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Three-Component Synthesis of Cyclic Enaminones via Ketene Cyclization

Hajime Seki and Gunda I. Georg*

Department of Chemistry and Department of Medicinal Chemistry, Institute for Therapeutics Discovery and Development, College of Pharmacy, University of Minnesota, 717 Delaware Street SE, Minneapolis, Minnesota 55414, United States

georg@umn.edu

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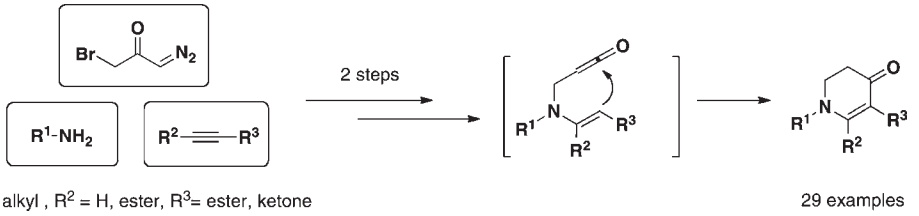
ABSTRACT



Cyclic six-membered enaminones were synthesized from three components (bromodiazoacetone, primary amine, and alkyne) in high yields via aza-Michael addition, Wolff rearrangement, and nucleophilic ketene cyclization.

Ketenes, first discovered by Staudinger in 1905, are among the best studied intermediates in organic chemistry.[1] Their versatile reactivity provides access to a number of valuable structural motifs. Ketenes can be readily prepared from several precursors including diazoketones and acid halides, which further underscores their value in synthetic organic chemistry.[2]

Reactions involving ketenes can be categorized into two major types: cycloaddition reactions and nucleophilic additions to ketenes. The so-called Staudinger reaction is a well-known example of a cycloaddition reaction, where a ketene reacts with an imine or a ketone to provide a β-lactam or β-lactone, respectively.[3] Ketenes can also undergo cycloadditions with alkenes or alkynes to form a C−C bond at the *sp* center of the ketene.[4]

The other type of reaction, the nucleophilic addition to a ketene,[5] is exemplified by the Arndt−Eistert homologation, where the acid functionality is homologated via the formation of a diazo intermediate, followed by a Wolff rearrangement, and subsequent nucleophilic addition to the intermediate ketene.[6] In nucleophilic additions to electrophilic ketenes, most often

(1) (a) Staudinger, H *Chem. Ber.* **1905**, *38*, 1735. (b) Tidewell, T. T. *Ketenes*, 2nd ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2006.

(2) (a) Meier, H.; Zeller, K. P. *Angew. Chem.* **1975**, *87*, 52. (b) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193. (c) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563. (d) Staudinger, H. *Chem. Ber.* **1911**, *44*, 1619.

(3) For review: (a) Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159. (b) Georg, G. I.; Ravikumar, V. T. Stereocontrolled Ketene-Imine Cycloaddition Reactions. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Verlag Chemie: New York, 1993; p 295.

(4) (a) Lee, S. Y.; Kulkarni, S.; Burbaum, B. W.; Snider, B. B. *J. Org. Chem.* **1988**, *53*, 1848. (b) Liebenskind, L. S. *Tetrahedron* **1989**, *45*, 3053. (c) Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273. (d) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.

(5) Examples of C−X bond forming ketene cyclizations: (a) Rahman, S. S.; Wakefield, B. J.; Roberts, S. M.; Dowle, M. D. *J. Chem. Soc., Chem Commun.* **1989**, 303. (b) Boeckman, R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. (c) Vernier, J. M.; Hegedus, L. S.; Miller, D. B. *J. Org. Chem.* **1992**, *57*, 6914. (d) Barton, D. H. R.; Quinkert, G. *J. Chem. Soc.* **1960**, 1. (e) Quinkert, G.; Kleiner, E.; Freitag, B. J.; Glenneberg, J.; Billhardt, U. M.; Cech, F.; Schmieder, K. R.; Schudok, C.; Steinmetzer, H. C.; Bats, J. W.; Zimmermann, G.; Dürner, G.; Rehm, D. *Helv. Chim. Acta* **1986**, *69*, 469. (f) Quinkert, G.; Billhardt, U. M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, V.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Dürner, G.; Zimmermann, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771. (g) Quinkert, G.; Nestler, H. P.; Schumacher, B.; Delgrosso, M.; Durner, G.; Bats, J. W. *Tetrahedron Lett.* **1992**, *33*, 1977. (h) Dillon, J. L.; Gao, Q.; Dillon, E. A.; Adams, N. *Tetrahedron Lett.* **1997**, *38*, 2231. (i) Coutts, I. G. C.; Saint, R. E.; Saint, S. L.; Chambers-Asman, D. M. *Synthesis* **2001**, 247. (j) Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun.* **2004**, 2482.

