

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

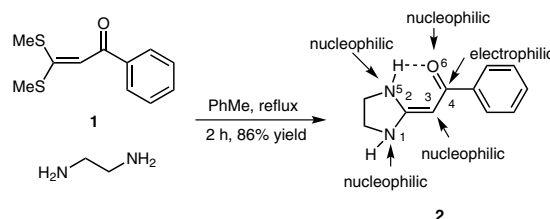
Li-Fen Yang was born in Yunnan, P. R. of China. She received her B.Sc. in chemistry from Yunnan Normal University in 2011. Currently she is a second-year postgraduate student with Professor Sheng-Jiao Yan and Professor Jun Lin at Yunnan University. Her research is focused on the development of new synthetic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

Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, P. R. of China
E-mail: yanglifenhgn@163.com

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).

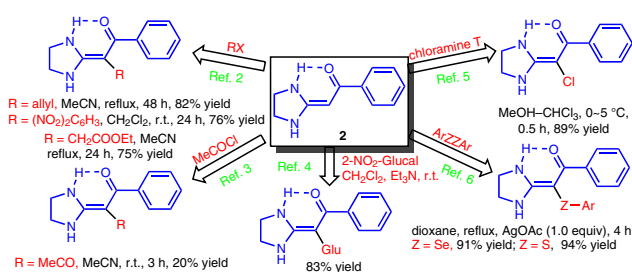


Scheme 1 Synthesis of heterocyclic ketene aminals

Abstracts

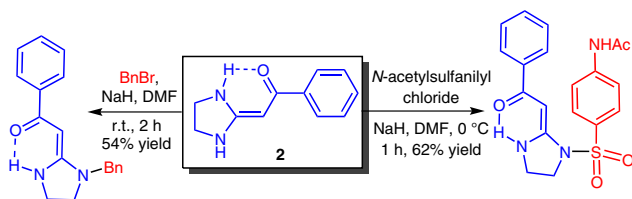
(A) Regioselective reaction of α -carbon:

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.



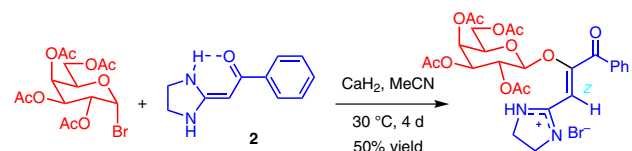
(B) Regioselective reaction of nitrogen:

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



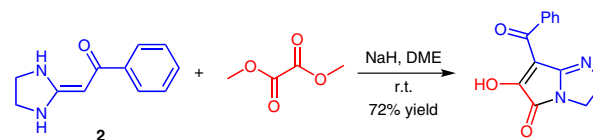
(C) Regioselective reaction of oxygen:

The Huang group investigated the stereoselective synthesis of *O*-galactosides from benzoyl-substituted HKAs with 2,3,4,6-tetra-*O*-acetyl- α -D-galactopyranosyl bromide.⁹

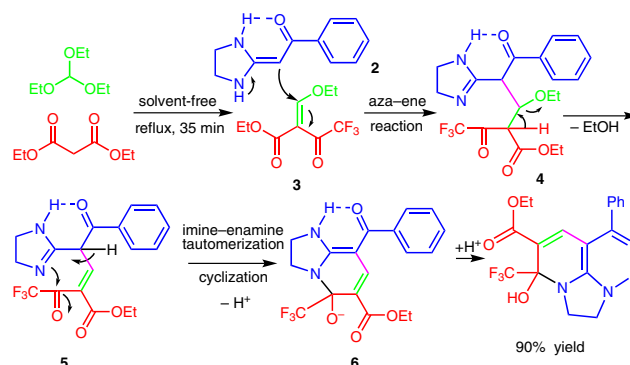


(D) *Synthesis of diazaheterocycles:*

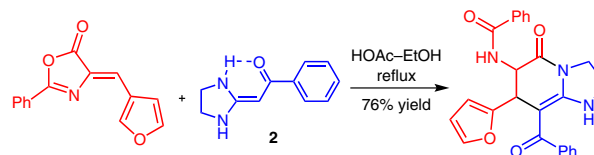
Yu and colleagues described an efficient method for the synthesis of γ -lactam-fused diazaheterocycles by HKAs and dimethyl oxalate at room temperature in the presence of sodium hydride.¹⁰

(E) *Synthesis of bicyclic pyridines:*

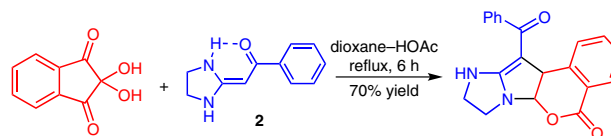
Our group reported concise and efficient one-pot syntheses of highly functionalized bicyclic pyridines under solvent- and catalyst-free conditions by utilizing various heterocyclic ketene amins and ethyl 4,4,4-trifluoroacetoacetate and triethyl orthoformate.¹¹ The proposed mechanism for the domino reaction: 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:*

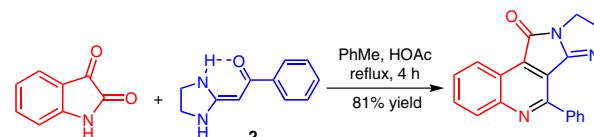
Our group reported the synthesis of bicyclic pyridones from HKAs and arylmethylene-2-phenyloxazol-5(4H)-ones through acetic acid catalysis under ethanol.¹³ The reaction proceeds via Michael addition, intramolecular cyclization and ring cleavage and enol–keto tautomerism.

(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



References

- (1) 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.
- (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.