JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Free-Radical-Mediated [2 + 2 + 1] Cycloaddition of Acetylenes, Amidines, and CO Leading to Five-Membered α,β-Unsaturated Lactams

Takahide Fukuyama, Nao Nakashima, Takuma Okada, and Ilhyong Ryu*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

Supporting Information

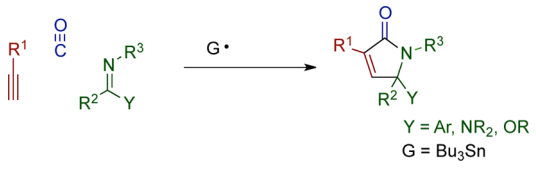
ABSTRACT: A free-radical-mediated [2 + 2 + 1] cycloaddition reaction comprising acetylenes, amidines, and CO was achieved by radical chain reaction to give five-membered α,β-unsaturated lactams in good yields. Both acyclic and cyclic amidines reacted with a variety of terminal acetylenes to afford monocyclic, bicyclic, and tricyclic lactams. We propose that vinyl radical carbonylation and nucleophilic addition of the amidine onto the resulting α-ketenyl radical give stable intermediates that are ready to undergo five-membered ring closure with elimination of tin radical.

Cycloaddition reactions incorporating CO provide a powerful means to access a wide range of cyclic and heterocyclic carbonyl compounds, and many efforts have been directed to transition-metal-catalyzed carbonylation reactions.[1] Previously, we found that acyl radicals generated by the addition of alkyl radicals to CO[2] undergo N-philic acyl radical cyclization onto the imine nitrogen, providing an annulation method for the synthesis of lactams.[3,4] The N-philic acyl radical cyclization can be rationalized by dual orbital interactions between the π* orbital of the acyl radical and the lone pair of the imine nitrogen and the singly occupied molecular orbital of the acyl radical and the π* orbital of the imine.[5] With successful examples of the *intramolecular* reaction using imines in hand, we then embarked on the challenge of *intermolecular* trapping of acyl radicals by N−C double bonds in the hope of developing a novel multicomponent radical reaction.[6] Herein we report that the intermolecular [2 + 2 + 1] cycloaddition reaction of acetylenes, amidines, and CO leading to five-membered α,β-unsaturated lactams proceeds efficiently under free-radical reaction conditions (Scheme 1), representing the first radical-mediated aza-Pauson−Khand reaction.[7,8]

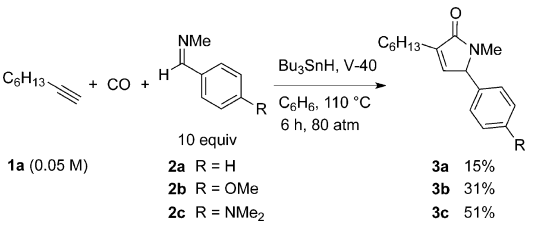
In our initial efforts, we focused on imines as the acyl radical trap. Unfortunately, however, the reactivity of imines in the intermolecular trapping reaction with acyl radicals was very modest. For example, the reaction of 1-octyne (**1a**), CO, and 10 equiv of imine **2a** gave the unusual [2 + 2 + 1] cycloaddition product **3a** in only 15% yield (Scheme 2). Imine **2b** having a methoxy group at the para position of the benzene ring gave a better yield of lactam **3b** (31%), and interestingly, *p*-dimethylamino-substituted imine **2c** gave lactam **3c** in a further improved yield of 51%. These trends led us to consider the use of amidines rather than imines as the acyl radical trap.

As a model reaction, we examined the intermolecular [2 + 2 + 1] cycloaddition reaction using **1a**, CO, and 1,8-

Scheme 1. Strategy for Lactam Synthesis by Radical-Mediated [2 + 2 + 1] Cycloaddition

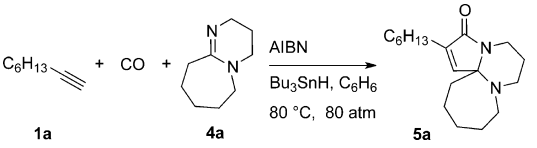


Scheme 2. Three-Component Coupling Reactions of Acetylenes, Imines, and CO[a]



[a]Conditions: **1a** (0.5 mmol), **2** (5 mmol), 1,1′-azobis(cyclohexane-1-carbonitrile) (V-40) (30 mol %), CO (80 atm), Bu_3SnH (1.2 equiv), C_6H_6 (10 mL), 110 °C, 6 h.

