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Copper-Catalyzed 1,2-Double Amination of 1-Halo-1-alkynes. Concise Synthesis of Protected Tetrahydropyrazines and Related Heterocyclic Compounds

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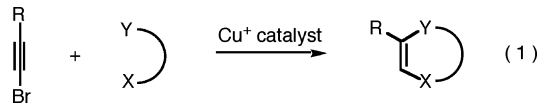
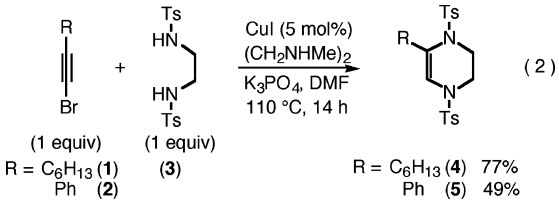
Unsaturated heterocyclic compounds are useful synthetic intermediates as well as important structural units found in natural and artificial products.[1] Their synthesis requires proper alignment of heteroatoms as well as unsaturation at a defined position in the ring system. This is often a critical issue, especially when the heterocycle has multiple heteroatoms.[1] Here we report a concise preparation of 1,4-diaza(or partially oxa)-2-cycloalkenes based on a new copper-catalyzed double amination of haloacetylenes, as formulated in eq 1 (X = N; Y = N or O).[2,3]



(1)

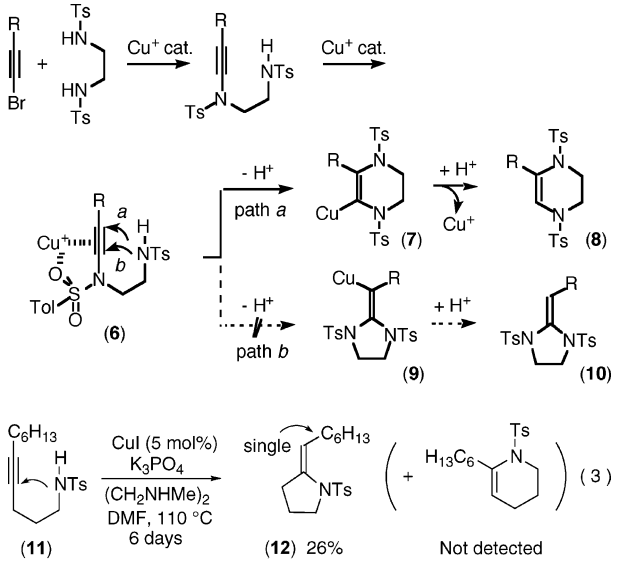
While investigating copper-catalyzed coupling of sulfonamides and haloacetylenes,[4] we attempted *N*,*N*′-dialkynylation of diamine derivative **3** (see eq 2, Ts = *p*-$MeC_6H_4SO_2$-). However, we were unable to obtain more than a trace amount of the expected dialkynylated product, and the actual isolated product was a 1,2,3,4-tetrahydropyrazine derivative **4**. Equation 2 shows the representative reaction conditions for the preparation of **4** and **5** from aliphatic and aromatic acetylenes **1** and **2**, respectively. The structure of **5** was confirmed by comparison with an authentic sample prepared by an alternative method.[5] As unprotected 1,2,3,4-tetrahydropyrazines, which are enamines doubly activated by two nitrogen atoms, are unstable compounds, this simple one-step method is suitable for the direct preparation of their protected surrogates.[6]



(2)

The proposed reaction course of eq 2 is shown in Scheme 1. After the first alkynylation of sulfonamide with haloacetylene proceeded as described previously,[4] the second amination of the acetylenic bond in **6** (Tol = *p*-MeC_6H_4-) proceeded in a 6-*endo*-*dig* manner under copper catalysis to produce **7** (path *a*), protonation of which completed the catalytic cycle to afford the observed product **8**. Note that the formation of isomeric tetrahydroimidazole **10** via the cyclization of 5-*exo*-*dig* mode (**6** → **9**, path *b*) was not observed.[7−9] The sulfonylamino group bearing the acetylene moiety of **6** should play an important role in effecting the *endo*-type ring closure, most likely due to coordination to the copper salt as depicted in **6**, because the control reaction of eq 3, where the carbon analogue **11** exclusively and much more slowly underwent 5-*exo*-*dig* ring closure to give pyrrolidine derivative **12** under the same conditions as eq 2 except for the reaction period.[10]

Scheme 1. Proposed Reaction Course



(3)

This reaction shows reasonable generality for the preparation of tetrahydropyrazines.[5] Both aliphatic and aromatic acetylenes afforded the desired products **4**, **5**, and **20** as shown in eq 2 and entries 1−3 of Table 1, where an ester group remains unattacked. Although the silyl group in **14** did not survive the reaction conditions, product **21** having a terminal acetylene was obtained (entry 4). Branched 1,2-diamine **15** afforded a mixture of two isomers **22**, where the methyl group shows little influence on product composition, but the isomers were separable by flash chromatography on silica gel (entry 5). Sterically more congested cyclic diamine derivative **16** still afforded the bicyclic heterocycle **23** with no decrease in product yield. It should be emphasized that the synthetic protocol shown in eq 1 proved to be applicable for the preparation of broader types of heterocycles. For example, 1,3-propanediamine derivatives **17** and **18** afforded the corresponding seven-membered heterocycles **24** and **25** (entries 7 and 8), where the hydroxy group in **18** did not need protection. On the contrary, the hydroxy group in *N*-tosylethanolamine **19** took part in the reaction to give a six-membered *N*,*O*-heterocycle **26** in a regioselective manner. These observations show that a heteroatom functional group at a suitable position could work as the second nucleophile in eq 2.

