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One-Pot Synthesis of 1,3-Disubstituted Allenes from 1-Alkynes, Aldehydes, and Morpholine

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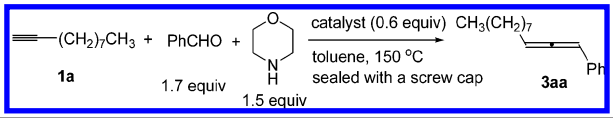
During the past 10−15 years, allenes have been shown to be versatile intermediates in organic synthesis.[1,2] In addition to this, many natural products and pharmaceuticals with an allene moiety have been identified.[3] Thus, synthetic methods for allenes from readily available organic compounds are of high interest for chemists to use as the starting materials in their target synthesis.[4] Crabbé et al. reported the first CuBr-mediated reaction to form terminal allenes from 1-alkynes and formaldehyde in the presence of diisopropylamine.[5a,b] Based on this, recently we have developed a modified one-step procedure for converting terminal alkynes to terminal allenes in higher yields by applying CuI, paraformaldehyde, and dicyclohexylamine.[5c] However, it should be noted that the reaction is limited to paraformaldehyde: no allene was formed when other aldehydes were used. Bertrand et al. employed a cationic gold(I) complex for the catalytic coupling of enamines and terminal alkynes to yield a wide range of nonterminal allenes.[6] Wong and Che et al. reported the synthesis of disubstituted allenes from propargylic amines.[7] Thus, a new one-step protocol, which just involves the easily available aldehydes beyond paraformaldehyde and terminal alkynes, is highly desirable. Herein, we wish to report the realization of such a protocol, which uses cost-effective ZnI_2 and morpholine affording 1,3-disubstituted allenes from aromatic or aliphatic aldehydes and terminal alkynes.[8]

Based on our experience in this area, we chose 1-decyne, benzaldehyde, and morpholine as the starting point: with $FeCl_3$ or MgI_2, the formation of allene **3aa** was not observed (entries 1 and 2, Table 1). After extensive screening, it is fortunate to observe that when CdI_2 was used, allene **3aa** was formed in 36% yield (entry 3, Table 1)! Further screening led to the observation that cheaper ZnI_2 may play the same role affording **3aa** in a slightly higher yield (entry 4, Table 1). ZnX_2 (Cl or Br) is not effective; $Zn(OTf)_2$ afforded **3aa** in 19% NMR yield after 4.8 h.

Table 1. Attempted One-Step Synthesis of Allene **3aa** from 1-Decyne and Benzaldehyde[a]



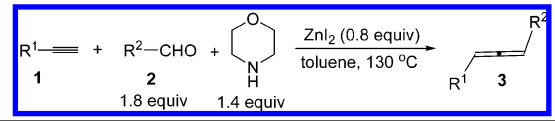
entry	cat.	yield of **3aa** (%)/time (h)	entry	cat.	yield of **3aa** (%)/time (h)
1	$FeCl_3$	0/20	4	ZnI_2	38[b]/2.6
2	MgI_2	0/2	5	$ZnCl_2$	16[c]/5.5
3	CdI_2	36[b]/2.6	6	$ZnBr_2$	17[c]/5.5

[a] The reactions were carried out in 0.3 mmol scale in 0.9 mL of toluene. [b] Isolated yield. [c] NMR yield.

Encouraged by these results, we started to study the solvent effect (Table S1): no product was formed in $MeNO_2$, $CHCl_3$, DCE, or MeCN; toluene turned out to be the best. Further screening on the structures of amines led us to find that the most appropriate amine for the allene forming reaction is morpholine; piperidine is less effective (Table S2). Then the experimental parameters have been thoroughly screened to improve the yield (Table S3), and we observed that the reaction of 1-alkyne with 1.8 equiv of aldehyde, 1.4 equiv of morpholine, and 0.8 equiv of ZnI_2 in toluene at 130 °C gave allene **3aa** in the highest yield (Table S3, entry 7). Further study on the concentration effect led us to observe that the reaction of a 1 mmol scale of **1a** in 1, 3, 5, or 7 mL of toluene afforded **3aa** in 37, 56, 65, 61% isolated yields, respectively, which indicates that the concentration has some influence on the reaction.

After these optimizations, the substrate scope and generality of the reaction have been investigated and the typical results are summarized in Table 2: simple terminal alkynes reacted with benzaldehyde or substituted benzaldehydes bearing *p*-Cl, *p*-Br, and *p*-CF_3 functionalities to afford the corresponding allenes in moderate yields (entries 1−3 and 5−8). Heteromatic aldehyde thiophene-3-carboaldehyde could also be applied in the transformation, albeit with a relatively lower yield (entry 4). Moreover, aliphatic aldehydes may also be used, although a longer time or a higher temperature is needed (entries 10 and 11).