Table 1. Radical-Mediated [2 + 2 + 1] Cycloaddition of 1-Octyne, CO, and DBU[a]



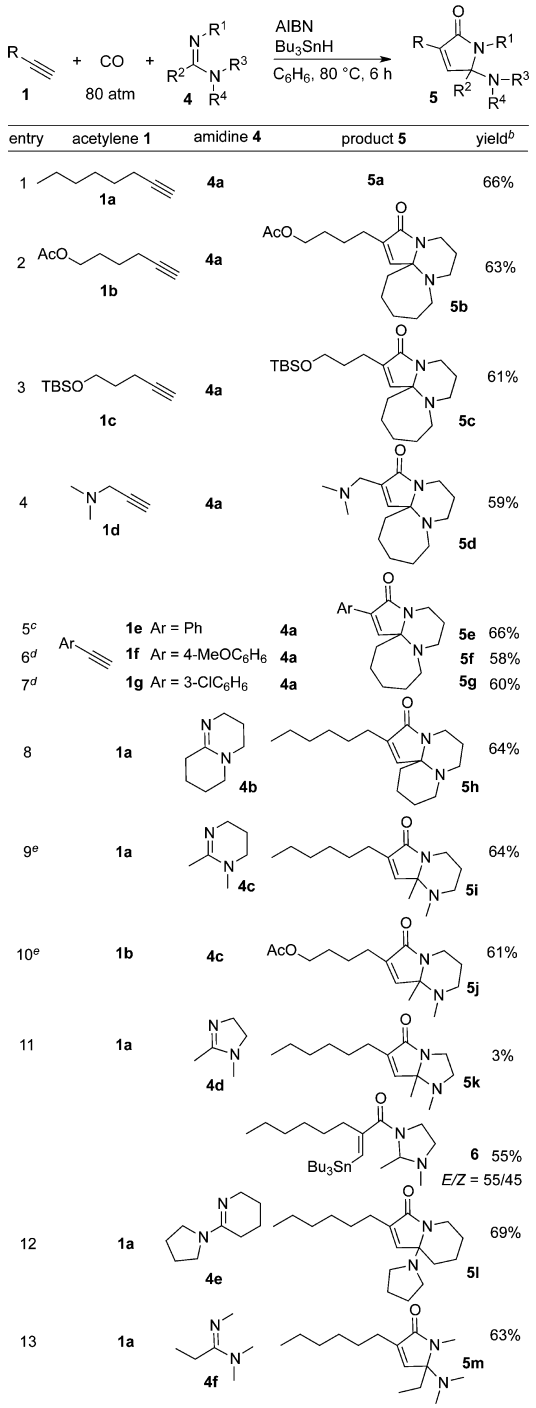
entry	equiv of **4a**	equiv of Bu_3SnH	time (h)	yield (%)[b]
1	2.0	1.2	3	39
2	5.0	1.2	3	60
3	5.0	0.6	3	68
4	5.0	0.3	3	62
5	5.0	0.3	6	66

[a]Conditions: **1a** (0.5 mmol), **4a**, AIBN (15−20 mol %), CO (80 atm), Bu_3SnH, C_6H_6 (10 mL), 80 °C. [b]Isolated yields as determined by flash chromatography.

Received: December 28, 2012

   dx.doi.org/10.1021/ja312654q | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

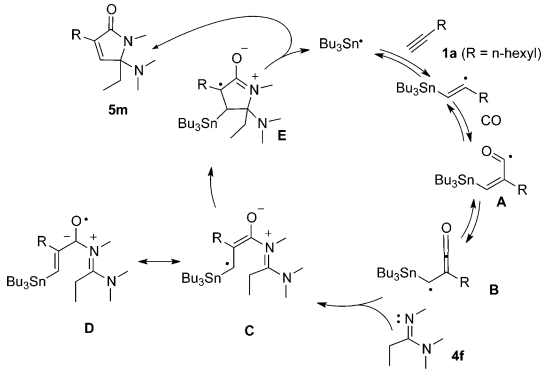
Table 2. Three-Component Reactions of 1, 4, and CO[a]



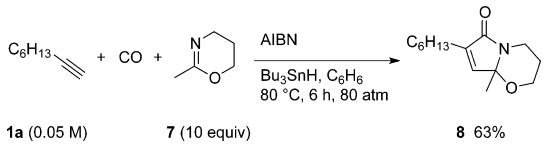
[a]Conditions; **1** (0.5 mmol), **2** (2.5 mmol), AIBN (15−30 mol %), CO (80 atm), Bu_3SnH (0.3 equiv for entries 1 and 3; 0.6 equiv for entries 2, 4−10, 12, and 13; 1.2 equiv for entry 11), C_6H_6 (10 mL), 80 °C, 6 h. [b]Isolated yields as determined by flash chromatography on silica gel and/or recycling preparative HPLC. [c]**1e** (0.01 M). [d]**1f** or **1g** (0.02 M). [e]**4c** (8.8 equiv).