(6) (a) Bachmann, W. E.; Struve, W. S. *Org. React.* **1942**, 38. (b) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587. (c) Matthews, J. L.; Braun, C.; Guibourdenche, C.; Overhand, M.; Seebach, D. *Enantiosel. Synth. β-Amino Acids* **1997**, 105.

(7) Nonorganometallic *C*-nucleophile addition to ketenes: (a) Hickmott, P. W.; Giasuddin Ahmed, M.; Ahmed, S. A.; Wood, S.; Kapon, M. *J. Chem. Soc., Perkin Trans.* **1985**, 2559. (b) Hickmott, P. W. *S. Afr. J. Chem.* **1989**, *42*, 17. (c) Yerxa, B. R.; Moore, H. W. *Tetrahedron Lett.* **1992**, *33*, 7811. (d) Byeon, C.-H.; Hart, D. J.; Lai, C.-S.; Unch, J. *Synlett* **2000**, 119.

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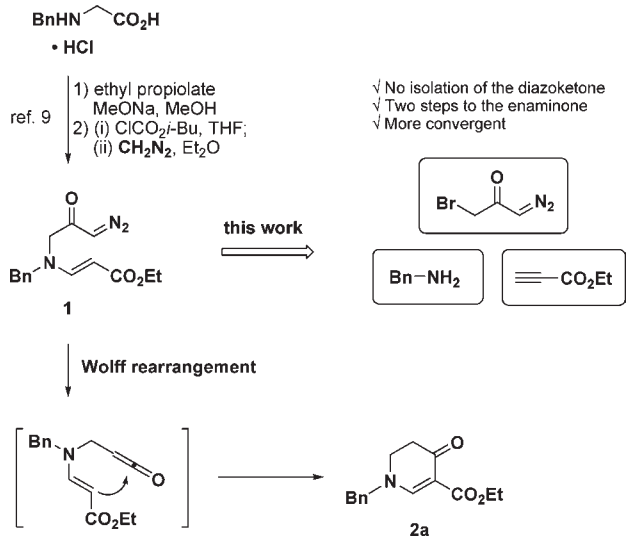


Figure 1. Two approaches for the synthesis of diazoketone **1**.

water, alcohol, and amines are used whereas carbon nucleophiles are used less frequently.[7] Although organometallic reagents such as RMgX and RLi have been explored in reactions with ketenes, few methods are of significant synthetic utility.[8]

Recently we reported a novel C−C bond forming cyclization with a ketene to synthesize six-membered enaminones, under very mild conditions (Figure 1).[9] In this cyclization, a ketene is generated from diazoketone **1**, employing a silver-catalyzed Wolff rearrangement, which subsequently reacts with a pendant vinylogous amide as a neutral nucleophile to form six-membered enaminones such as **2a**.

In our recently reported method, the diazoketone precursors were obtained from amino acids using diazomethane. Although the incorporation of chirality derived from an amino acid into the enaminone is advantageous, the use of diazomethane as well as the limited solubility of amino acids in organic solvents diminishes the scale and scope of this method. To address these issues, an alternative approach to synthesize the diazoketones was sought. We envisioned that the diazoketones can be

