ORGANIC LETTERS

2009
Vol. 11, No. 19
4454−4457

Synthesis of Ketene *N,N*-Acetals by Copper-Catalyzed Double-Amidation of 1,1-Dibromo-1-alkenes

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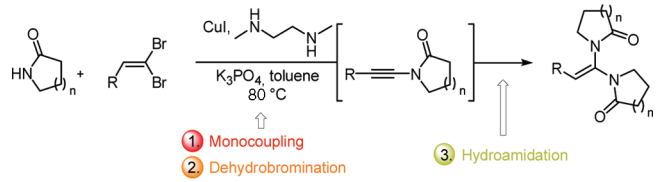
Received August 7, 2009

ABSTRACT



An efficient procedure for the preparation of ketene *N,N*-acetals by copper-catalyzed double amidation of 1,1-dibromo-1-alkenes is reported. The reaction was found to be general, and ketene aminals could be obtained in good yields when potassium phosphate in toluene was used at 80 °C. The reaction was found to proceed through a regioselective monocoupling reaction followed by dehydrobromination and hydroamidation.

Ketene *N,N*-acetals **1**, also named ketene aminals or 1,1-enediamines, are useful intermediates in organic synthesis. They combine two enamines in one functional group and exhibit significant nucleophilicity at C-2 due to the delocalization of the lone pairs of both nitrogen atoms into the double bond. However, their exceptional reactivity renders their synthesis, preparation, and storage difficult, which probably accounts for how seldom they have been used, especially compared to their *O,O*-, *S,S*-, *N,O*-, or *N,S* counterparts.[1,2]

Stable derivatives of ketene aminals include their push−pull derivatives **2** (Figure 1). While their synthesis and reactivity have been extensively studied over the past 20 years,[3,4] their applications are still limited, mostly because of the requirement for an electron-withdrawing group at C-2. An interesting alternative to balance the reactivity and stability of ketene *N,N*-acetals relies on the substitution of the nitrogen atoms by electron-withdrawing groups such as in **3**. These groups serve to diminish the electron-donating ability of the nitrogen atoms, therefore offering greater stability compared to traditional ketene aminals. In addition, it also allows substitution at C-2 with aryl, alkyl, or vinyl groups.

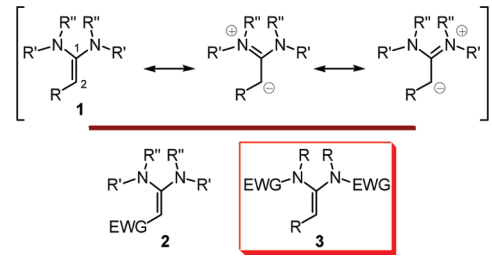


Figure 1. Resonance structures and stable derivatives of ketene *N,N*-acetals.

(1) For a general reference, see: Kantlehner, W. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; de Meijere, A., Ed.; Thieme: Stuttgart, 2005; Vol. 24, pp 571−746.

(2) For examples, see: (a) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027. (b) Ye, G.; Henry, W. P.; Chen, C.; Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2009**, *50*, 2135.

(3) For a review, see: Huang, Z. T.; Wang, M. X. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley: New York, 1994; pp 1303−1363.

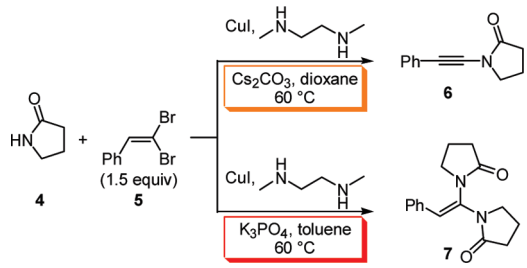
(4) For selected recent examples, see: (a) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.; Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. *J. Org. Chem.* **2004**, *69*, 188. (b) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, 1825. (c) Naito, H.; Hata, T.; Urabe, H. *Tetrahedron Lett.* **2008**, *49*, 2298. (d) Yaqub, M.; Yu, C.-Y.; Jia, Y.-M.; Huang, Z.-T. *Synlett* **2008**, 1357.