diazabicyclo[5.4.0]undec-7-ene (DBU, **4a**) as the amidine (Table 1). When 1-octyne (0.05 M) was treated with DBU (2 equiv) under CO pressure (80 atm) in the presence of tributyltin hydride (1.2 equiv) and 2,2′-azobis(isobutyronitrile) (AIBN) (20 mol %) at 80 °C for 3 h, the expected five-membered α,β-unsaturated lactam **5a** was obtained in 39% yield (entry 1). Using a larger excess of DBU (5 equiv)

Scheme 3. Radical Chain Mechanism for the [2 + 2 + 1] Cycloaddition



Scheme 4. [2 + 2 + 1] Cycloaddition Using Dihydrooxazine 7



increased the yield of **5a** to 60% (entry 2). Since the product does not contain a tributyltin moiety, we examined the reaction with a decreased amount of Bu_3SnH. Gratifyingly, the results when 0.6 or 0.3 equiv of Bu_3SnH was used were essentially equivalent to those when a stoichiometric amount was used (entries 3−5).

To examine the generality of the present [2 + 2 + 1] cycloaddition reaction, a variety of acetylenes **1** and amidines **4** were exposed to similar radical carbonylation conditions (Table 2). The reactions of acetylenes bearing acetoxy, silyloxy, or amino functional groups all worked well to give the corresponding lactams, each having the desired functionality intact (entries 2−4). Arylacetylenes **1e−g** also participated in the three-component reaction to give the corresponding 2-aryl-substituted lactams **5e−g** (entries 5−7). The reaction of **1a** with **4b** having a 6,6-fused ring system also gave a good yield of the corresponding tricyclic lactam **5h** (entry 8). We also tested monocyclic amidines **4c** and **4d**. The reactions of **1a** and **1b** with six-membered amidine **4c** gave the corresponding lactams **5i** and **5j** having a bicyclo[4.3.0] skeleton (entries 9 and 10). In contrast, the reaction of **1a** with five-membered amidine **4d** gave the uncyclized three-component product **6** as the major product (entry 11). The very low yield of lactam **5k** in this case may be due to the steric demands of the bicyclo[3.3.0] system, which could prevent the cyclization. Amidine **4e** gave bicyclic lactam **5l** in 69% yield (entry 12). The reaction using acyclic amidine **4f** was also successful (entry 13).

A possible reaction mechanism for the present radical-mediated [2 + 2 + 1] cycloaddition is shown in Scheme 3, using entry 13 of Table 2 as the specific example. The addition of a tributyltin radical to the acetylene terminus of **1a** would generate a β-stannylated vinyl radical, which would undergo carbonylation to generate α,β-unsaturated acyl radical **A** and the isomeric α-ketenyl radical **B**.[9] Intermolecular trapping of the α-ketenyl radical[10] by amidine **4f** would then afford intermediate **C**, which can be drawn in several canonical forms, including **D**. 5-Endo cyclization of **C** to give **E**[11] followed by β-

dx.doi.org/10.1021/ja312654q | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

fission would lead to the formation of α,β-unsaturated lactam **5m** and regenerate the tributyltin radical.

The proposed key intermediate **C** should be highly stabilized by the two nitrogen atoms originating from the amidine starting material. In support of the importance of doubly donating groups, dihydrooxazine **7** reacted smoothly to give the corresponding bicyclic lactam ring **8** in good yield (Scheme 4).

In summary, we have developed a novel method for constructing five-membered α,β-unsaturated lactam rings by a [2 + 2 + 1] cycloaddition reaction between acetylenes, amidines, and CO, which is accomplished by a free-radical chain reaction. In this reaction, intermolecular trapping of α-ketenyl radicals by the nitrogen of the amidine gives a highly conjugated, highly stabilized radical species, which then undergoes five-membered-ring closure leading to unique heterocyclic ring systems. Thus, polarity-controlled radical reactions clearly represent a promising strategy for exploring multicomponent radical sequences, and we are continuing our efforts along this line.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and sample spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

ryu@c.s.osakafu-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, and Technology (MEXT), Japan, and the Japan Society for the Promotion of Science (JSPS).