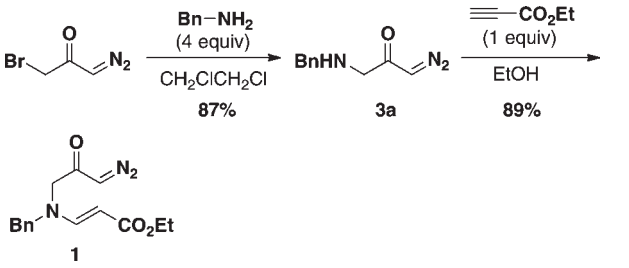
(8) For ketene reactions with organo lithium/magnesium reagents, see: (a) Haener, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396. (b) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391. For reactions with other type of carbon nucleophiles, see:(c) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, 1297. (d) Kita, Y.; Matsuda, S.; Kitagaki, S.; Tsuzuki, Y.; Akai, S. *Synlett* **1991**, 401. (e) Negri, G.; Kascheres, C. *J. Heterocycl. Chem.* **2001**, *38*, 109.

(9) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512.

(10) A recent report of a three-component synthesis using a ketene: Leon, F.; Rivera, D. G.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 1762.

(11) (a) Comins, D. L.; Joseph, S. P. *Adv. Nitrogen Heterocycl.* **1996**, *2*, 251. (b) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870. (c) Comins, D. L.; O'Connor, S.; Al-awar, R. S. In *Comprehensive Heterocyclic Chemistry III*; Alan, R. K., Christopher, A. R., Eric, F. V. S., Richard, J. K. T., Eds.; Elsevier: Oxford, 2008; p 41. (d) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702. (e) Niphakis, M. J.; Turunen, B. I.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793. (f) Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6019. (g) Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 196.

Scheme 1. Synthesis of Diazoketone **1**

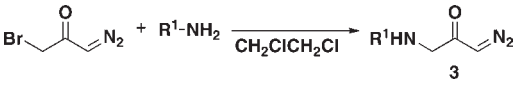


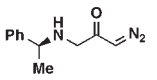
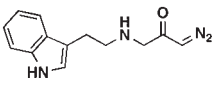
derived from three components: a primary amine, an alkyne, and a bromodiazoacetone.[10]

Herein, we are communicating a new synthetic method to obtain cyclic enaminones from amines and alkynes in two steps. This disconnection enabled us to vary the substituents on the enaminone structure in a convergent fashion and to limit the use of diazomethane to the preparation of the common diazoacetone intermediate **3a** (Scheme 1). The enaminone reaction products are well-known to be versatile intermediates for alkaloid synthesis.[11]

To test our hypothesis, we first investigated the synthesis of known diazoketone **1**. We found that the desired product could be readily synthesized by aza-Michael addition of benzylamino diazoacetone to ethyl propiolate in ethanol (Scheme 1). Benzylamino diazoacetone (**3a**) was prepared by the treatment of readily available bromodiazoacetone[12] with an excess of benzylamine.

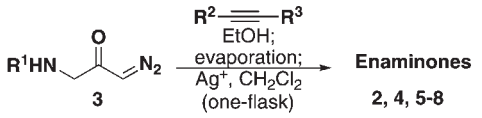
Table 1. Synthesis of Amino Diazoketones



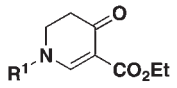
entry[a]	product (**3**)	yield	
1	R^1 = Bn	87%	**3a**
2	R^1 = Et	65%	**3b**
3	R^1 = *n*-Pr	63%	**3c**
4	R^1 = Allyl	72%	**3d**
5	R^1 = *n*-Bu	80%	**3e**
6	R^1 = -CH_2Cy	81%	**3f**
7		93%	**3g**
8[b]		73%	**3h**

[a] Reaction conditions: Bromodiazoacetone was treated with the amine (4 equiv) in dichloroethane (0.25 M) at 50 °C. [b] Bromodiazoacetone was treated with tryptamine hydrochloride (2 equiv) in a 0.5 M MeONa/MeOH solution (0.25 M) at 50 °C.