Table 2. ZnI_2-Promoted Reaction of Various 1-Alkynes with Aldehydes in the Presence of Morpholine[a]



entry	R^1 (**1**); R^2 (**2**)	time (h)	yield of **3** (%)
1[b]	$CH_3(CH_2)_7$ (**1a**); Ph (**2a**)	7.2	65 (**3aa**)
2	**1a**; *p*-ClC_6H_4 (**2b**)	6.7	52 (**3ab**)
3	**1a**; *p*-BrC_6H_4 (**2c**)	6.8	53 (**3ac**)
4	**1a**; 3-thienyl (**2d**)	13.7	30 (**3ad**)
5[b]	$CH_3(CH_2)_9$ (**1b**); **2a**	9.7	57 (**3ba**)
6	**1b**; *p*-ClC_6H_4 (**2b**)	8.5	53 (**3bb**)
7	**1b**; *p*-BrC_6H_4 (**2c**)	8.5	55 (**3bc**)
8	**1b**; *p*-$F_3CC_6H_4$ (**2e**)	9.0	58 (**3be**)
9[b]	*p*-$O_2NC_6H_4CH_2O(CH_2)_2$ (**1c**); **2a**	9.2	51 (**3ca**)
10[b,c]	*p*-$O_2NC_6H_4CH_2OCH_2$ (**1d**); *i*-Pr (**2f**)	22	56 (**3df**)
11[b,c,d]	*p*-$O_2NC_6H_4CH_2OCH_2$ (**1d**); *n*-Bu (**2g**)	6	42 (**3dg**)

[a] The reactions were carried out in 1.0 mmol scale in 3 mL of toluene. [b] The reactions were carried out in 1.0 mmol scale in 5 mL of toluene. [c] The reaction was carried out in a reaction tube sealed with a screw cap. [d] The reaction was carried out at 150 °C.

As we know, 2,3-allenols and 2,3-allenyl amines are usful in organic synthesis.[1,2] 4-Substituted 2,3-allenyl alcohols or amines[4c,9,10] could also be obtained as a mixture of ∼1:1 diastereoisomers through this protocol: the reaction of terminal propargylic alcohols (**4a**−**c**) with benzaldehyde afforded the corresponding 2,3-allenols **5a**−**c** in 52−62% isolated yields; the reaction of terminal propargylic tosylamide **6** with

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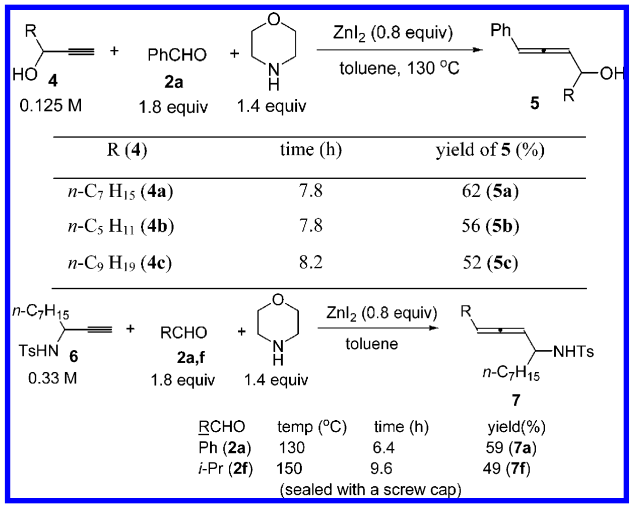
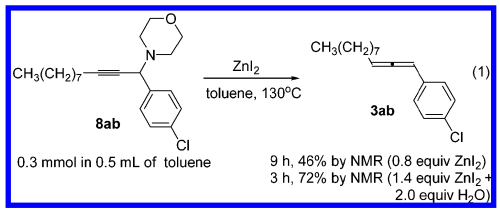
benzaldehyde or *i*-PrCHO afforded the corresponding 2,3-allenyl tosylamides **7a** and **7f** in 59% and 49% isolated yields, respectively (Scheme 1).

Scheme 1

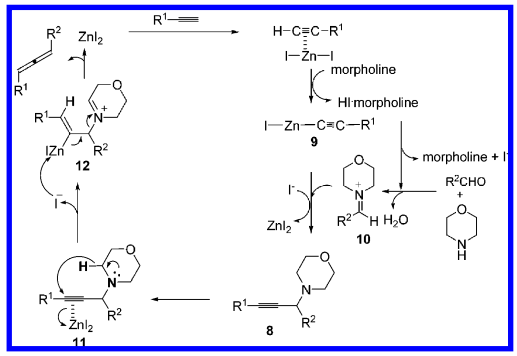


Propargylic amine **8ab** was formed in the reaction of 1-decyne, *p*-chlorobenzaldehyde, and morpholine. When a solution of **8ab** and ZnI_2 in toluene was heated at 130 °C, allene **3ab** was formed in 46% NMR yield (eq 1). In the presence of 2 equiv of water and 1.4 equiv of ZnI_2, the yield of **3ab** was 72%, indicating the importance of water *in situ* generated during the formation of **8ab** and the loading of ZnI_2. No reaction was observed in the absence of ZnI_2.



Based on these data and the previous understanding of this type of reactions,[5,7,11] a mechanism has been proposed (Scheme 2): The reaction of ZnI_2 with terminal alkyne generates the corresponding 1-alkynyl zinc species **9**, which then reacts with the iminium ion **10** formed *in situ* from an aldehyde and morpholine to yield the corresponding propargylic amine intermediate **8** and regenerate ZnI_2. ZnI_2 coordinates to the carbon−carbon triple bond in **8** to give complex **11,** which undergoes a 1,5-hydride transfer[12] and β-elimination to afford the allene product. Although the data listed in Table S2 seem to indicate that morpholine is superior to other electron-rich amines, more detailed studies are required to fully understand this transformation, and the reaction pathway outlined in Scheme 2 should be considered a mechanistic framework.

Scheme 2



In conclusion, we have established an efficient ZnI_2-mediated protocol for one-pot synthesis of 1,3-disubstituted allenes from 1-alkynes, aldehydes, and morpholine. Although the mechanism needs further attention, due to the easy availability of all the reagents used and potential of the allene products,[1−3] this reaction will be of high interest to the scientific community. Further investigations in this area are being pursued in our laboratory.

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Supporting Information Available: Spectroscopic data and general procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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