished the synthesis of N-containing heteroaryl amides through the reaction of 2-chloroquinoxaline (**280**) and benzotriazol-1-ylacetonitrile (**281**) in the presence of sodium hexamethyldisilazanide (NaHMDS) at room temperature (Scheme 94).[124] The reaction proceeded through the intermediate nitrile derivative **282** which was further transformed into amide **285** (66% yield) on treatment with *m*-CPBA. The desired product **285** is proposed to be formed from **282** through a sequence of steps in which a cyanohydrin **283** is first generated from **282** and this undergoes elimination of HCN to afford 1-acylbenzotriazole **284** that reacts with NaHMDS followed by hydrolysis during workup to furnish amide **285**.

4 *N*-Acylbenzotriazoles as Catalysts and Ligands

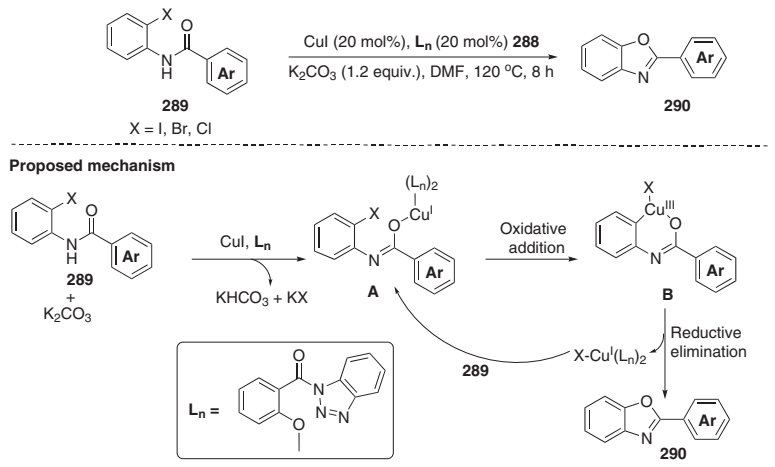
The availability of unique ligation sites on benzotriazole moieties has paved the way for the development of efficient ligands, predominantly for application in coupling reactions.[125] Several ligand-mediated approaches were reported for the synthesis of heterocycles *via* coupling reactions.[126]

In 2016, Unver and Yılmaz reported the application of *N*-acylbenzotriazole-based complexes of Rh(I) **286** and Ru(III) **287** as hydrogenation catalysts in ionic liquid media (Scheme 95).[127] Both complexes were capable of catalyzing the hydrogenation of styrene and oct-1-ene and were fully soluble in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4]. While ethylbenzene conversion in the styrene hydrogenation process reached 84% when the Ru complex **287** was used, under the same conditions (393 K in 6 h) the Rh complex **286** produced 100% conversion. Additionally, using the Rh complex in [bmim][BF_4] media, 100% of the hydrogenation of oct-1-ene was achieved. To compare the impact of the solvent on the catalytic system, the hydrogenation of styrene and oct-1-ene in dimethyl sulfoxide and toluene was also investigated and found to be inferior. The relationship between the conversion and some catalytic parameters, including temperature, H_2 (g) pressure, and catalyst amount was investigated, and it was observed that the conversion increased in tandem with the rising temperature and H_2 pressure. It was found that the Rh complex in particular retained its activity for at least 10 cycles when the recyclability of catalysts was examined.[127]



Scheme 95 Hydrogenation of alkene by benzotriazole-based rhodium complexes

In 2017, the Tiwari group employed *N*-acylbenzotriazoles as efficient ligands for the synthesis of diverse benzoxazoles *via* a copper-catalyzed intramolecular cyclization of *N*-(2-halophenyl)benzamides. Various substituted *N*-acylbenzotriazoles were screened amongst which (1*H*-benzotriazol-1-yl)(2-methoxyphenyl)methanone **288** was found to be satisfactory. After screening, various *N*-(2-halophenyl)benzamides **289** were reacted with CuI (0.2 equiv), ligand **288** (0.2 equiv), and K_2CO_3 (1.2 equiv) in DMF at 120 °C for 8 h to obtain benzoxazoles **290** in up to 93% yield (Scheme 96).[128] The effect on yield with variation of the halo substituent on the *N*-(2-halophenyl)benzamide was also checked and *N*-(2-iodophenyl)benzamide was found a more appropriate substrate in contrast to bromo and chloro derivatives. The proposed reaction pathway is by coordination of the ligand with copper iodide which then is tethered to the amido group of the benzamide to afford intermediate **A** that on subsequent oxidation gives complex **B**, followed by reductive elimination to give benzoxazoles **290**.



