

SYNLETT Spotlight

Heterocyclic Ketene Aminals

Compiled by Li-Fen Yang



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

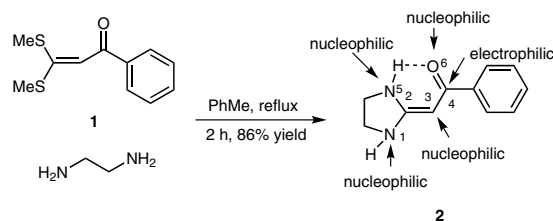
Li-Fen Yang was born in Yunnan, P. R. of China. She received her B.Sc. in chemistry from Yunnan Normal University in 2011. Currently she is a second-year postgraduate student with Professor Sheng-Jiao Yan and Professor Jun Lin at Yunnan University. Her research is focused on the development of new synthetic methodologies and on the synthesis of heterocycles.

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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).

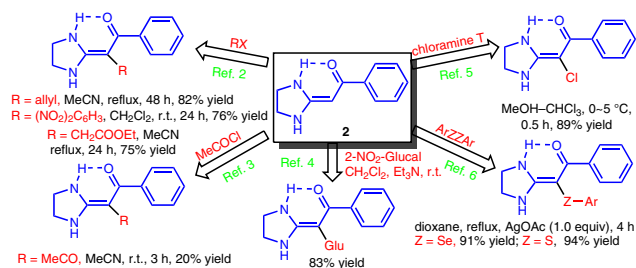


Scheme 1 Synthesis of heterocyclic ketene aminals

Abstracts

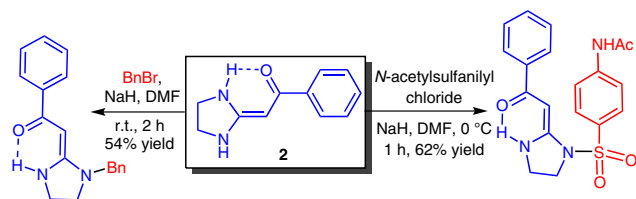
(A) Regioselective reaction of α -carbon:

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 glycosylation,⁴ halogenations,⁵ and arylthio- and phenyl-selenylation.⁶ These reagents are haloalkanes, acyl chlorides, isothiocyanate precursors, glucopyranosyl bromides, *N*-bromobutanamides, or diaryl dichalcogenides under neutral or weak alkali conditions.



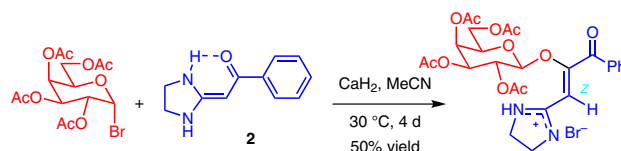
(B) Regioselective reaction of nitrogen:

HKAs can undergo regioselective reaction on the nitrogen to form *N*-benzylated products between HKAs and benzyl bromide,⁷ as well as *N*-sulfanyl products between HKAs and *N*-acetylsulfanyl chloride⁸ under strong alkali such as sodium hydride conditions.



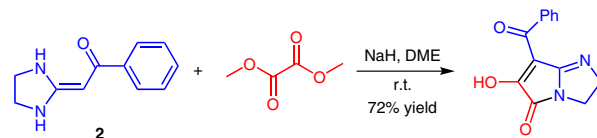
(C) Regioselective reaction of oxygen:

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

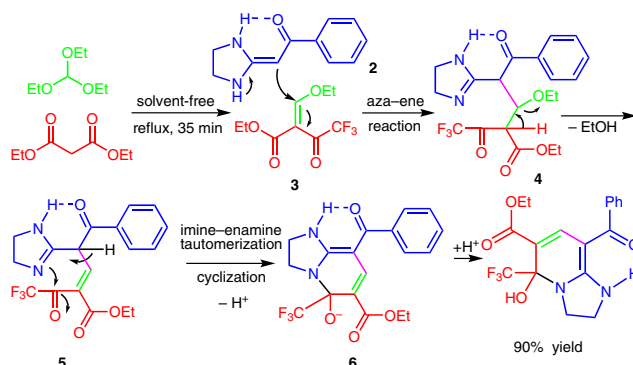


(D) *Synthesis of diazaheterocycles:*

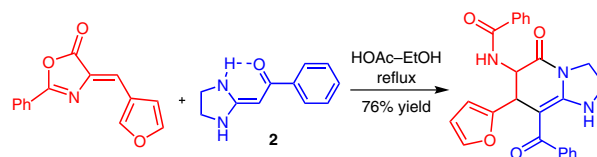
Yu and colleagues described an efficient method for the synthesis of γ -lactam-fused diazaheterocycles by HKAs and dimethyl oxalate at room temperature in the presence of sodium hydride.¹⁰

(E) *Synthesis of bicyclic pyridines:*

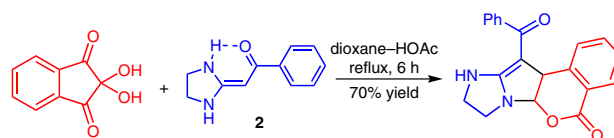
Our group reported concise and efficient one-pot syntheses of highly functionalized bicyclic pyridines under solvent- and catalyst-free conditions by utilizing various heterocyclic ketene amins and ethyl 4,4,4-trifluoroacetoacetate and triethyl orthoformate.¹¹ The proposed mechanism for the domino reaction: First, triethoxymethane reacts with ethyl 4,4,4-trifluoro-3-oxobutanoate to form **3**. Then, **3** reacts with HKA **2** via an aza-ene¹² 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:*

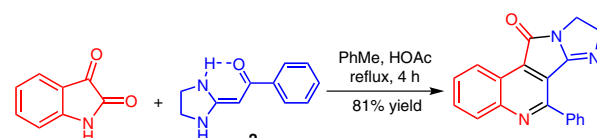
Our group reported the synthesis of bicyclic pyridones from HKAs and arylmethylene-2-phenyloxazol-5(4H)-ones through acetic acid catalysis under ethanol.¹³ The reaction proceeds via Michael addition, intramolecular cyclization and ring cleavage and enol–keto tautomerism.

(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 through HKAs and isatins in toluene at reflux with acetic acid as catalyst. The reaction has good to excellent yields.¹⁵



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