SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/08

SYNSTORIES

- **Fluorine and Fluorous in Wyoming**
- **Direct Transformation of Methyl Arenes to Aryl Nitriles at Room Temperature**
- **Benzonaphthyridines from Morita–Baylis–Hillman Adduct Acetates**

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Dear readers,

there is little doubt that Chinese chemistry is becoming a major player in the global arena of international science. In a period when most of the Western countries are cutting research expenses and funding is becoming increasingly tight, P. R. of China is boosting its investments in science and technology, and the effects are evident both in terms of quantity and quality of the Chinese research production, including patents and publications. It is therefore not surprising that two ***SYNSTORIES*** in this issue of ***SYNFORM*** come indeed from the P. R. of China: Professor Weike Su (Zhejiang University) and his new approach to benzonaphthyridines, and Professor Ning Jiao (Peking University) and his direct transformation of methyl arenes to aryl nitriles. The issue is completed by a brief report on the 19th International Symposium on Fluorine Chemistry that was held from August 23–28, 2009, in Jackson Hole, Wyoming, USA.

Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

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If you have any questions or wish to send feedback, please write to Matteo Zanda at:
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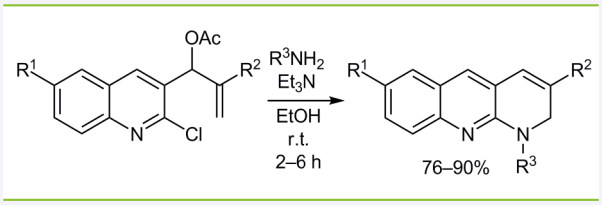

COMING SOON *A75*

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Fluorine and Fluorous in Wyoming

The 19th International Symposium on Fluorine Chemistry (ISFC-19) and The International Symposium on Fluorous Technologies (ISoFT-09) were held jointly from August 23–28, 2009 in the spectacular mountain landscape of Jackson Hole (Wyoming, USA), in the Grand Teton National Park. The conference was superbly organized by Professors Joseph S. Thrasher (Chair, University of Alabama, USA), Olga V. Boltalina and Steven H. Strauss (Co-Chairs, Colorado State University, USA), Richard E. Fernandez (Co-Chair, University of Alabama, USA), and Dennis P. Curran (Co-Chair, University of Pittsburgh, USA).

The symposium was attended by about 400 registered participants, who were updated on the most recent advances of fluorine chemistry in materials science, energy, biomedicine, and drug discovery from a scientific program of very good average level. The attendees also enjoyed a number of cultural and entertainment events of high quality, including a birds of prey exhibition, two Native American cultural events with singers, drummers and dancers, a horse whispering demonstration, a tour of Yellowstone National Park, a very rich accompanying-persons program, and much more. The prestigious Prix Henry Moissan 2009, managed by the "Fondation de la Maison de la Chimie" (Paris, France) was awarded to Professor Herbert Roesky, University of Göttingen, Germany. The next events for fluorine chemists are the European and International Symposia on Fluorine Chemistry (Ljubljana, Slovenia, in 2010 and Kyoto, Japan, in 2012, respectively).

The ISFC-19 organizers, from left to right: O. V. Boltalina, J. S. Thrasher, R. E. Fernandez, S. H. Strauss

Matteo Zanda

Group picture of the ISFC-19 participants

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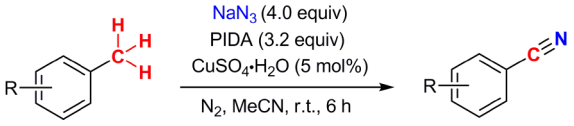
Direct Transformation of Methyl Arenes into Aryl Nitriles at Room Temperature