Scheme 96 Synthesis of benzoxazole from *N*-(2-halophenyl)benzamides using *N*-acylbenzotriazoles as ligands in a copper-mediated coupling reaction

5 Pharmacological Applications of *N*-Acylbenzotriazoles

N-Acyl/aroylbenzotriazoles have been widely explored as a leaving group in various synthetic approaches. Also, the benzotriazole ring cleavage (BtRC) methodology is well-established protocol that recently used in modern organic synthesis for an easy access of wide range of biologically relevant scaffolds.[1d,129] In addition to the versatile synthetic utilities of *N*-acylbenzotriazoles, this scaffold possesses some notable bioactivities and explored in medicinal chemistry.[130] The structures of some biologically potent *N*-acylbenzotriazoles are depicted in Figure 3. For example, *N*-acyl/aroylbenzotriazoles **291** (IC_{50} = 1.7 nM) and **292** (IC_{50} = 14 nM) with 3,4,5-trimethoxy-substitution exhibited potent activities against oral epidermoid carcinoma KB cells, non-small-cell lung carcinoma H460 cells, and stomach carcinoma MKN45 cells with respect to doxorubicin.[131] Furthermore, compound **291** has moderate HDAC inhibitory activity. It depicts the necessity of more series and molecular library exploration.

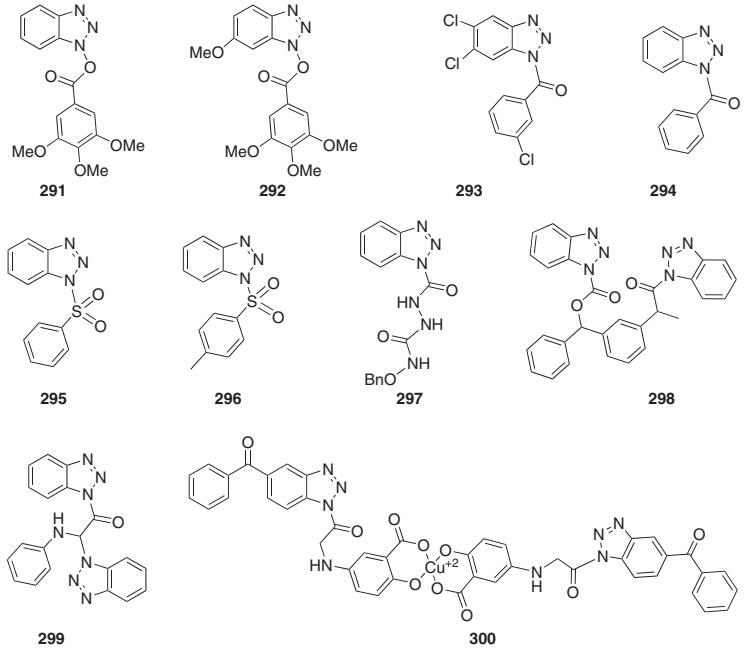


Figure 3 Structure of some biologically active *N*-acylbenzotriazoles

The antidiabetic activity of compound **293** (IC_{50} = 2.99 ± 1.43 mM against α-amylase and IC_{50} = 3.00 ± 1.21 mM against α-glucosidase) was reported by Khan and co-workers.[132] Molecular docking revealed that the aryl ring substitution is the key interactive point in this case and the kinetic studies supported that **293** has competitive inhibitory action against α-amylase and noncompetitive mode of inhibition against α-glucosidase enzyme. The NHE-1 inhibitory *via in vitro* platelet swelling assay of *N*-aroylbenzotriazoles with an oxygen atom in benzoyl **294** (IC_{50} = 51.57 mM) and a sulfonyl group **295** (IC_{50} = 50.89 mM) and **296** (IC_{50} = 49.95 mM) was reported by Singh and Silakari.[133]

In a free radical scavenging study, *N*-acylbenzotriazole analogue **297** exhibited appreciable DPPH (2,2-diphenyl-1-picrylhydrazyl) interaction value (85%) comparable to the reference nordihydroguaiaretic acid (91%). Besides, **297** has lipid peroxidation (LP) inhibition of 31%, which further encourages its efficiency as an antioxidant scaffold.[134] Bis-*N*-aroylbenzotriazole **298** displayed notable analgesic and antipyretic activities with minimal side effects, prolonged plasma half-life, increased solubility, and antioxidative potentiality than ketoprofen, a commercial non-steroidal anti-inflammatory drug (NSAID). This exhibited interaction with DPPH in iron-free system as well as its reducing activity. Besides, it has significantly higher LP inhibition (98%) with respect to parent motif (69.3%) with remarkable soybean LOX activity of 95%.[135] Tasneem *et al.* reported the antitubercular activity of compound **299** (minimal inhibitory concentration, MIC = 4.5 μg/mL against *M. tuberculosis* compared to first line drugs, streptomycin (MIC = 7.5 μg/mL) and pyrazinamide (MIC = 10 μg/mL).[136]

