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Alkynylation of carbonyl compounds with terminal acetylenes promoted by $ZnCl_2$ and Et_3N: simple, mild and efficient preparation of propargylic alcohols

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Abstract—A mild and efficient addition of terminal acetylenes to carbonyl compounds in the presence of $ZnCl_2$ and Et_3N gives propargylic alcohols in good to high yields.

Propargylic alcohols are often key intermediates in the synthesis of many natural products such as prostaglandins, steroids, carotenoids etc.[1] The most common method to obtain propargylic alcohols is the addition of alkynylmetals to aldehydes and ketones. However, the high reactivity and strong basicity of many alkynylmetals including alkynyl-Li, Na, K and Mg, also cause undesired side reactions.[2] Several improved procedures including addition of alkynyl-B,[3] Al,[4] Ce[5] and V[6] prepared from the transmetallation of alkali or alkali earth metal derivatives to carbonyl compounds have been reported. However, these methods are not straightforward. The addition of the metal acetylide generated in situ to carbonyl compounds is a good choice for this purpose. Recently, considerable progress has been developed in the alkynylation of aldehydes using a Lewis acid in combination with a base. For example, $SnCl_4$,[7] GaI_3,[8] $Sn(OTf)_2$[9] and $Zn(OTf)_2$[10] were all reported to promote the addition of alkynes to aldehydes successfully. In contrast, a few successes have been achieved in the nucleophilic alkynylation of ketones with zinc alkynide complexes.[11] Despite a number of Lewis acid and Lewis base systems having been developed for the alkynylation of aldehydes, no attention was paid to the inexpensive $ZnCl_2$ as a promoter. In this communication, we disclose the alkynylation of aldehydes and ketones simply promoted by $ZnCl_2$ in the presence of Et_3N, furnishing propargylic alcohols in moderate to high yields.

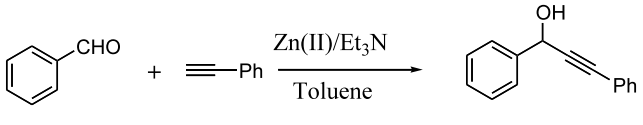
A preliminary screening of commercially available zinc salts as promoters for the alkynylation reaction is summarized in Table 1. We found that $ZnCl_2$ efficiently promoted the alkynylation reaction of benzaldehyde **1a** with phenylacetylene **2a** as did $Zn(OTf)_2$. It is worth noting that the inexpensive $ZnCl_2$ gave almost the same yield as $Zn(OTf)_2$ (Scheme 1).

In subsequent studies, we used $ZnCl_2$ to promote the alkynylation reaction of various carbonyl compounds. Thus, a mixture of terminal alkyne (1.1 mmol), anhydrous $ZnCl_2$ (1.5 mmol) and Et_3N (1.5 mmol) in toluene was stirred at 35°C for 1 h, then a carbonyl

Table 1. Reaction of phenylacetylene with benzaldehyde in the presence of zinc salts and Et_3N[a]

Entry	Zinc salts	Yield[b]
1	$Zn(OTf)_2$	92
2	$ZnCl_2$	91
3	$ZnCO_3$	15
4	$Zn_3(PO_4)_2$	0

[a] Carried out with 1.0 molar equiv. of benzaldehyde, 1.1 molar equiv. of phenylacetylene , 1.5 molar equiv. of the zinc(II) salt, 1.5 molar equiv. of Et_3N in toluene at 35°C for 10 h.
[b] Isolated yields.



1a **2a** **3a**

Scheme 1.

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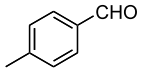
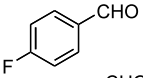
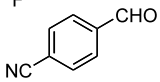
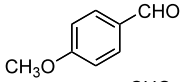
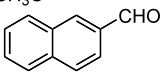
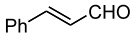
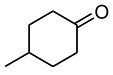
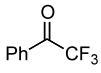
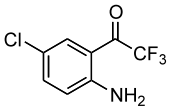
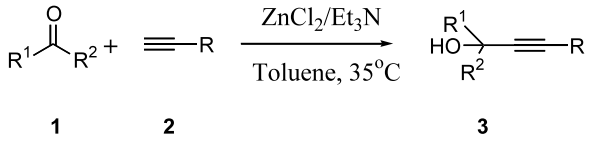
Table 2. The alkynylation of carbonyl compound **1** via $ZnCl_2$ and Et_3N[a]

entry	1	2	yield (%)[b]
1			79
2			65
3			83
4			46
5			80
6			50
7	*c*-C_6H_9CHO		85
8	*i*-C_3H_7-CHO		76
9	*n*-$C_8H_{17}CHO$		45
10			90
11			88[c]
12			60
13	PhCHO		65
14	PhCHO		60
15			70