Angew. Chem. Int. Ed. **2009**, *48*, 7094–7097



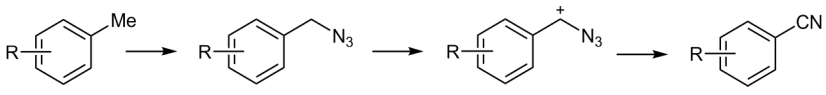
Efficient and selective functionalization of benzyl C–H bonds has been an interesting topic in recent years due to the potential application of this synthetic strategy in concise and economical organic synthetic processes. However, the related developments are limited. Recently, an important advance in this area of research was published by the group of Professor Ning Jiao from Peking University, Beijing (P. R. of China), who showed that a toluene derivative can be transformed into the corresponding benzonitrile using a simple yet powerful procedure. "One of the goals in our group is to develop some new and efficient synthetic methodologies for the synthesis of bioactive molecules through catalysis and/or radical reactions," said Professor Jiao. "In this concept, the radical reaction, such as the famous Wohl–Ziegler bromination, is a useful approach to realize benzyl C–H bond functionalizations efficiently. Thus," he continued, "it is one of our ongoing interests to investigate the functionalization of methyl aromatics through radical reactions."

After many failures, Professor Jiao and his co-workers discovered the system under which 4-methylanisole could be successfully converted into 4-methoxybenzonitrile, at room temperature in the presence of PIDA (phenyliodonium diacetate) and NaN_3. "As we know, aryl nitriles are useful precursors for the synthesis of amines, amides, amidines, ketones, carboxylic acids, and esters," explained Professor Jiao. "Therefore, aryl nitriles have been versatile building blocks in organic synthesis for natural products, pharmaceuticals, agricultural chemicals, materials, and dyes. Compared to traditional strategies for the synthesis of aryl nitriles, as we summarized in our paper, our method provides a unique pathway for the synthesis of aryl nitiriles from simple methyl arenes at room temperature via C–H functionalization, which turns out to be an attractive research area and is of great importance because of its valuable atom economy. Moreover," continued Professor Jiao, "toxic cyanide sources and high reaction temperatures were avoided. This process may be useful for the preparation of functionalized aryl nitriles from the corresponding methyl arenes avoiding the decomposition of the functional groups. Furthermore, it is very interesting and useful to find that the chemoselectivity of this kind of transformation is very high when there is more than one methyl group in the substrate, with the *para*-heteroatom as the directing group."

Based on these results, Professor Jiao proposed a mechanism and proved it through the characterization of a by-product and other tailored experiments. According to this mechanism, methyl arenes are initially converted into benzylic azides and then further oxidized to afford benzylic cations, which finally undergo a Schmidt-type rearrangement reaction to afford the corresponding aryl nitriles.

"We have applied this novel method to the synthesis of tetrazole analogues related to disoxaril which exhibits MIC_{80} values in the order of 0.20 μM for 15 rhinovirus serotypes (*J. Med. Chem.* **1993**, *36*, 3240) from inexpensive and easily available starting materials," said Professor Jiao. "Highly selective transformation of one methyl group indicates the merit and practicability of the approach. We believe that this method has great potential in organic synthesis. There are still some limitations, for example the scope of substrate and the large loading of NaN_3 and PIDA. Investigations are ongoing in our lab to solve these problems," he concluded.

Matteo Zanda



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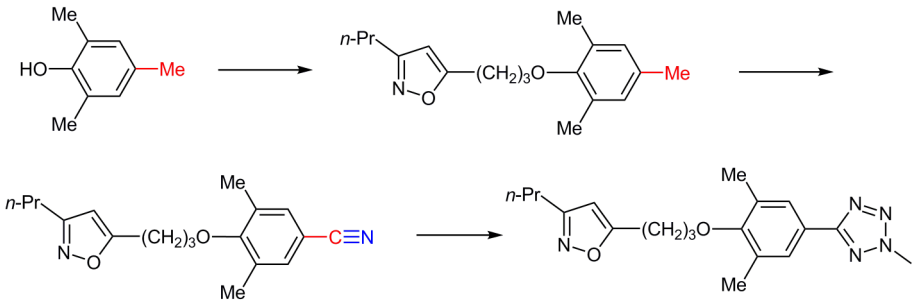

tetrazole analogues related to disoxaril

About the authors

W. Zhou

Wang Zhou was born in Hunan (P. R. of China) in 1981. He received his M.Sc. at Hunan Normal University in 2006. In 2007, he joined Professor Ning Jiao's group at Peking University as a Ph.D. student. His current research interest is organic methodology.

