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

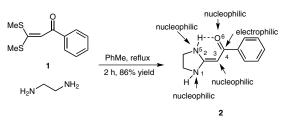
Compiled by Li-Fen Yang

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

CH₂Cl₂, r.t., 24 h,

DEt. MeCN

ux, 24 h, 75% yield

R = MeCO, MeCN, r.t., 3 h, 20% yield

BnBr

NaH, DMF

r.t., 2 h

54% yield

Abstracts

(A) Regioselective reaction of α -carbon:

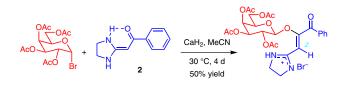
Due to the high electron density of the α -carbon (C3) the substituted targets of the α -carbon have been obtained with high selectivity via alkylation,² acylation,³ glycosation,⁴ halogenations,⁵ and arylthioand phenyl-selanylation.⁶ These reagents are haloalkanes, acyl chlorides, isothiocyanate precursors, 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 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*-ace-tyl- α -D-galactopyranosyl bromide.⁹



83% vield

xane, reflux, AgO Se, 91% vield: Z

acetvlsulfanilv

chloride

NaH, DMF, 0 °C

h, 62% yield

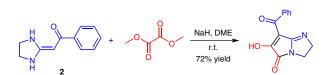
.0 equiv), 4 94% yield

SYNLETT 2014, 25, 2964–2965 Advanced online publication: 19.11.2014 DOI: 10.1055/s-0034-1379541; Art ID: st-2014-v0500-v © Georg Thieme Verlag Stuttgart · New York

SPOTLIGHT

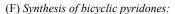
(D) Synthesis of diazaheterocycles:

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-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.



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

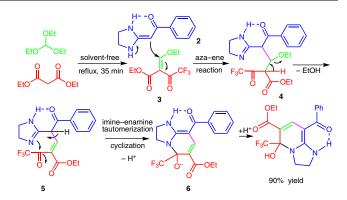
(H) Synthesis of imidazopyrroloquinolines:

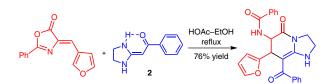
Our group has investigated a highly efficient reaction for the construction of imidazopyrroloquinolines though HKAs and isatins in toluene at reflux with acetic acid as catalyst. The reaction has good to excellent yields.¹⁵

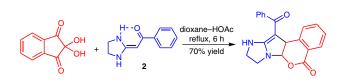
References

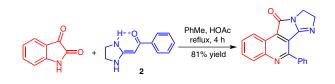
- Baum, K.; Bigelow, S. S.; Nauyen, N. V.; Archibald, T. G.; Gilardi, R.; Flippen-Anderson, J. L.; Georeg, C. J. Org. *Chem.* **1992**, *57*, 235.
- (2) (a) Huang, Z.-T.; Liu, Z.-R. Chem. Ber. 1989, 122, 95.
 (b) Wang, M.-X.; Huang, Z.-T. J. Org. Chem. 1995, 60, 2807. (c) Nie, X.-P.; Wang, M.-X.; Huang, Z.-T. Synthesis 2000, 1439. (d) Yu, F.-C.; Chen, Z.-Q.; Hao, X.-P.; Jiang, X.-Y.; Yan, S.-J.; Lin, J. RSC Adv. 2013, 3, 13183.
- (3) (a) Kollmeyer, W. D. US Patent 4053622, *Chem. Abstr.* 1978, 88, 37797h. (b) Huang, Z.-T.; Wang, J.-C.; Wang, L.-B. *Synth. Commun.* 1996, 26, 2285.
- (4) (a) Yu, C.-Y.; Yan, S.-J.; Zhang, T.; Huang, Z.-T. CN Patent 101041660B, *Chem. Abstr.* 2007, *147*, 469361. (b) Yu, C.-Y.; Yan, S.-J.; Huang, Z.-T.; Yu, A.-J. CN Patent 100537578C, *Chem. Abstr.* 2007, *147*, 418654.
- (5) Liu, B.; Wang, M.-X.; Huang, Z.-T. Synth. Commun. 1999, 29, 4241.
- (6) Jiang, X.-Y.; Liu, Z.-C.; Fang, L.; Yan, S.-J.; Lin, J. RSC Adv. 2014, 4, 26389.

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- (7) Wang, M.-X.; Wu, X.-D.; Wang, L.-B.; Huang, Z.-T. Synth. Commun. 1995, 25, 343.
- (8) Ren, Z.-X.; Li, Z.-J.; Huang, Z.-T. Synth. Commun. 1998, 28, 4241.
- (9) Ren, Z.-X.; Wang, L.-B.; Li, Z.-J.; Huang, Z.-T. Carbohydr. Res. 1998, 309, 251.
- (10) Yu, C.-Y.; Wang, L.-B.; Li, W.-Y.; Huang, Z.-T. Synthesis 1996, 959.
- (11) Yan, S.-J.; Chen, Y.-L.; Liu, L.; He, N.-Q.; Lin, J. Green Chem. 2010, 12, 2043.
- (12) Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. J. Chem. Soc., Perkin Trans. 1 1999, 2087.
- (13) Chen, X.-B.; Zhu, D.-D.; Wang, X.-Y.; Yan, S.-J.; Lin, J. *Tetrahedron* **2013**, *69*, 9224.
- (14) Yan, S.-J.; Chen, Y.-L.; Liu, L.; Tang, Y.-J.; Lin, J. *Tetrahedron Lett.* **2011**, *52*, 465.
- (15) Yu, F.-C.; Yan, S.-J.; Hu, L.; Wang, Y.-C.; Lin, J. Org. Lett. 2011, 13, 4782.