

Synthesis of Tertiary Propargylamines by Sequential Reactions of in Situ Generated Thioiminium Salts with Organolithium and -magnesium Reagents

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It would become a useful synthetic reaction if two kinds of organometallic reagents¹ are incorporated into an electrophilic organic molecule in one pot. It is important to choose appropriate organometallic reagents of suitable nucleophilicity to achieve such a stepwise transformation. During the course of our studies on thio- and selenoamides,² we have found that thioiminium salts generated in situ from thioamides and methyl triflate (MeOTf) are highly electrophilic acyl equivalents.^{2f} We report here a new carbon-carbon bond forming reaction in which organolithium and -magnesium reagents are sequentially incorporated into thioiminium salts. A variety of tertiary propargylamines are conveniently synthesized by this protocol.

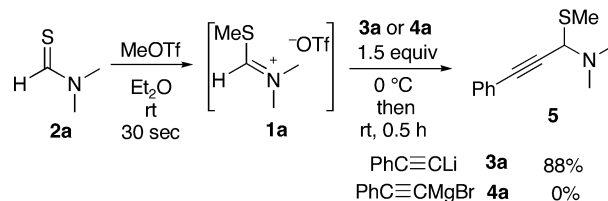
Initially, the reaction of in situ generated thioiminium salt **1a** with various organometallic reagents was tested (Scheme 1). As a result, a substantial difference in reactivity was observed between alkynyllithium and -magnesium reagents, both among the most common organometallics. Whereas the reaction of the salt **1a** with (phenylethynyl)lithium (**3a**) selectively gave *S,N*-acetal **5** at a purity higher than 95%,^{3,4} the use of (phenylethynyl)magnesium bromide (**4a**) afforded, after aqueous workup, unreacted phenylacetylene mainly with decomposition products of **1a**.

Next, the second reaction of *S,N*-acetal **5** thus obtained from **1a** and **3a** was examined also with the alkynyllithium and -magnesium reagents (Scheme 2). Notably, the reactivity order was reversed. (Phenylethynyl)lithium (**3a**) failed to react with the *S,N*-acetal **5**.⁵ In contrast, *S,N*-acetal **5** was selectively converted to 3-amino-1,4-diyne **6** by the reaction with (phenylethynyl)magnesium bromide (**4a**).⁶ We assume that thioiminium salt **1a** reacts with more ionic alkynyllithium rather than with alkynylmagnesium bromide. On the other hand, the neutral *S,N*-acetal **5** prefers more Lewis acidic alkynylmagnesium bromide as the reacting partner.

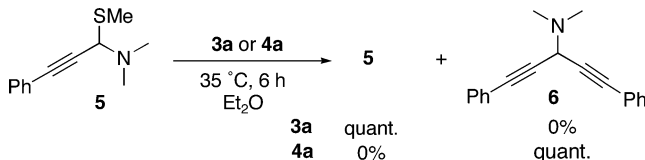
On the basis of these results, we envisioned sequential additions of two different alkynylmetals to thioiminium salt **1** would present a reaction forming two carbon-carbon bonds with a high efficiency. In fact, the salt **1a** was sequentially reacted with (phenylethynyl)lithium (**3a**, 1.5 equiv) and ethynylmagnesium bromide (**4b**, 1.5 equiv) to give 3-amino-1,4-diyne **7** in 91% yield (Scheme 3). A product that incorporated two molecules of **3a** was not formed at all even with the use of excess **3a**.

We examined the generality of the present sequential protocol and found a wide applicability (Table 1). Unsymmetrically substituted 3-amino-1,4-diyne **8** was efficiently obtained by reacting different alkynylmetals (entry 1). Not only alkynylmagnesium bromides, but a wide range of organomagnesium reagents successfully reacted with the intermediate *S,N*-acetals. A variety of alkynyllithiums **3a–3d** gave propargylamines in good yields (entries 2–4, 6, 8, 11, and 12).⁸ Ene-yne are useful compounds for making various cyclic frameworks. These classes of compounds were

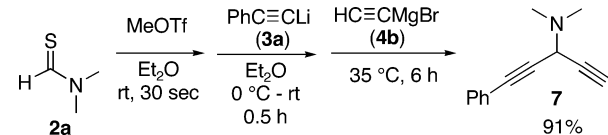
Scheme 1



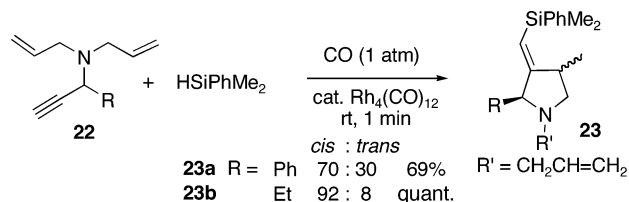
Scheme 2



Scheme 3



Scheme 4



conveniently synthesized by the present reaction (entries 5, 7, 9, 10, 13, and 14), although they are otherwise hardly accessible.^{9,10} Thioacetamide **2c** and aromatic thioamides **2d–2f** worked well as the starting thioamide to give tertiary amines bearing a tertiary carbon atom adjacent to a nitrogen atom (entries 11–14).