Interestingly, Cu(II) coordinated *N*-aroylbenzotriazole complex **300** displayed potent antibacterial activity.[137] This complex exhibited moderate inhibitions against both Gram-positive (*B. subtills* and *S. aureus*) and Gram-negative (*E. coli* and *S. typhi*) bacteria. However, in lieu of dependable stability, variation in structural coordination of the complex may vary in the final pharmacological application and cell inhibitory activity.

N-Acyl/aroylbenzotriazoles have exerted great potentiality as versatile pharmacophore including excellent antibacterial, antifungal properties, along with the efficacy as antioxidant agents. Hopefully, these inspiring outcomes will help to investigate more molecular library genesis as *N*-acyl/aroylbenzotriazole agents against other diseases along with opening up new prospects for the motif.

6 Conclusions and Future Outlook

In this review, we highlighted the various synthetic methodologies for efficient preparation of *N*-acylbenzotriazoles which have developed over time. The diverse applications of *N*-acylbenzotriazoles as *N*-, *O*-, *C*-, and *S*- acylating agents for the convenient synthesis of a range of important organic compounds and synthesis of diverse compounds has also been incorporated by using benzotriazole ring cleavage (BtRC) methodology in this review. The review also emphasized the role of *N*-acylbenzotriazoles as a ligand in various transformations and illuminated on the medicinal importance of the *N*-acylbenzotriazolyl scaffold by including the pharmacological applications of various medicinally active compounds containing the benzotriazolyl framework. For future perspective, theses inspiring outcomes will help to explore the role of *N*-acylbenzotriazoles in organic synthesis as well as for therapeutic resolutions.

Conflict of Interest

The authors declare no conflict of interest.

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References

(1) (a) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409. (b) Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564. (c) Kale, R. R.; Prasad, V.; Mohapatra, P. P.; Tiwari, V. K. *Monatsh. Chem.* **2010**, *141*, 1159. (d) Yu, J.; Singh, A. S.; Yan, G.; Yu, J.; Tiwari, V. K. *Synthesis* **2020**, *52*, 3781.

(2) Katritzky, A. R.; Belyakov, S. A. *Aldrichimica Acta* **1998**, *31*, 35.

(3) (a) Katritzky, A. R.; Rogovoy, B. V.; Kirichenko, N.; Vvedensky, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1809. (b) Katritzky, A. R.; Suzuki, K.; Singh, S. K.; He, H.-Y. *J. Org. Chem.* **2003**, *68*, 5720. (c) Wang, X.; Zhang, Y. *Synth. Commun.* **2003**, *33*, 2627. (d) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 4932. (e) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. *J. Org. Chem.* **2003**, *68*, 1443. (f) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *Synthesis* **2004**, 1806. (g) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Gromova, A. V.; Witek, R.; Steel, P. J. *J. Org. Chem.* **2005**, *70*, 9211. (h) Katritzky, A. R.; Suzuki, K.; Wang, Z. *Synlett* **2005**, 1656. (i) Katritzky, A. R.; Widyan, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 5802. (j) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139. (k) Wang, X.; Wang, W.; Wen, Y.; He, L.; Zhu, X. *Synthesis* **2008**, 3223. (l) Zhou, G.; Lim, D.; Fang, F.; Coltart, D. M. *Synthesis* **2009**, 3350. (m) Li, J.; Sun, Y.; Chen, Z.; Su, W. *Synth. Commun.* **2010**, *40*, 3669. (n) Katritzky, A. R.; Tala, S. R.; Abo-Dya, N. E.; Gyanda, K.; El-Gendy, B. E.-D. M.; Abdel-Samii, Z. K.; Steel, P. J. *J. Org. Chem.* **2009**, *74*, 7165. (o) Xia, Z.; Lv, X.; Wang, W.; Wang, X. *Tetrahedron Lett.* **2011**, *52*, 4906.

(4) Gaylord, N. G. *J. Am. Chem. Soc.* **1954**, *76*, 285.

(5) Gasparini, J. P.; Gassend, R.; Maire, J. C.; Elguero, J. *J. Organomet. Chem.* **1980**, *188*, 141.

(6) Katritzky, A. R.; Shobana, N.; Pernak, J.; Afridi, A. S.; Fan, W.-Q. *Tetrahedron* **1992**, *48*, 7817.

