SYNLETT
Spotlight

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Heterocyclic Ketene Aminals

Compiled by Li-Fen Yang

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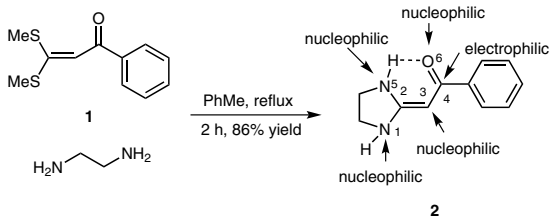
Introduction

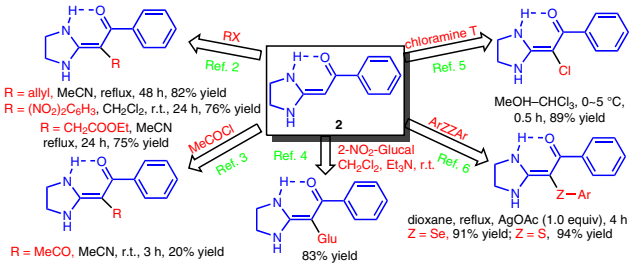
Heterocyclic ketene aminals (HKAs) are important precursors in organic synthesis of a variety of heterocyclic compounds. HKAs are conjugated with electron-donating amino groups and an electron-withdrawing carbonyl group, as well as a highly polarized double bond (C=C).[1] This leads to higher electron density of the α-carbon (C3) than that of the secondary amino groups (N1 and N5) and makes the reaction at the α-carbon very easy. HKAs have four nucleophilic sites (N1, N5, C3, O6). As a result, they are usually used as regioselective building blocks. Especially, they can serve as bis-nucleophiles (C3 and N1) and react with bis-electrophiles to synthesize the fused heterocycles. HKAs can be easily prepared from the corresponding acetophenone and diamine (Scheme 1).



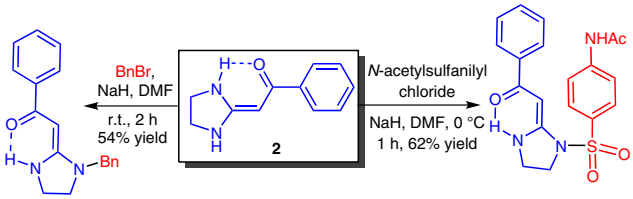
Scheme 1 Synthesis of heterocyclic ketene aminals

Abstracts

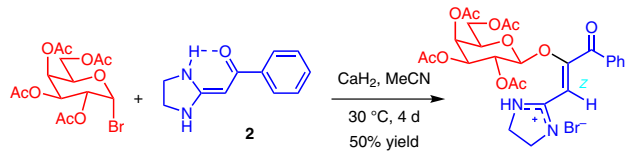
(A) *Regioselective reaction of α-carbon:*
Due to the high electron density of the α-carbon (C3) the substituted targets of the α-carbon have been obtained with high selectivity via alkylation,[2] acylation,[3] glycosation,[4] halogenations,[5] and arylthio- and phenyl-selanylation.[6] These reagents are haloalkanes, acyl chlorides, isothiocyanate precursors, glucopyranosyl bromides, *N*-bromobutanimides, or diaryl dichalcogenides under neutral or weak alkali conditions.



(B) *Regioselective reaction of nitrogen:*
HKAs can undergo regioselective reaction on the nitrogen to form N-benzylated products between HKAs and benzyl bromide,[7] as well as *N*-sulfanilyl products between HKAs and *N*-acetylsulfanilyl chloride[8] under strong alkali such as sodium hydride conditions.