A wide variety of elegant methods for synthesizing propargylamines via the addition of alkynylmetals to imines, iminium salts, and enamines¹¹ have been developed, but they use single organometallic reagents. In contrast, in the present reaction, two different organometallic reagents are nucleophilically introduced to the carbon atom of the thiocarbonyl group of thioamides **2** in one operation.

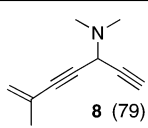
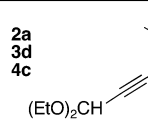
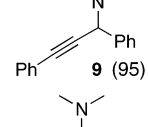
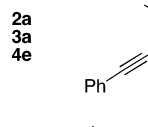
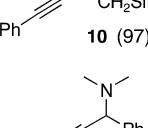
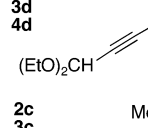
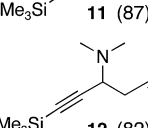

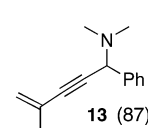
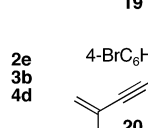
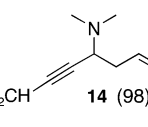
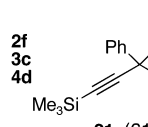
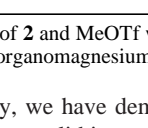
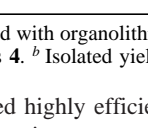
Finally, propargylamines obtained in the present reaction were subjected to silylcarbocyclization.¹² *N,N*-Diallyl propargylamines **22** were reacted with PhMe₂SiH in the presence of a catalytic amount of Rh₄(CO)₁₂ to give 2,3,4-trisubstituted pyrrolidines **23** with high regio- and stereoselectivity (Scheme 4).

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Table 1. Sequential Reactions of in Situ Generated Thioiminium Salts **1** from **2** and MeOTf with **3** and **4**^a

R ¹	R ²	R ³	R ⁴
2a	H	3a C≡CPh	4b C≡CH
2b	CH ₂ CH=CH ₂	3b C≡CC(CH ₃)=CH ₂	4c Ph
2c	Me	3c C≡CSiMe ₃	4d CH ₂ CH=CH ₂
2d	Ph	3d C≡CCH(OEt) ₂	4e CH=CH ₂
2e	C ₆ H ₄ -Br-4		4f Et
2f	Ph		4g CH ₂ SiMe ₃

entry	substrate	product yield (%) ^b	entry	substrate	product yield (%) ^b
1	2a 3b 4b		8	2a 3d 4c	
2	2a 3a 4c		9	2a 3a 4e	
3	2a 3a 4g		10	2b 3d 4d	
4	2a 3c 4c		11	2c 3c 4c	
5	2a 3c 4d		12	2d 3c 4f	
6	2a 3b 4c		13	2e 3b 4d	
7	2a 3d 4d		14	2f 3c 4d	

^a A mixture of **2** and MeOTf was stirred with organolithium reagents **3**, and then with organomagnesium reagents **4**. ^b Isolated yields.

In summary, we have demonstrated highly efficient sequential reactions of organolithium and -magnesium reagents with in situ

generated thioiminium salts leading to tertiary propargylamines. The substantial differences in the reactivity of these two reagents toward thioiminium salts and *S,N*-acetals have played important roles in achieving the transformations. The versatility of these starting materials allows for the construction of diverse sets of tertiary propargylamines. Further mechanistic studies on the present reactions and synthetic applications of thioiminium salts and *S,N*-acetals are in progress.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (4) Further purification of **5** through column chromatography was not successful, and the decomposition products of **5** were recovered.
- (5) This difference in the reactivity of these reagents is in marked contrast to the general understanding that organolithium and -magnesium reagents competitively react with carbonyl compounds. Furthermore, the reaction of a cyclic *O,N*-acetal with organolithium reagents takes place. See: (a) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (b) Itoh, T.; Yamazaki, N.; Kibayashi, C. *Org. Lett.* **2002**, *4*, 2469.
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