(7) Katritzky, A. R.; Wang, M.; Yang, H.; Zhang, S.; Akhmedov, N. G. *ARKIVOC* **2002**, *(viii)*, 134.
(8) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795.
(9) (a) Duangkamol, C.; Wangngae, S.; Pattarawarapan, M.; Phakhodee, W. *Eur. J. Org. Chem.* **2014**, 7109. (b) Singh, M.; Agrahari, A. K.; Mishra, N.; Singh, A. S.; Tiwari, V. K. *Ind. J. Heterocycl. Chem.* **2018**, *28*, 125.
(10) Sirawit, W.; Duangkamol, C.; Pattarawarapan, M.; Phakhodee, W. *Monatsh. Chem.* **2015**, *146*, 959.
(11) Wet-osot, S.; Phakhodee, W.; Pattarawarapan, M. *Tetrahedron Lett.* **2015**, *56*, 6998.
(12) Agha, K. A.; Abo-Dya, N. E.; Ibrahim, T. S.; Abdel-Aal, E. H. *ARKIVOC* **2016**, *(iii)*, 161.
(13) Kale, R. R.; Prasad, V.; Tiwari, V. K. *Lett. Org. Chem.* **2010**, *7*, 136.
(14) Singh, A. S.; Agrahari, A. K.; Singh, M.; Mishra, N.; Tiwari, V. K. *ARKIVOC* **2017**, *(v)*, 80.
(15) Singh, A. S.; Agrahari, A. K.; Mishra, N.; Singh, M.; Tiwari, V. K. *Synthesis* **2019**, *51*, 470.
(16) Singh, M.; Singh, A. S.; Mishra, N.; Agrahari, A. K.; Tiwari, V. K. *Synthesis* **2019**, *51*, 2183.
(17) Yadav, M. S.; Jaiswal, M. K.; Kumar, S.; Tiwari, V. K. *SynOpen* **2021**, *5*, 301.
(18) Laconde, G.; Amblard, M.; Martinez, J. *Tetrahedron Lett.* **2019**, *60*, 341.
(19) Wang, L.; Chen, Z.-C. *Synth. Commun.* **2001**, *31*, 1633.
(20) Katritzky, A. R.; Vakulenko, A. V.; Jain, R. *ARKIVOC* **2003**, *(xiv)*, 131.
(21) Fischer, E.; Otto, E. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2106.
(22) Carpino, L. A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611.
(23) Katritzky, A. R.; Khelashvili, L.; Mohapatra, P. P.; Steel, P. J. *Synthesis* **2007**, 3673.
(24) Katritzky, A. R.; He, H.-Y.; Suzuki, K. *J. Org. Chem.* **2000**, *65*, 8210.
(25) (a) Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 965. (b) Furusawa, M.; Hashimoto, T.; Noma, Y.; Asakawa, Y. *Chem. Pharm. Bull.* **2006**, *54*, 996.
(26) Barreiros, M. L.; David, J. M.; David, J. P. *Quim. Nova* **2005**, *28*, 1061.
(27) Katritzky, A. R.; Mohapatra, P. P.; Fedoseyenko, D.; Duncton, M.; Steel, P. J. *J. Org. Chem.* **2007**, *72*, 4268.
(28) Katritzky, A. R.; Pleynet, D. P. M.; Yang, B. *J. Org. Chem.* **1997**, *62*, 4155.
(29) Katritzky, A. R.; Kirichenko, N.; Rogovoy, B. V. *ARKIVOC* **2003**, *(viii)*, 8.
(30) Katritzky, A. R.; Cai, C.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375.
(31) Katritzky, A. R.; El-Gendy, B. E. M.; Todadze, E.; Abdel-Fattah, A. A. A. *J. Org. Chem.* **2008**, *73*, 5442.
(32) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Synthesis* **2004**, 2645.
(33) Katritzky, A. R.; Angrish, P.; Hür, D.; Suzuki, K. *Synthesis* **2005**, 397.
(34) Katritzky, A. R.; Yang, H.; Zhang, S.; Wang, M. *ARKIVOC* **2002**, *(xi)*, 39.
(35) Katritzky, A. R.; Kirichenko, N.; Rogovoy, B. V. *Synthesis* **2003**, 2777.
(36) Katritzky, A. R.; Hoffmann, S.; Suzuki, K. *ARKIVOC* **2004**, *(xii)*, 14.
(37) Vertesaljai, P.; Biswas, S.; Lebedyeva, I.; Broggi, E.; Asiri, A. M.; Katritzky, A. R. *J. Org. Chem.* **2014**, *79*, 2688.
(38) Katritzky, A. R.; Narindoshvili, T.; Draghici, B.; Angrish, P. *J. Org. Chem.* **2008**, *73*, 511.
(39) Katritzky, A. R.; Sakhuja, R.; Khelashvili, L.; Shanab, K. *J. Org. Chem.* **2009**, *74*, 3062.