Prof. L. Zhang

Liangren Zhang was born in Hunan (P. R. of China) in 1963. He received his B.Sc. at Hunan Normal University (1983), his M.Sc. (1986) and Ph.D. (1991) at the Lanzhou Institute of Chemical Physics (P. R. of China). From 1988 to 1991 he spent two years as a joint Ph.D. student at Kyushu University (Japan). He worked as Postdoctoral Fellow at Beijing Medical University (P. R. of China) from 1991 to 1993. He was an Associate Professor (1994) at Beijing Medical University (P. R. of China), and a visiting scientist at the University of California at San Francisco (USA) in 1998 and the University of Michigan (USA) in 1999. Since 2002 he holds a Full Professorship at Peking University. His current research interests are the synthesis of bioactive organic molecules and drug design based on the structure of biomolecular targets.

Prof. N. Jiao

Ning Jiao was born in Shandong (P. R. of China) in 1976. He received his B.Sc. at Shandong University in 1999, and his Ph.D. in 2004 at the Shanghai Institute of Organic Chemistry (P. R. of China) under the guidance of Professor Shengming Ma. He spent 2004–2006 as an Alexander von Humboldt Postdoctoral Fellow with Professor Manfred T. Reetz at the Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr (Germany). In 2007, he joined the faculty at Peking University as an Associate Professor. His current research efforts are focused on: 1) the development of some new and efficient synthetic methodologies for the synthesis of heterocycles, bioactive molecules and potential drugs; 2) radical reactions and the activation of inert chemical bonds; and 3) the directed evolution of enzymes and protein hybrid catalysts.

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Benzonaphthyridines from Morita–Baylis–Hillman Adduct Acetates

Synthesis **2009**, 2333–2340; *Synfacts* **2009**, 976 (*Synfact* of the Month)

2
R^1 = H, Me, Cl
R^2 = CO_2Me, CO_2Et, $CO_2(n\text{-Bu})$, CN

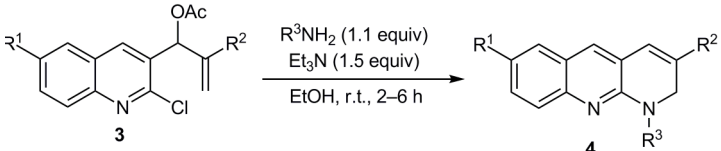
3
70–73%

New synthetic methods to effectively prepare heteroaromatic structures are of great interest in medicinal chemistry and drug discovery, and represent a priority research area for the pharmaceutical industry. Recently, an interesting piece of research in this area was published by the group of Professor Weike Su from Zhejiang University (P. R. of China) which disclosed a very efficient entry to benzonaphthyridines using a Morita–Baylis–Hillman reaction followed by an amination reaction involving the intermediate acetates.

"The Morita–Baylis–Hillman (MBH) reaction is one of the most powerful carbon–carbon bond-forming methods in organic synthesis," said Professor Su. "MBH adducts, due to their special characteristics, have great potential for further transformations into cyclic compounds. In our group we are interested in transforming MBH adducts into heterocycles such as polyhydrochromenes, polyhydroquinolines, 1,2,4-triazole derivatives and 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones, which are important core structures in many natural products."

Professor Su pointed out that his group has also successfully applied bis(trichloromethyl)carbonate (BTC)/DMF instead of the DMF/$POCl_3$ system as an environmentally benign Vilsmeier reagent for various chemical transformations, especially for chloroformylation. Then Professor Su and co-workers tried to design and construct different complex molecules with potential bioactivities from simple starting substrates by combination of the Vilsmeier and MBH reactions. "We found that 2-chloro-3-formylquinolines **2** could be easily formed in high yields by reaction of *N*-phenylacetamide using the BTC/DMF system under reflux conditions," said Professor Su. "Then, the corresponding MBH adduct acetates could be readily prepared in satisfactory yields by treatment of 2-chloro-3-formylquinolines **2** with activated olefins catalyzed by DABCO and followed by acetylation."

