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Intramolecular nucleophilic carbonyl trapping of α-ketenyl radicals by an amino group†

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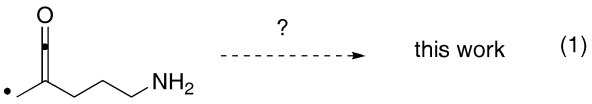
Free-radical carbonylation of ω-alkynylamines with tributyltin hydride gives a mixture of α-methylene lactams and α-stannylmethylene lactams. Nucleophilic addition of an internal amino group to the carbonyl group of α-ketenyl radicals is proposed as the cyclization step. The subsequent unusual 1,4-H shift from the resulting 1-hydroxyallyl radical, followed by elimination of the β-tributyltin radical leads to the formation of α-methylene lactams.

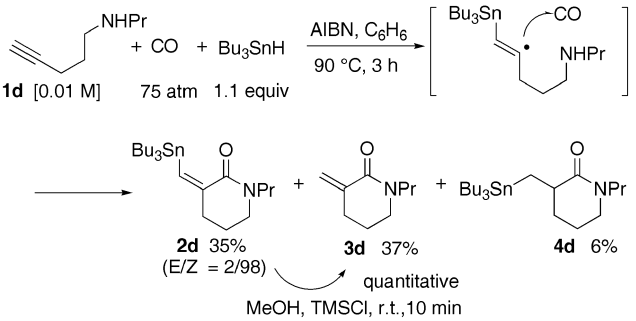
The reaction between ketenes and nucleophilic reagents, such as amines, alcohols, and carbon nucleophiles, is a well known reaction that provides access to a wealth of carbonyl compounds.[1] In the particular case of a ketene bearing an internal amino group, the reaction gives rise to lactams of various ring sizes. Having developed a facile method for the preparation of α-ketenyl radicals by radical carbonylation,[2,3] we examined the reaction of amine containing substrates, to determine whether or not a similar cyclization will occur in the radical version of simple ketenes (eqn. (1)). α-Ketenyl radicals are elusive but suggested frequently in the reaction of α,β-unsaturated acyl radicals.[2,4] *Ab initio* calculations predict a slightly higher energy with low energy barriers between two radicals.[5] In this communication, we report that α-ketenyl radicals, which are generated by radical carbonylation of amino acetylenes, can be trapped by internal amino groups leading to the formation of lactam rings.[6] This work represents a useful concept that nucleophilic addition to a polar function of radical species can generate novel radical species.



(1)

Thus treatment of 4-pentynylpropylamine (**1d**) with tributyltin hydride as radical mediator (1.1 equiv.) under CO pressure (75 atm.) in the presence of AIBN (2,2′-azobisisobutyronitrile) as a radical initiator at 90 °C for 3 h gave a set of six-membered ring lactams. After chromatographic separation, unsaturated six-membered ring lactams **2d** (35%) and **3d** (37%) were obtained as major products, along with α-stannylmethyl lactam **4d** (6%) as a byproduct (Scheme 1). The stannylcarbonylation of **1d**, when coupled with the subsequent protodestannylation procedure (TMSCl (7 equiv.) plus MeOH, room temperature, 10 min) gave α-methylene lactam **3d** in 71% yield after isolation by silica gel chromatography.

In order to test the generality of the radical ring forming reaction, a variety of substrates were examined (Table 1). Method A corresponds to the stannylcarbonylation, whereas method B is a combined procedure of stannylcarbonylation (Method A) and subsequent protodestannylation. As shown in Table 1, the reaction permitted the efficient formation of five-, six-, seven-, and



Scheme 1 Carbonylation of 4-pentynylpropylamine.

eight-membered ring lactams. Primary alkynylamines gave rise to lactams having no alkyl substituent at the lactam nitrogen (runs 1, 4, 7, 10, and 11). It is interesting to note that the amount of the destannylated product **3** seems to increase as the ring size increases. With exception of 7-amino-1-heptyne (**1g**), saturated α-stannylmethyl lactams were observed as byproducts. These are most likely produced by further hydrostannylation of the initial α-methylene lactam products **3**. In a separate experiment, we confirmed that the eight-membered ring product **3g** did not undergo hydrostannylation using standard radical conditions (AIBN/Bu_3SnH), whereas five- and six-membered compounds **3a** and **3c** undergo smooth hydrostannylation leading to **4a** and **4c**, respectively.

Having these basic results in hand, we examined alkynes having cyclic amine moieties (Scheme 2). When alkynes **1h** and **1i**, having piperidine and tetrahydroisoquinoline moieties were subjected to method B, the corresponding bicyclic and tricyclic α-methylene lactams, **3h** and **3i** were obtained in 61% and 48% yields, respectively. Similarly, an alkynylamine **1j** derived from L-proline gave a chiral α-methylene lactam **3j** in 52% yield.