(40) Wet-osot, S.; Duangkamol, C.; Phakhodee, W.; Pattarawarapan, M. *ACS Comb. Sci.* **2016**, *18*, 279.
(41) Katritzky, A. R.; Munawar, M. A.; Kovacs, J.; Khelashvili, L. *Org. Biomol. Chem.* **2009**, *7*, 2359.
(42) Wang, X.; Zou, X.; Li, J.; Hu, Q. *Synlett* **2005**, 3042; corrigendum: Synlett 2005, 3228.
(43) Wang, X.; Li, Z.; Zhu, X.; Mao, H.; Zou, X.; Kong, L.; Li, X. *Tetrahedron* **2008**, *64*, 6510.
(44) (a) Andersen, K. E.; Jørgensen, A. S.; Bræstrup, C. *Eur. J. Med. Chem.* **1994**, *29*, 393. (b) Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S. *J. Med. Chem.* **1994**, *37*, 2421. (c) Saunders, J.; Cassidy, M.; Freedman, S. B.; Harley, E. A.; Iversen, L. L.; Kneen, C.; Macleod, A. M.; Merchant, K. J.; Snow, R. J.; Baker, R. *J. Med. Chem.* **1990**, *33*, 1128. (d) Jochims, J. C. In *Comprehensive Heterocyclic Chemistry II, Vol. 4*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Ed.; Pergamon: Oxford, **1996**, 179.
(45) Katritzky, A. R.; Shestopalov, A. A.; Suzuki, K. *ARKIVOC* **2005**, *(vii)*, 36.
(46) Katritzky, A. R.; Cai, C.; Suzuki, K.; Singh, S. K. *J. Org. Chem.* **2004**, *69*, 811.
(47) Wet-osot, S.; Phakhodee, W.; Pattarawarapan, M. *J. Org. Chem.* **2017**, *82*, 9923.
(48) (a) Ballard, C. E.; Yu, H.; Wang, B. *Curr. Med. Chem.* **2002**, *9*, 471. (b) Sarabia, F.; Chammaa, S.; Ruiz, A. S.; Ortiz, L. M.; Herrera, F. J. L. *Curr. Med. Chem.* **2004**, *11*, 1309.
(49) Avan, I.; Tala, S. R.; Steel, P. J.; Katritzky, A. R. *J. Org. Chem.* **2011**, *76*, 4884.
(50) Katritzky, A. R.; Angrish, P.; Narindoshvili, T. *Bioconjugate Chem.* **2007**, *18*, 994.
(51) Katritzky, A. R.; Cusido, J.; Narindoshvili, T. *Bioconjugate Chem.* **2008**, *19*, 1471.
(52) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. *Liebigs Ann.* **1996**, 881.
(53) Katritzky, A. R.; Yang, B.; Qian, Y. *Synlett* **1996**, 701.
(54) Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem.* **2006**, *71*, 9861.
(55) Katritzky, A. R.; Suzuki, K.; Singh, S. K. *Croat. Chem. Acta* **2004**, *77*, 175.
(56) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II, Vol. 2*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Ed.; Pergamon: Oxford, **1996**, 207.
(57) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Akhmedova, R. G. *ARKIVOC* **2005**, *(vi)*, 329.
(58) Katritzky, A. R.; Bajaj, K.; Charpentier, M.; Zadeh, E. G. *J. Org. Chem.* **2010**, *75*, 3938.
(59) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514.
(60) Caine, D. In *Carbon-Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, **1979**, 250–258.
(61) Black, T. H. *Org. Prep. Proced. Int.* **1989**, *21*, 179.
(62) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, *18*, 1187.
(63) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
(64) Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249.
(65) Sucrow, W.; Brockmann, R. *Liebigs Ann. Chem.* **1982**, 1891.
(66) Stiles, M. *J. Am. Chem. Soc.* **1959**, *81*, 2598.
(67) Katritzky, A. R.; Pastor, A. *J. Org. Chem.* **2000**, *65*, 3679.
(68) Marco, J. L. *J. Org. Chem.* **1997**, *62*, 6575.
(69) Wolf, W. M. *J. Mol. Struct.* **1999**, *474*, 113.
(70) Gotor, V.; Rebolledo, F.; Liz, R. *Tetrahedron: Asymmetry* **2001**, *12*, 513.
(71) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854.