With the MBH adducts in hand, Professor Su and co-workers developed a novel procedure for the preparation of benzo[*b*][1,8]naphthyridine-3-carboxylate derivatives from MBH adduct acetates and primary amines, ammonium acetate or



3
R^1 = H, Me, Cl
R^2 = CO_2Me, CO_2Et, $CO_2(n\text{-Bu})$, CN
R^3 = H, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3,4-$F_2C_6H_3$, Bn, Cy, *n*-Bu, *t*-Bu

4
76–90%

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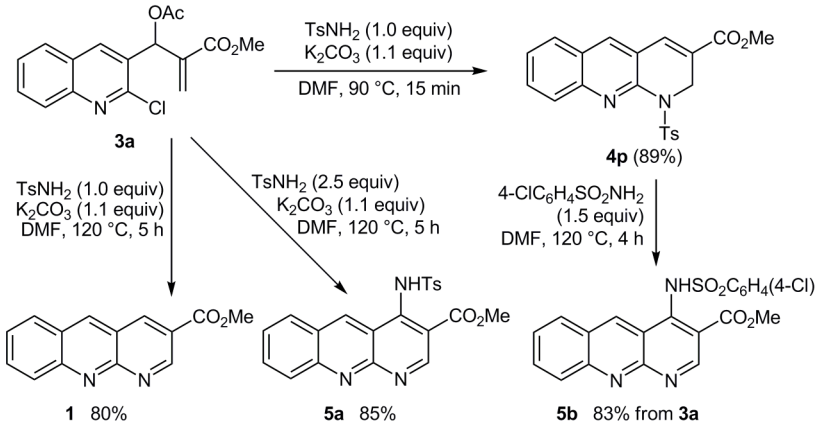
benzenesulfonamides, respectively. "Very interestingly, in the case of benzenesulfonamides, the ratio of reactants and reaction temperature evidently had an influence on the type of products and their yields," said Professor Su. "The unexpected naphthyridines **5a** and **5b** could be obtained in satisfactory yields when an excess of toluenesulfonamide or 4-chlorophenylsulfonamide was mixed with MBH adduct acetates in DMF at 120 °C for five hours."

"It is well known that naphthyridines are an important class of pharmaceutical compounds due to their broad range of bioactivities such as antimicrobial, antitumor, anti-inflammatory, antiallergic, anticonvulsant, and antihypertensive," concluded Professor Su, "therefore, we are confident that our work will soon find further application."

Matteo Zanda



About the authors

Prof. W. Su

Weike Su was born in Zhejiang (P. R. of China) in 1961. He received his B.Sc. from Zhejiang University of Technology in 1983, and his M.Sc. and Ph.D. degrees from the same university in 1988 and 2001, respectively. He was an Associate Professor (1996), and is now a Full Professor at Zhejiang University of Technology in green/medicinal chemistry. His current research efforts are focused on developing innovative and clean syntheses of drugs and drug intermediates.

Prof. W. Zhong

Weihui Zhong was born in Jiangxi province (P. R. of China) in 1970. He received his B.Sc. and M.Sc. degrees from Huazhong University of Science and Technology, Wuhan (P. R. of China) in 1992 and 1998, respectively, and his Ph.D. from Zhejiang University in 2001. He worked at Tokushima Bunri University (Japan) from 2001–2003 and at Tokushima University (Japan) from 2003–2004 as a Postdoctoral Fellow. He became Full Professor at Zhejiang University of Technology in 2004. His current research interest is focused on transforming Morita–Baylis–Hillman adducts into nitrogen-based heterocycles.

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Efficient Synthesis of Benzothiophenes by an Unusual Palladium-Catalyzed Vinylic C–S Coupling
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Synfact of the Month in category "Synthesis of Heterocycles":
Mn(III)-Mediated Synthesis of Pyridines

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