The formation of α-methylene lactams **3** in this study brings about intriguing mechanistic questions. We propose that these species are formed by a 1,4-H shift from 1-hydroxyallyl radicals, which are formed by addition of an amine NH bond to the ketene carbonyl. Scheme 3 illustrates such a mechanism using **1c** as the substrate. Thus, nucleophilic addition of the internal amino group to the carbonyl group of α-ketenyl radical **A** would give rise to zwitterionic intermediate **B**, which would give hydroxyallyl radical **C**. The subsequent 1,4-H shift from the hydroxyallyl radical **C**,[7] followed by β-elimination of tributyltin radical from the resulting radical **D**, would lead to the formation of α-methylene lactam **3c**.[8] The formation of α-stannylmethylene lactam **2c** requires a formal "oxidation" step, which serves as a chain termination step.[9] One possibility is hydrogen abstraction from the hydroxyallyl radical **C**.

In summary, five- to eight-membered ring lactams were prepared by free-radical mediated stannylcarbonylations of ω-alkynylamines. The nucleophilic trapping of the α-ketenyl radical by an amino group to give a hydroxyallyl radical and the 1,4-hydrogen shift would account for the formation of α-methylene lactams. We believe that the basic concept that nucleophilic trap of polar radical species can generate novel radical species would find many useful applications in synthesis.

† Electronic supplementary information (ESI) available: Experimental procedure and characterization for all compounds. See http://www.rsc.org/suppdata/cc/b4/b408746a/

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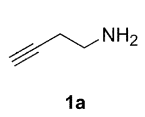
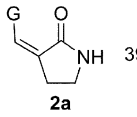
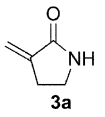
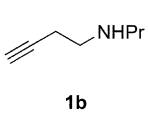
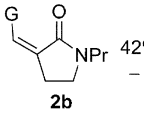
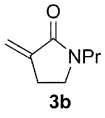
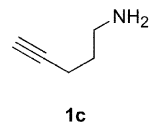
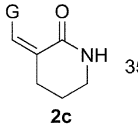
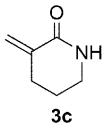
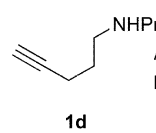
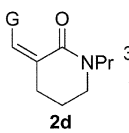
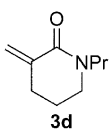
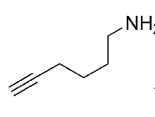
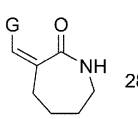
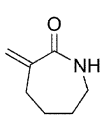
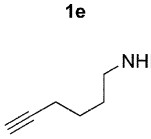
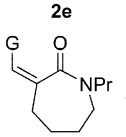
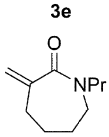
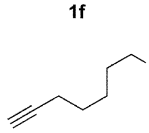
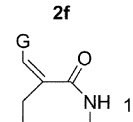
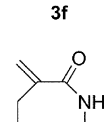
Table 1 Cyclizative carbonylation of alkynylamines **1** using tributyltin hydride

Run	**1**	Method[a]	Products[b] (G = Bu_3Sn), Yield (*E*/*Z*)[c]	
1	 **1a**	A	 **2a** 39% (23/77)	 **3a** 13%
2	 **1b**	A	 **2b** 42% (17/83)	 **3b** 13%
3		B	–	64%
4	 **1c**	A	 **2c** 35% (3/97)	 **3c** 21%
5	 **1d**	A	 **2d** 35% (2/98)	 **3d** 37%
6		B	–	71%
7	 **1e**	A	 **2e** 28% (23/77)	 **3e** 25%
8	 **1f**	A	 **2f** 21% (33/67)	 **3f** 50%
9		B	–	69%
10	 **1g**	A	 **2g** 10% (34/66)	 **3g** 44%
11		B	–	59%

[a] Method A: **1** (0.5–0.6 mmol), Bu_3SnH (0.53–1 mmol), CO (70–80 atm.), AIBN (0.1–0.15 mmol), benzene (50 mL), 90 °C, 3–8 h. Method B (Method A plus protodestannylation): After the stannylcarbonylation (Method A), crude reaction mixture was treated with TMSCl (3.5–5.0 mmol) in MeOH at room temperature. [b] With exceptions of runs 10 and 11, stannylmethyl lactams were formed as byproduct: **4a** (26%), **4b** (20%), **4c** (5%), **4d** (6%), **4e** (5%), **4f** (5%). *E*/*Z* ratio of **2** was determined by ^1H NMR. [c] Isolated yields by flash chromatography on SiO_2.