(72) (a) Rowinsky, E. K.; Donehower, R. C. *Pharmacol. Ther.* **1991**, *52*, 35. (b) Namikoshi, M.; Rinehart, K. L.; Dahlem, A. M.; Beasley, V. R.; Carmichael, W. W. *Tetrahedron Lett.* **1989**, *30*, 4349. (c) Haddad, M.; Botuha, C.; Larcheveque, M. *Synlett* **1999**, 1118.
(73) Katritzky, A. R.; Tao, H.; Jiang, R.; Suzuki, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 407.
(74) Katritzky, A. R.; Fang, Y.; Donkor, A.; Xu, J. *Synthesis* **2000**, 2029.
(75) Murphy, W. S.; Bertrand, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4115.
(76) Trautwein, A. W.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 8263.
(77) Maeba, I.; Ito, Y.; Wakimura, M.; Ito, C. *Heterocycles* **1993**, *36*, 1617.
(78) Kirschbaum, S.; Waldman, H. *J. Org. Chem.* **1998**, *63*, 4936.
(79) Nishimura, N.; Koyano, Y.; Sugiura, M.; Maeba, I. *Heterocycles* **1999**, *51*, 803.
(80) Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617.
(81) Frank, R. L.; Phillips, R. R. *J. Am. Chem. Soc.* **1949**, *71*, 2804.
(82) Baruah, B.; Boruah, A.; Prajaparti, D.; Sandhu, J. S. *Tetrahedron Lett.* **1997**, *38*, 7603.
(83) Wang, X.; Zhang, Y. *Tetrahedron Lett.* **2002**, *43*, 5431.
(84) Katritzky, A. R.; Soleiman, M.; Yang, B. *Heteroat. Chem.* **1996**, *7*, 365.
(85) Katritzky, A. R.; Denisko, O. V. *J. Org. Chem.* **2002**, *67*, 3104.
(86) Zhou, G.; Lim, D.; Coltart, D. M. *Org. Lett.* **2008**, *10*, 3809.
(87) Furuta, T.; Nakayama, M.; Suzuki, H.; Tajimi, H.; Inai, M.; Nukaya, H.; Wakimoto, T.; Kan, T. *Org. Lett.* **2009**, *11*, 2233.
(88) Brookfield, F.; Eustache, F.; Dillon, M. P.; Goldstein, D. M.; Gong, L.; Han, X.; Hogg, J. H.; Park, J.; Reuter, D. C.; Sjogren, E. B. US2009270389, **2009**.
(89) (a) Sheehan, J. C.; Daves, G. D. Jr. *J. Org. Chem.* **1965**, *30*, 3247. (b) Ohtsuka, Y. *J. Org. Chem.* **1978**, *43*, 3231.
(90) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925.
(91) Katritzky, A. R.; Huang, T. B.; Voronkov, M. V.; Steel, P. J. *J. Org. Chem.* **2000**, *65*, 8069.
(92) Chu, M.; Truumees, I.; Mierzwa, R.; Terracciano, J.; Patel, M.; Das, P. R.; Puar, M. S.; Chan, T. M. *Tetrahedron Lett.* **1998**, *39*, 7649.
(93) Walker, E. R.; Leung, S. Y.; Barrett, A. G. M. *Tetrahedron Lett.* **2005**, *46*, 6537.
(94) Katritzky, A. R.; Vincek, A. S.; Steel, P. J. *Heterocycles* **2008**, *76*, 1401.
(95) Katritzky, A. R.; Singh, S. K.; Akhmedova, R.; Cai, C.; Bobrov, S. *ARKIVOC* **2007**, *(vi)*, 6.
(96) Smith, R. L.; Barette, R. J.; Sanders-Bush, E. *J. Pharmacol. Exp. Ther.* **1995**, *275*, 1050.
(97) Awouters, F.; Vermeire, J.; Smeyers, F.; Vermote, P.; Van Beek, R.; Niemegeers, C. J. E. *Drug Dev. Res.* **1986**, *8*, 95.
(98) Matsutani, S.; Mizushima, Y. EP0329126 A1, **1989**
(99) Yanagihara, Y.; Kasai, H.; Kawashima, T.; Shida, T. *Jpn. J. Pharamacol.* **1988**, *48*, 91.
(100) Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair, S. K. *ARKIVOC* **2004**, *(viii)*, 52.
(101) Katritzky, A. R.; Meher, N. K.; Singh, S. K. *J. Org. Chem.* **2005**, *70*, 7792.
(102) Katritzky, A. R.; Angrish, P.; Todadze, E.; Ghiviriga, I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6000.
(103) (a) Rajic, Z.; Zorc, B.; Raic-Malic, S.; Ester, K.; Kralj, M.; Pavelic, K.; Balzarini, J.; De Clercq, E.; Mintas, M. *Molecules* **2006**, *11*, 837. (b) Opacic, N.; Barbaric, M.; Zorc, B.; Cetina, M.; Nagl, A.; Frkovic, D.; Kralj, M.; Pavelic, K.; Balzarini, J.; Andrei, G.; Snoeck, R.; De Clercq, E.; Raic-Malic, S.; Mintas, M. *J. Med. Chem.* **2005**, *48*, 475.
(104) (a) Katritzky, A. R.; Fali, C. N.; Li, J.; Ager, D. J.; Prakash, I. *Synth. Commun.* **1997**, *27*, 1623. (b) Butula, I.; Jadrijevic-Mladar Takac, M. *Croat. Chem. Acta* **2000**, *73*, 569. (c) Kalcic, I.; Zovko, M.; Jadrijevic-Mladar Takac, M.; Zorc, B.; Butula, I. *Croat. Chem. Acta* **2003**, *76*, 217.