A convenient modification of the above transformation is that dibromoolefins **27**−**30**, readily prepared from the corresponding aldehydes,[11] work equally well in place of bromoacetylenes to produce tetrahydropyrazines **31**−**34** in good yields, as shown in eq 4. The reaction most likely involves in situ formation of

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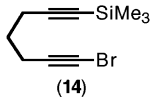
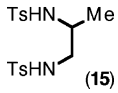
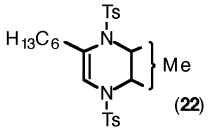
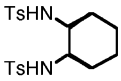
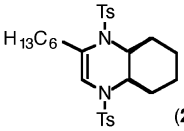
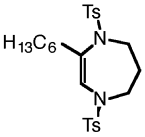
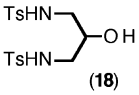
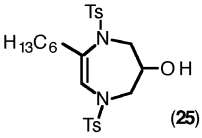
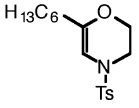
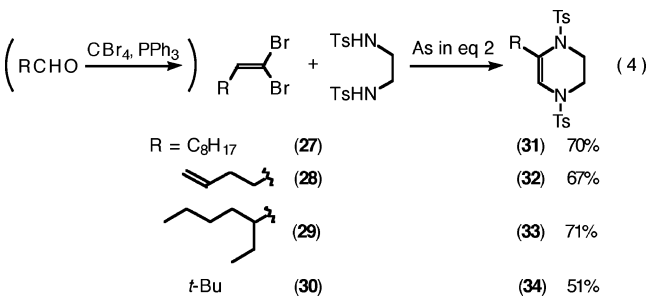
Table 1. Preparation of Unsaturated Heterocycles According to eq 2

Entry	Acetylene	Diamine	Product	Yield (%)[a]
1	R = C_6H_{13} (**1**)	(**3**)	R = C_6H_{13} (**4**)	77
2	Ph (**2**)		Ph (**5**)	49
3	$(CH_2)_3CO_2Et$ (**13**)		$(CH_2)_3CO_2Et$ (**20**)	62
4	 (**14**)	**3**	(**21**)	47
5	**1**	 (**15**)	 (**22**)	68[b]
6	**1**	 (**16**)	 (**23**)	63
7	**1**	 (**17**)	 (**24**)	77[c]
8	**1**	 (**18**)	 (**25**)	71
9	**1**	 (**19**)	 (**26**)	71[d]

[a] Isolated yields, which are not necessarily optimized. [b] The methyl positions have not been assigned to major and minor isomers, which were separable by silica gel chromatography in 41% and 27% yields, respectively. [c] *N*,*N*′-Di(1-octynyl)-*N*,*N*′-di(*p*-toluenesulfonyl)-1,3-propanediamine was also formed in 13% yield. [d] This reaction was performed at 130 °C for 21 h.

bromoacetylenes via dehydrobromination of dibromoolefins under the basic reaction conditions prior to the catalytic cycle in Scheme 1.[12]



In conclusion, we report a simple procedure for the facile preparation of unsaturated heterocyclic compounds having two heteroatoms. The scope and limitations of the reaction itself and the synthetic applications of the products obtained are now under investigation.

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Supporting Information Available: Experimental procedures and physical properties of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For a recent preparation of similar heterocycles starting with terminal acetylenes via olefin isomerization, see: Zulys, A.; Dochnahl, M.; Hollmann, D.; Löhnwitz, K.; Herrmann, J.-S.; Roesky, P. W.; Blechert, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7794−7798.

(4) (a) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727−729. (b) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011−4014. (c) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368−2369. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669.

(5) For details, see the Supporting Information.

(6) The use of sulfonamides is essential for this reaction, as $(CH_2NHMs)_2$ in place of **3** afforded the desired product like **4** in 58% yield, but $(CH_2NHR)_2$ (R = Ac or Boc) did not give such products. For deprotection of sulfonamides, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 379−385.

(7) The direction of this ring closure (paths *a* or *b*) is hardly predictable a priori based on the available data such as those in refs 8 and 9.

(8) Both 6-*endo-dig* and 5-*exo-dig* are favorable modes for ring closure. For Baldwin's rule, see: (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. For 5-*exo-dig* cyclization with a nitrogen nucleophile, see: (b) Schomaker, J. M.; Geiser, A. R.; Huang, R.; Borhan, B. *J. Am. Chem. Soc.* **2007**, *129*, 3794−3795. For 6-*endo-dig* cyclization, see: (c) Yanada, R.; Obika, S.; Kono, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3822−3825.

(9) A nucleophile could be introduced to either 1- or 2-position of 1-(sulfonylamino)-1-alkynes depending upon the kind of reactions. For a reaction at the 1-position, see: (a) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047−1050. For the 2-position, see: (b) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098−2100. For reviews on the chemistry of (1-alkynyl)amine derivatives, see: (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455−1475. (d) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575−7606. (e) Hsung, R. P., Ed. *Tetrahedron* **2006**, *62*, 3783−3938.

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