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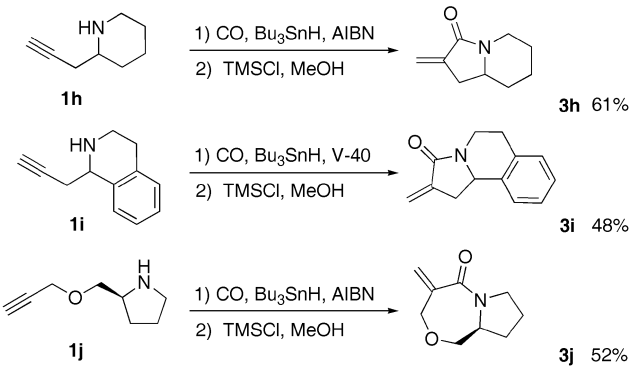
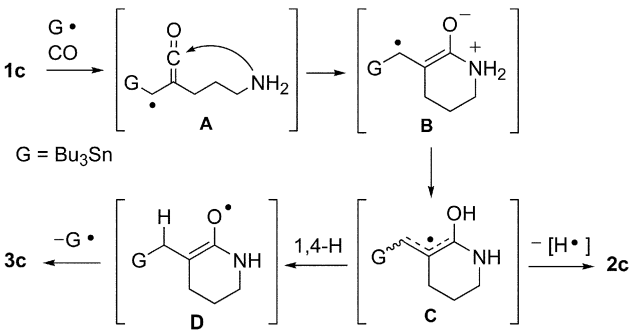
Notes and references

1 (*a*) A. D. Allen and T. T. Tidwell, *J. Org. Chem.*, 1999, **64**, 266 and references cited therein; (*b*) C. E. Cannizzaro, T. Strassner and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 2668; (*c*) H. Buschmann, H.-D. Scharf, N. Hoffmann and P. Esser, *Angew. Chem. Int. Ed. Engl.*, 1991, **30**, 477; (*d*) B. L. Hodous and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 10006.



Scheme 2 Preparation of bicyclic and tricyclic α-methylene lactams.



Scheme 3 Possible reaction mechanisms leading to unsaturated lactams.

2 (*a*) I. Ryu, T. Okuda, K. Nagahara, N. Kambe, M. Komatsu and N. Sonoda, *J. Org. Chem.*, 1997, **62**, 7550; (*b*) D. P. Curran, J. Sisko, A. Balog, N. Sonoda, K. Nagahara and I. Ryu, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1591.

3 For reviews on radical carbonylations, see: (*a*) I. Ryu and N. Sonoda, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 1050; (*b*) I. Ryu, N. Sonoda and D. P. Curran, *Chem. Rev.*, 1996, **96**, 177; (*c*) I. Ryu, *Chem. Soc. Rev.*, 2001, **30**, 16; (*d*) I. Ryu, *Chem. Rec.*, 2002, **4**, 249; (*e*) also see a review on acyl radicals: C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991.

4 (*a*) C. J. Hayas and G. Pattenden, *Tetrahedron Lett.*, 1996, **37**, 271; (*b*) G. Pattenden and L. Roberts, *Tetrahedron Lett.*, 1996, **37**, 4191; (*c*) G. Pattenden, L. Roberts and A. J. Blake, *J. Chem. Soc., Perkin Trans. 1*, 1998, 863.

5 MO calculations at the level of BHandHLYP/aug-cc-pVTZ//BHandHLYP/cc-pVDZ predicted that α-ketenyl radical ($CH_3CH(\bullet)CH{=}C{=}O$), are slightly more stable compared with the corresponding α,β-unsaturated acyl radical ($CH_3CH{=}CH{-}C(\bullet){=}O$).

6 We recently reported that acyl radical/imine cyclizations proceed *via* attack of the radical on nitrogen. (*a*) I. Ryu, K. Matsu, S. Minakata and M. Komatsu, *J. Am. Chem. Soc.*, 1998, **120**, 5838; (*b*) C. Falzon, I. Ryu and C. H. Schiesser, *Chem. Commun.*, 2002, 2338; (*c*) I. Ryu, H. Miyazato, H. Kuriyama, K. Matsu, M. Tojino, T. Fukuyama, S. Minakata and M. Komatsu, *J. Am. Chem. Soc.*, 2003, **125**, 5632; (*d*) M. Tojino, N. Ostuka, T. Fukuyama, H. Matsubara, C. H. Schiesser, H. Kuriyama, H. Miyazato, S. Minakata, M. Komatsu and I. Ryu, *Org. Biomol. Chem.*, 2003, **1**, 4262.

7 Radical 1,4-H shifts are rare, for examples, see: (*a*) M. Gulea, J. M. López-Romero, L. Fensterbank and M. Malacria, *Org. Lett.*, 2000, **2**, 2591; (*b*) P. C. Montevecci and M. C. Navacchia, *Tetrahedron Lett.*, 1996, **37**, 6583; (*c*) D. Crich, S. Sun and J. Brunckova, *J. Org. Chem.*, 1996, **61**, 605; (*d*) S.-H. Chen, S. Huang, Q. Gao, J. Golik and V. Farina, *J. Org. Chem.*, 1994, **59**, 1475.

8 Another possibility is direct protonation from canonical form of a radical anion **B** to give **D**.

9 A. L. J. Beckwith, V. W. Bowry, W. R. Bowman, E. Mann, J. Parr and J. M. D. Storey, *Angew. Chem. Int. Ed.*, 2004, **43**, 95.