(105) Katritzky, A. R.; Zhang, Y.; Singh, S. K.; Steel, P. J. *ARKIVOC* **2003**, *(xv)*, 47.
(106) Katritzky, A. R.; Singh, S. K.; Bobrov, S. *J. Org. Chem.* **2004**, *69*, 9313.
(107) Singh, A. S.; Kumar, D.; Mishra, N.; Tiwari, V. K. *RSC Adv.* **2016**, *6*, 84512.
(108) Singh, A. S.; Agrahari, A. K.; Singh, S. K.; Yadav, M. S.; Tiwari, V. K. *Synthesis* **2019**, *51*, 3443.
(109) Yadav, M. S.; Singh, S. K.; Agrahari, A. K.; Singh, A. S.; Tiwari, V. K. *Synthesis* **2021**, *53*, 2494.
(110) Katritzky, A. R.; Huang, T.-B.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 1043.
(111) Katritzky, A. R.; Singh, S. K.; Cai, C.; Bobrov, S. *J. Org. Chem.* **2006**, *71*, 3364.
(112) Katritzky, A. R.; Khatib, M. E.; Shakov, O. B.; Khelashvili, L.; Steel, P. J. *J. Org. Chem.* **2010**, *75*, 6532.
(113) Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2125.
(114) Saracoglu, N. *Top. Heterocycl. Chem.* **2007**, *11*, 145.
(115) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (b) Pennington, L. D.; Moustakas, D. T. *J. Med. Chem.* **2017**, *60*, 3552. (c) Jarhad, D. B.; Mashelkar, K. K.; Kim, H.-R.; Noh, M.; Jeong, L. S. *J. Med. Chem.* **2018**, *61*, 9791.
(116) (a) Wang, S.; Xi, C. *Chem. Soc. Rev.* **2019**, *48*, 382. (b) Bariwal, J.; Voskressensky, L. G.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2018**, *47*, 3831.
(117) (a) Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. *Org. Lett.* **2009**, *11*, 1055. (b) Teders, M.; Pitzer, L.; Buss, S.; Glorius, F. *ACS Catal.* **2017**, *7*, 4053. (c) Wang, Y.; Wang, Z.; Chen, X.; Tang, Y. *Org. Chem. Front.* **2018**, *5*, 2815. (d) Wang, Y. H.; Li, Y. H.; Fan, Y. J.; Wang, Z. G.; Tang, Y. F. *Chem. Commun.* **2017**, *53*, 11873. (e) Zhang, P.-C.; Han, J.; Zhang, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 11444. (f) Yin, Z. P.; Wang, Z. C.; Wu, X. F. *Org. Lett.* **2017**, *19*, 6232. (g) Battula, S.; Kumar, A.; Gupta, A. P.; Ahmed, Q. N. *Org. Lett.* **2015**, *17*, 5562. (h) Su, Y.; Petersen, J. L.; Gregg, T. L.; Shi, X. *Org. Lett.* **2015**, *17*, 1208. (i) Kumar, D.; Mishra, A.; Mishra, B. B.; Bhattacharya, S.; Tiwari, V. K. *J. Org. Chem.* **2013**, *78*, 899. (j) Kumar, D.; Mishra, B. B.; Tiwari, V. K. *J. Org. Chem.* **2014**, *79*, 251. (k) Yadav, M. S.; Singh, A. S.; Agrahari, A. K.; Mishra, N.; Tiwari, V. K. *ACS Omega* **2019**, *4*, 6681. (l) Singh, A. S.; Mishra, N.; Yadav, M. S.; Tiwari, V. K. *J. Heterocycl. Chem.* **2019**, *56*, 275. (m) Singh, A. S.; Mishra, N.; Kumar, D.; Tiwari, V. K. *ACS Omega* **2017**, *2*, 5044. (n) Kumar, D.; Singh, A. S.; Tiwari, V. K. *RSC Adv.* **2015**, *5*, 31584. (o) Singh, A. S.; Kumar, D.; Mishra, N.; Tiwari, V. K. *ChemistrySelect* **2017**, *2*, 224.
(118) Teders, M.; Gómez-Suárez, A.; Pitzer, L.; Hopkinson, M. N.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 902.
(119) (a) Dhakshinamoorthy, A.; Asiri, A. M.; Garcia, H. *Chem. Soc. Rev.* **2015**, *44*, 1922. (b) Zhu, X.; Chiba, S. *Chem. Soc. Rev.* **2016**, *45*, 4504. (c) Fu, J.; Zanoni, G.; Anderson, E. A.; Bi, X. *Chem. Soc. Rev.* **2017**, *46*, 7208. (d) Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, *46*, 5864. (e) Dhakshinamoorthy, A.; Asiri, A. M.; Garcia, H. *ACS Catal.* **2019**, *9*, 1081.
(120) (a) Festa, A. A.; Voskressensky, L. G.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2019**, *48*, 4401. (b) Chu, X.-Q.; Ge, D.; Shen, Z.-L.; Loh, T.-P. *ACS Catal.* **2018**, *8*, 258. (c) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138.
(121) Jian, Y.; Chen, M.; Huang, B.; Jia, W.; Yang, C.; Xia, W. *Org. Lett.* **2018**, *20*, 5370.