[a] All the reactions were carried out with 1.0 molar equiv. of carbonyl compound, 1.1 molar equiv. of acetylene, 1.5 molar equiv. of zinc(II) salt, 1.5 molar equiv. of Et_3N in toluene at 35°C for 10 h.
[b] Isolated yields.
[c] A 1:1 mixture of diastereomeric propargyl alcohols was isolated.

compound (1.0 mmol) in neat form was added. The results are summarized in Table 2. All aryl aldehydes and alkyl aldehydes reacted with phenylacetylene smoothly in good to high yields. Reaction of alkyl acetylenes with aryl aldehydes gave moderate yields. Aryl aldehydes with an electron-withdrawing group afforded better yields than those with an electron-donating group (entries 1–4). It is worth noting that alkyl ketones underwent the same alkynylation reaction under these mild conditions to give high yields of the alkynylation products (entries 10 and 11). However, when phenyl acetone was employed as substrate, only a



Scheme 2.

low yield (10%) of an addition product was obtained. This may be due to enolization of the aryl ketone in the presence of the base, so that the alkynylation reaction was inhibited. Using trifluoroacetylbenzene to avoid the enolization led to the corresponding trifluoromethylated propargylic alcohol in good yield (entry 12). When the phenylacetylene was changed to alkyl acetylenes, such as cyclopropylacetylene or hindered *t*-butylacetylene, propargylic alcohols were isolated in good yields (entries 13 and 14). In particular, 4-chloro-2-trifluoroacetylaniline underwent the addition reaction with cyclopropylacetylene to furnish the corresponding trifluoromethylated propargylic alcohol in 70% yield (entry 15), which is a cost-effective process for the preparation of a new class of potent non-nucleoside reverse transcriptase inhibitors (Scheme 2).[12,13]

In conclusion, we have described an extensive study of addition reactions to aldehydes and ketones by terminal acetylenes utilizing inexpensive $ZnCl_2$ as the promoter. This simple and cost-effective process is attractive for the chemical industry.

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References

1. (a) Fried, J.; Lin, C.; Mehro, M.; Kao, W.; Dahren, P. *Ann. N.Y. Acad. Sci.* **1971**, *180*, 38; (b) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, U. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341; (c) Chan, K. K.; Cohen, N. C.; Denoble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497.
2. (a) Friedrich, K. In *The Chemistry of Triple-bonded Functional Groups*, *Supplement C*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons: New York, 1983; Chapter 28; (b) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes*, *Allenes and Cumulenes*; Elsevier: Amsterdam, 1981.
3. (a) Brown, H. C.; Molander, G. A.; Singh, S. M.; Racherla, U. S. *J. Org. Chem.* **1985**, *50*, 1577; (b) Evans, J. C.; Goralski, C. T.; Hasha, D. L. *J. Org. Chem.* **1992**, *57*, 2941.
4. Ahn, J. H.; Joung, M. J.; Yoon, N. M. *J. Org. Chem.* **1995**, *60*, 6173.
5. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

6. Hirao, T.; Misu, D.; Agawa, T. *Tetrahedron Lett*. **1986**, *27*, 933.
7. Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett*. **1992**, 2479.
8. Han, Y.; Huang, Y. Z. *Tetrahedron Lett*. **1995**, *36*, 7277.
9. Yamaguchi, M.; Hayashi, A.; Minami, T. *J. Org. Chem*. **1991**, *56*, 4091.
10. Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc*. **2001**, *123*, 9687.
11. Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc*. **1999**, *121*, 11245.
12. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Jeffrey, S.; Bacheler, L. T.; Klabe, R. M.; Diamond, S.; Lai, C-M.; Rabel, S. R.; Saye, J. A.; Adams, S. P.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *Antimicrob. Agents Chemother*. **1999**, *43*, 2893.
13. (a) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 8937; (b) Thompson, A. S.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc*. **1998**, *120*, 2038; (c) Li, Z.; Upadhyay, V.; DeCamp, A. E.; DiMichele, L.; Reider, P. J. *Synthesis* **1999**, 1453; (d) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 711.