(C) *Regioselective reaction of oxygen:*
The Huang group investigated the stereoselective synthesis of *O*-galactosides from benzoyl-substituted HKAs with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide.[9]



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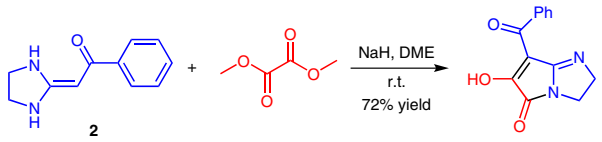
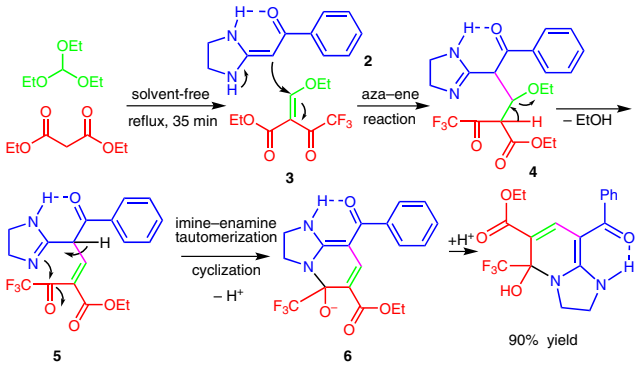
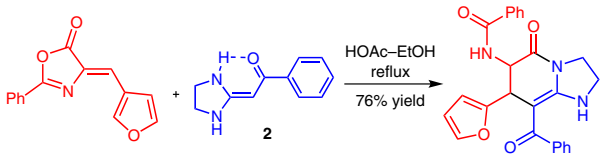
(D) *Synthesis of diazaheterocycles:*
Yu and colleagues described an efficient method for the synthesis of γ-lactam-fused diazaheterocycles by HKAs and dimethyl oxalate at room temperature in the presence of sodium hydride.[10]



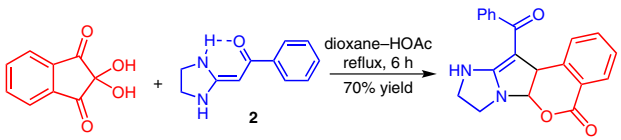
(E) *Synthesis of bicyclic pyridines:*
Our group reported concise and efficient one-pot syntheses of highly functionalized bicyclic pyridines under solvent- and catalyst-free conditions by utilizing various heterocyclic ketene aminals and ethyl 4,4,4-trifluoroacetoacetate and triethyl orthoformate.[11] The proposed mechanism for the domino reaction: First, triethoxymethane reacts with ethyl 4,4,4-trifluoro-3-oxobutanoate to form **3**. Then, **3** reacts with HKA **2** via an aza–ene[12] mechanism to obtain **4**. Then, intermediate **4** removes the ethanol to give **5**. Compound **5** undergoes a process of imine–enamine tautomerization and cyclization to form **6**. Compound **6** then forms the final product.



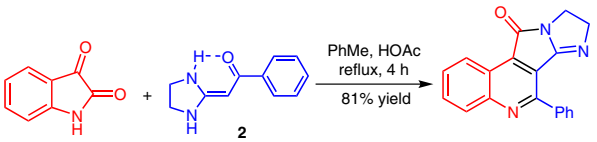
(F) *Synthesis of bicyclic pyridones:*
Our group reported the synthesis of bicyclic pyridones from HKAs and arylmethylene-2-phenyloxazol-5(4*H*)-ones through acetic acid catalysis under ethanol.[13] The reaction proceeds via Michael addition, intramolecular cyclization and ring cleavage and enol–keto tautomerism.



(G) *Synthesis of isocoumarin-containing tetracycles:*
Isocoumarins are well-known heterocyclic scaffolds for the construction of various natural products possessing a wide range of biological activities. Yan and co-workers demonstrated the acetic acid catalyzed synthesis of isocoumarin-containing tetracycles by utilizing various HKAs and 2,2-dihydroxy-2H-indene-1,3-dione as starting materials. The reactions with good yields usually took 6 h at reflux in 1,4-dioxane.[14]



(H) *Synthesis of imidazopyrroloquinolines:*
Our group has investigated a highly efficient reaction for the construction of imidazopyrroloquinolines though HKAs and isatins in toluene at reflux with acetic acid as catalyst. The reaction has good to excellent yields.[15]



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