(122) Wang, X.; Zhang, Y. *Tetrahedron* **2003**, *59*, 4201.
(123) Al-Awadi, N. A.; George, B. J.; Dib, H. H.; Ibrahim, M. R.; Ibrahim, Y. A.; El-Dusouqui, O. M. E. *Tetrahedron* **2005**, *61*, 8257.
(124) Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *Synlett* **2004**, 2323.
(125) (a) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086. (b) Verma, A. K. *Adv. Heterocycl. Chem.* **2012**, *107*, 101. (c) Agrahari, A. K.; Bose, P.; Singh, A. S.; Rajkhowa, S.; Jaiswal, M. K.; Hotha, S.; Mishra, N.; Tiwari, V. K. *Chem. Rev.* **2021**, *121*, 7638.
(126) (a) Yang, D.; Zhu, X.; Wei, W.; Jiang, M.; Zhang, N.; Ren, D.; You, J.; Wang, H. *Synlett* **2014**, *25*, 729. (b) Ali, M. A.; Suri, M.; Punniyamurthy, T. *Synthesis* **2013**, 501.
(127) Ünver, H.; Yılmaz, F. *Catalysts* **2016**, *6*, 147.
(128) Singh, A. S.; Singh, M.; Mishra, N.; Mishra, S.; Agrahari, A. K.; Tiwari, V. K. *ChemistrySelect* **2017**, *2*, 154.
(129) Tiwari, V. K. *Chem. Rec.* **2021**, *21*, 3029.
(130) Bollikolla, H. B.; Boddapati, S. N. M.; Thangamani, S.; Mutchu, B. R.; Alam, M. M.; Hussien, M.; Jonnalagadda, S. B. *J. Heterocycl. Chem.* **2023**, *60*, 705.
(131) Fu, J.; Yang, Y.; Zhang, X. W.; Mao, W. J.; Zhang, Z. M.; Zhu, H. L. *Bioorg. Med. Chem.* **2010**, *18*, 8457.
(132) Hameed, S.; Kanwal; Seraj, F.; Rafique, R.; Chigurupati, S.; Wadood, A.; Rehman, A. U.; Venugopal, V.; Salar, U.; Taha, M.; Khan, K. M. *Eur. J. Med. Chem.* **2019**, *183*, 111677.
(133) Singh, D.; Silakari, O. *Eur. J. Med. Chem.* **2017**, *126*, 183.
(134) Perkovic, I.; Butula, I.; Kralj, M.; Martin-Kleiner, I.; Balzarini, J. *Eur. J. Med. Chem.* **2012**, *51*, 227.
(135) Rajic, Z.; Hadjipavlou-Litina, D.; Pontiki, E.; Balzarini, J.; Zorc, B. *Med. Chem. Res.* **2011**, *20*, 210.
(136) Tasneem, T.; Raikar, S. V.; Kamble, R. R. *Arab. J. Chem.* **2014**, *7*, 900.
(137) Parekh, D. V.; Desai, P. S. *Adv. Appl. Sci. Res.* **2012**, *3*, 1992.