10.1021/ol901831s CCC: $40.75
Published on Web 09/02/2009

While these stable derivatives clearly hold great potential in organic synthesis, a careful examination of the literature reveals a lack of general methods for their preparation.[5] In this context, we report a general and straightforward procedure for the preparation of electron-deficient ketene *N*,*N*-acetals **3** by copper-catalyzed double amidation of 1,1-dibromo-1-alkenes.

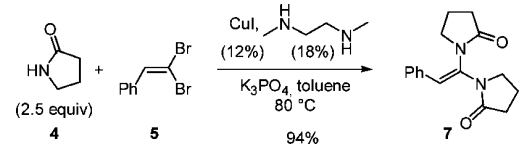
Drawing from recent experiences in the field of copper-catalyzed cross-coupling reactions,[6,7] and in the course of our investigations on the copper-catalyzed cross-coupling between 1,1-dibromo-1-alkenes and *N*-nucleophiles,[8,9] we found that ketene *N*,*N*-acetals could be cleanly isolated as the sole products. Indeed, while the copper-catalyzed (12% CuI, 18% *N*,*N*′-dimethylethylenediamine) reaction between lactam **4** and dibromide **5** cleanly gave the expected ynamide **6** when cesium carbonate in dioxane was used, we unexpectedly isolated ketene acetal **7** by switching to potassium phosphate in toluene (Scheme 1).[10]

Scheme 1. Ketene *N*,*N*-Acetals from 1,1-Dibromo-1-alkenes



Motivated by this encouraging result and by the lack of general synthetic methods for the preparation of electron-deficient ketene *N*,*N*-acetals such as **7**, we briefly optimized the reaction conditions and found that it was best performed at 80 °C for 20−24 h, using a slight excess (2.5 equiv) of γ-lactam (Scheme 2). Under these conditions, ketene aminal **7** could be

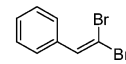
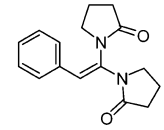
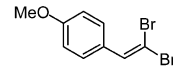
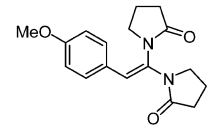
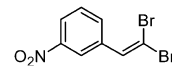
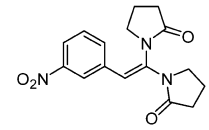
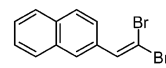
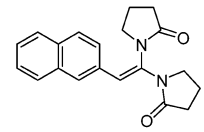
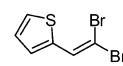
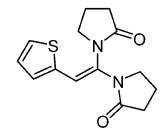
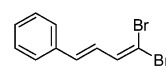
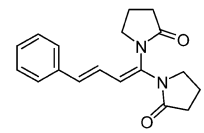
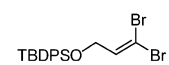
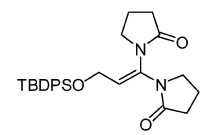
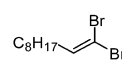
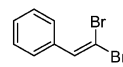
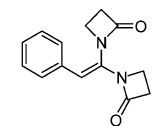
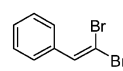
Scheme 2. Optimized Reaction Conditions for the Synthesis of Ketene *N*,*N*-Acetals from 1,1-Dibromo-1-alkenes



obtained in 94% yield after simple filtration of the crude reaction mixture and removal of excess pyrrolidin-2-one.