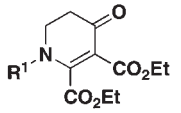
Scheme 2. Synthesis of an Enaminone Library via the Sequence of aza-Michael Addition, Wolff Rearrangement, and Ketene Cyclization[a]



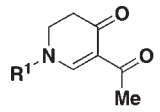
products & yields



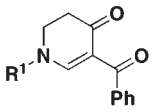
2a (R^1 = Bn) 82%
2b (R^1 = Et) 85%
2c (R^1 = *n*-Pr) 67%
2d (R^1 = Allyl) 76%
2e (R^1 = *n*-Bu) 78%
2f (R^1 = -CH_2Cy) 88%



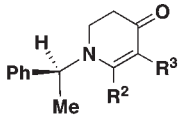
4a (R^1 = Bn) 92%
4b (R^1 = Et) 90%
4c (R^1 = *n*-Pr) 60%
4d (R^1 = Allyl) quant
4e (R^1 = *n*-Bu) 93%
4f (R^1 = -CH_2Cy) 86%



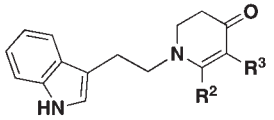
5a (R^1 = Bn) 85%
5b (R^1 = Et) 94%
5c (R^1 = *n*-Pr) 84%
5d (R^1 = Allyl) 90%
5e (R^1 = *n*-Bu) 81%
5f (R^1 = -CH_2Cy) 92%



6a (R^1 = Bn) 68%
6b (R^1 = Et) 81%
6c (R^1 = Allyl) 63%
6d (R^1 = -CH_2Cy) 88%



7a (R^2 = H, R^3 = CO_2Et) 86%
7b (R^2 = R^3 = CO_2Et) 67%
7c (R^2 = H, R^3 = C(O)Me) 75%
7d (R^2 = H, R^3 = C(O)Ph) 81%



8a (R^2 = H, R^3 = CO_2Et) 76%
8b (R^2 = R^3 = CO_2Et) 73%
8c (R^2 = H, R^3 = C(O)Me) 61%

[a] Reaction conditions: The amino diazoacetone was reacted with an alkyne (1.2 equiv) in EtOH (0.2 M). Upon evaporation, the reaction mixture was treated with the Ag catalyst (20 mol %, $PhCO_2Ag$, underline: Ag_2O) in dichloromethane (0.2 M) in the dark.

Encouraged by the successful synthesis of diazoketone **1**, amino diazoketones **3a**–**3h** (Table 1) were prepared in the same fashion using bromodiazoacetone and alkyl amines. A variety of primary alkyl amines (entry 1–6), as well as a chiral amine (entry 7), and an amino acid derived amine (entry 8) afforded the corresponding amino diazoketones in good yields.

With amino diazoketones **3a**–**3h** in hand, we carried out the aza-Michael addition to the alkynes[13] and subsequent Wolff rearrangement in a one-flask procedure. In order to obtain optimal yields, the use of two different solvents was necessary. Ethanol was employed for the aza-Michael addition, and dichloromethane for the Wolff rearrangement. Using these reaction conditions, the enaminone reaction products **2**, **4**, and **5**–**8** were obtained in good to excellent yields (Scheme 2). In several instances, Ag_2O was found to be a better catalyst for the Wolff rearrangement than $PhCO_2Ag$.

In summary, we have discovered an efficient, convergent synthesis of cyclic enaminones from bromodiazoacetone, primary amines, and alkynes. Aza-Michael addition, Wolff rearrangement, and nucleophilic ketene cyclization were carried out sequencially in one flask, providing facile access to an enaminone library. Exploration of other *C*-nucleophiles in this methodology is currently ongoing.

Acknowledgment. This work was supported by the National Institutes of Health (GM081267) and the University of Minnesota through the Vince and McKnight Endowed Chairs. We thank Dr. Subhashree Francis (University of Minnesota) for mass spectrometry assistance.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Bromodiazoacetone is currently commercially available or can be prepared as described in the following references: (a) Pace, V; Verniest, G.; Sinisterra, J.-V.; Alcantara, A. R.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 5760. (b) Padwa, A.; Austin, D. J.; Precode, L.; Zhi, L. *J. Org. Chem.* **1993**, *58*, 1144.

(13) The alkynes are commercially available with the exception of 1-phenylprop-2-yn-1-one, used for the synthesis of enaminones **6**, which was prepared using a reported method: Chassaing, S.; Kueny-Stotz, M.; Isorez, G.; Brouillard, R. *Eur. J. Org. Chem.* **2007**, 2438.