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). 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).

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, acylation, glycosation, halogenations, and arylthio- and phenyl-selanylation. 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, as well as N-sulfanilyl products between HKAs and N-acetylsulfanilyl chloride under strong alkali such as sodium hydride conditions.

(C) Regioselective reaction of oxygen:
The Huang group investigated the stereo-selective synthesis of O-galactosides from benzyl-substituted HKAs with 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide.
**SPOTLIGHT**

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(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-trifluoro-3-oxobutanato. The proposed mechanism for the domino reaction: First, triethylisoxethane reacts with ethyl 4,4,4-trifluoro-3-oxobutanate to form 3. Then, 3 reacts with HKA 2 via an aza–ene 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.

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(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 catalyzed synthesis of isocoumarin-containing tetracycles by utilizing various heterocyclic ketene aminals and ethyl 4,4,4-trifluoro-3-oxobutanato to form 3. Then, 3 reacts with HKA 2 via an aza–ene 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.

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(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.

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(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.

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**References**