With these optimized conditions in hand, the scope of the reaction with various 1,1-dibromo-1-alkenes was next investigated. Results from these studies are shown in Table 1. A variety of ketene *N*,*N*-acetals could be obtained in moderate to good yields.[11] The reaction was found to be compatible with a variety of aromatic groups, including heteroaromatic compounds such

Table 1. Scope and Limitations[a]

entry	amide	1,1-dibromo-1-alkene	ketene *N*,*N*-acetal	yield[b]
1				94% (88%[c])
2				56%
3				60%
4				58%
5				73%
6				85%
7				51%
8			–	–[d]
9				84%
10			–	NR[e]

[a] Conditions: CuI (12 mol %), *N*,*N*′-dimethylethylenediamine (18 mol %), K_3PO_4 (3 equiv), toluene (0.1 mol·L^{-1}), 80 °C, 20−24 h. [b] Yield of pure, isolated product. [c] Reaction performed on a 2 g scale. [d] Decomposition of the dibromide. [e] No reaction.

as thiophene (Table 1, entry 5), and the presence of electron-withdrawing (Table 1, entry 3) or donating (Table 1, entry 2) groups had virtually no effect on the reaction.

Cinnamaldehyde-derived dibromide was also found to be an excellent reaction partner, providing the corresponding styryl-substituted ketene aminal in excellent yield (Table 1, entry 6).

(5) Ketene *N*,*N*-acetals related to **3** have been prepared by acylation of acetamidines. See: (a) Miescher, K.; Marxer, A.; Urech, E. *Helv. Chim. Acta* **1951**, *34*, 16. (b) Ono, M.; Tanaka, H.; Hayakawa, K.; Tamura, S. *Chem. Pharm. Bull.* **1983**, *31*, 3534.

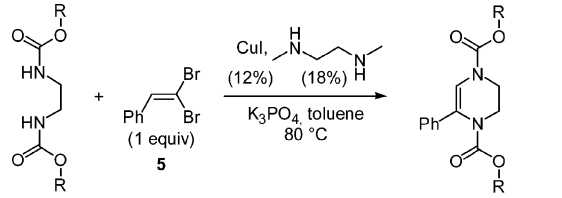
The double amidation of alkyl-substituted dibromoalkenes turned out to be more substrate-dependent since only the bulky TBDSP-protected hydroxymethylene was tolerated (Table 1, entry 7). In the case of a smaller group such as an octyl, extensive degradation was observed (Table 1, entry 8), which could be attributed to the higher unstability of the corresponding ketene aminal under the reaction conditions.

As expected, β-lactam was also smoothly transformed to the corresponding aminal (Table 1, entry 9), while acyclic secondary amides such as *N*-methylacetamide, which are definitely not the best reaction partners in copper-catalyzed cross-coupling reactions, were not suitable substrates (Table 1, entry 10).

We finally checked that the double amidation was not limited to the small scale used for the coupling reactions described above. Gratifyingly, it could be conveniently performed on a 2 g scale, and ketene *N*,*N*-acetal **7** could be isolated in 88% yield (Table 1, entry 1).

To further evaluate the scope of the double amidation and to gain insight into its mechanism, the reactivity of protected 1,2-diamines was next examined. Carbamate-protected diamines **8a** (R = Me) and **8b** (R = allyl) were selected for solubility purposes and reacted with dibromide **5** under our standard conditions (Scheme 3). Instead of the expected

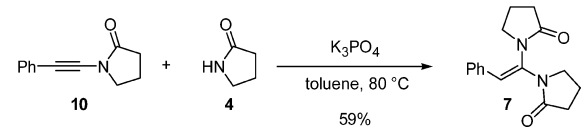
Scheme 3. Copper-Catalyzed Coupling of Protected 1,2-Diamines with 1,1-Dibromo-1-alkenes



cyclic ketene aminals, protected tetrahydropyrazine derivatives **9a** and **9b** were isolated in moderate yields, which is in accordance with similar results from the Urabe group.[12]

The formation of tetrahydropyrazines starting from protected 1,2-diamines shows that the formation of ketene *N*,*N*-acetals from 1,1-dibromo-1-alkenes is probably more than just a simple result from two consecutive copper-catalyzed C(sp^2)−N bond formations. Driven by these results and by the feeling that ketene aminals might arise from the hydroamidation of intermediate ynamides,[13] a reaction that had already been observed by Skrydstrup and co-workers,[14] ynamide **10** was reacted with 1 equiv of lactam **4** and excess potassium phosphate. As suspected, the hydroamidation product **7** was isolated as a single regioisomer in 59% yield (Scheme 4).