■ REFERENCES

(1) For reviews, see: (a) Vizer, S. A.; Yerzhanov, K. B.; Quntar, A. A. A. A.; Demebitsky, V. M. *Tetrahedron* **2004**, *60*, 5499. (b) Gibson, S. E.; Lewis, S. E.; Mainolfi, N. *J. Organomet. Chem.* **2004**, *689*, 3873. (c) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795. (d) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328. (e) Park, J. H.; Chang, K.-M.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461. (f) Omae, I. *Cood. Chem. Rev.* **2011**, *255*, 139.

(2) For reviews of radical carbonylations, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. (d) Ryu, I. *Chem. Rec.* **2002**, *2*, 249. Also see a review on acyl radicals: (e) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(3) For acyl radical cyclizations onto imine nitrogen, see: (a) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838. (b) Ryu, I.; Miyazato, H.; Kuriyama, H.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632. (c) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Schiesser, C. H.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Ryu, I. *Org. Biomol. Chem.* **2003**, *1*, 4262. (d) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006**, *128*, 7712. For a kinetic study, see: (e) Kyne, S. H.; Lin, C. Y.; Ryu, I.; Coote, M. L.; Schiesser, C. H. *Chem. Commun.* **2010**, *46*, 6521.

(4) For reviews of radical cyclizations leading to heterocyclic compounds, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (c) Bowman, W. R.; Fletcher, J.; Potts, B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747. (d) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem.—Eur. J.* **2009**, *15*, 7830. (e) Rowlands, G. J. *Tetrahedron* **2010**, *66*, 1593.

(5) For theoretical studies of dual orbital interactions, see: (a) Schiesser, C. H.; Wille, U.; Matsubara, H.; Ryu, I. *Acc. Chem. Res.* **2007**, *40*, 303. (b) Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Chem. Commun.* **2002**, 2338. (c) Schiesser, C. H.; Matsubara, H.; Ritsner, I.; Wille, U. *Chem. Commun.* **2006**, 1067. (d) Matsubara, H.; Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Org. Biomol. Chem.* **2006**, *4*, 1920. (e) Kyne, S. H.; Schiesser, C. H.; Matsubara, H. *J. Org. Chem.* **2008**, *73*, 427.

(6) C-philic additions to N−C double bonds are well-documented. See: (a) Kim, S.; Kim, S.; Otsuka, N.; Ryu, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 6183. (b) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099. (c) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729. (d) Korapala, C. S.; Qin, J.; Friestad, G. K. *Org. Lett.* **2007**, *9*, 4243. (e) Kim, S.; Lim, K.-C.; Kim, S.; Ryu, I. *Adv. Synth. Catal.* **2007**, *349*, 527. (f) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662. (g) Yamada, K.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805. (h) Friestad, G. K.; Banerjee, K. *Org. Lett.* **2009**, *11*, 1095. (i) Ueda, M.; Miyabe, H.; Miyata, O.; Naito, T. *Tetrahedron* **2009**, *65*, 1321. Also see the following reviews: (j) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140. (k) Kim, S. *Adv. Synth. Catal.* **2004**, *346*, 19.

(7) For recent reviews of Pauson−Khand reactions, see ref 1 and: (a) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800. (b) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, 789.

(8) For Ru-catalyzed aza-Pauson−Khand reactions, see: (a) Chatani, N.; Morimoto, T.; Kamitani, A.; Fukumoto, Y.; Murai, S. *J. Organomet. Chem.* **1999**, *579*, 177. (b) Chatani, N.; Tobisu, M.; Asaumi, T.; Murai, S. *Synthesis* **2000**, 925.

(9) Matsubara, H.; Ryu, I.; Schiesser, C. H. *J. Org. Chem.* **2005**, *70*, 3610.

(10) For trapping of α-ketenyl radicals by amines, see: (a) Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun.* **2004**, 2482. (b) Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 1075. (c) Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2007**, *9*, 935. (d) Ryu, I.; Fukuyama, T.; Tojino, M.; Uenoyama, Y.; Yonamine, Y.; Terasoma, N.; Matsubara, H. *Org. Biomol. Chem.* **2011**, *9*, 3780.

(11) We have not precluded an alternative mechanism involving 6π electrocyclization for the ring closure. For 6π electrocyclization of pentadienyl anion, see: (a) Bates, R. B.; McCombs, D. A. *Tetrahedron Lett.* **1969**, *10*, 977. (b) Shoppee, C. W.; Henderson, G. N. *J. Chem. Soc., Chem. Commun.* **1974**, 561. (c) Hunter, D. H.; Sim, S. K.; Steiner, R. P. *Can. J. Chem.* **1977**, *55*, 1229. (d) Williams, D. R.; Reeves, J. T.; Nag, P. P.; Pitcock, W. H., Jr.; Baik, M.-H. *J. Am. Chem. Soc.* **2006**, *128*, 12339.