Scheme 4. Hydroamidation of Ynamide to Ketene *N*,*N*-Acetal



On the basis of these results, it is reasonable to assume that this double amidation of 1,1-dibromo-1-alkenes proceeds in three steps (Figure 2) and that ynamides are formed as

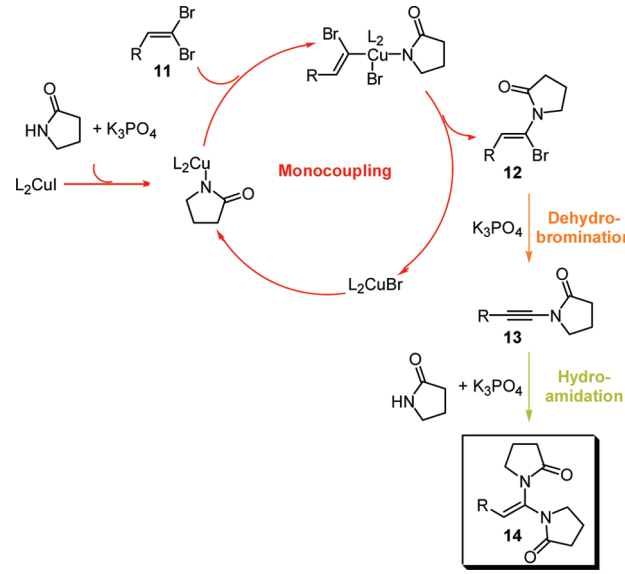


Figure 2. Mechanism of the copper-catalyzed double amidation of 1,1-dibromo-1-alkenes.

intermediates. The first steps would involve a regioselective monocoupling at the more reactive *trans* C−Br bond of dibromides **11** followed by dehydrobromination to ynamides **13**.[8] Then, a regioselective hydroamidation,[14] with introduction of the lactam ring at the more electrophilic C(sp)

(6) (a) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572. (b) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2007**, *72*, 9003. (c) Toumi, M.; Couty, F.; Evano, G. *Synlett* **2008**, 29. (d) Coste, A.; Toumi, M.; Wright, K.; Razafimahaléo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841. (e) Toumi, M.; Rincheval, V.; Young, A.; Gergeres, D.; Turos, E.; Couty, F.; Mignotte, B.; Evano, G. *Eur. J. Org. Chem.* **2009**, 3368. (f) Evano, G.; Toumi, M.; Coste, A. *Chem. Commun.* **2009**, 4166.

(7) For recent reviews, see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.

(8) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381.

(9) For leading references on the copper-catalyzed amidation of vinyl halides, see : (a) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (d) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (e) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117.

(10) For metal-catalyzed reactions of vinyl dibromides with N-nucleophiles, see: (a) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549. (b) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (c) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955. (d) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

center,[15] would account for the formation of ketene *N*,*N*-acetals **14**. In the case of protected 1,2-diamines, formation of tetrahydropyrazines would result from a 6-*endo-dig* cyclization being more favorable compared to the 5-*exo-dig* one.[12]

In conclusion, we have developed an efficient synthesis of ketene *N*,*N*-acetals by copper-catalyzed double amidation of 1,1-dibromo-1-alkenes. The reaction was found to proceed through a cross-coupling/dehydrobromination/hydroamidation sequence. Further applications of this method and of the ketene aminals obtained are underway and will be reported in due course

Acknowledgment. We thank the CNRS and the ANR (project ProteInh) for financial support. A.C. acknowledges the National Cancer Institute for a graduate fellowship.

Supporting Information Available: Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) As pointed out by one reviewer, the yield seems to depend on the nature of the aromatic group of the dibromide. The basis for this difference in reactivity is, however, not well understood at this stage.

(12) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.

(13) For reviews on ynamides and electron-deficient ynamines, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.

(14) Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 9447.

(15) For introduction of a nucleophile at the α-position of ynamides, see, for example: Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547. (b) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047. (c) Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.