Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 4171–4174

TETRAHEDRON LETTERS

$InBr_3$–Et_3N promoted alkynylation of aldehydes and *N,O*-acetals under mild conditions: facile and simple preparation of propargylic alcohols and amines

Norio Sakai,* Maki Hirasawa and Takeo Konakahara*

Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, Noda, Chiba 278-8510, Japan

Received 18 March 2003; revised 9 April 2003; accepted 10 April 2003

Abstract—The use of a novel $InBr_3$–Et_3N reagent system to promote addition reactions of 1-alkynes not only with a variety of aromatic or bulky aliphatic aldehydes but also with *N,O*-acetals is described. The corresponding propargylic alcohols or amines are produced in good to excellent yields.

The synthesis of propargylic alcohols has been extensively studied because a number of their derivatives constitute basic units in natural products and related biologically active substances.[1] The nucleophilic addition of alkynylmetals containing Ce,[2] B,[3] V[4] and Al[5] to carbonyl compounds has been typically used for this purpose in the past. However, these methods are not straightforward, because most of these alkynylmetals must be generated by the transmetalation of Li, Na, or Mg acetylides,[6] and low temperature condition is required to stabilize the metal acetylides which may undergo side reactions such as the base-induced formation of by-products. Hence, development of alkynylation of carbonyl compounds without such strong bases that can be used under mild conditions would be highly desirable in terms of simplifying with the reaction processes. After some trials, a practical manner in which the combined use of a Lewis acid, such as $Sn(OTf)_2$,[7] GaI_3,[8] $Zn(OTf)_2$,[9a] and $ZnCl_2$[9b] and a Lewis base, such as an amine promotes or catalyzes the alkynylation of carbonyl compounds, was developed. On the other hand, indium(III) halide has attracted considerable attention in synthetic organic chemistry due to its low toxicity in the laboratory, high stability under aqueous conditions, and strong tolerance to oxygen- and nitrogen-containing functional groups.[10,11] Hence, we became interested in developing a method for the highly efficient and widely applicable alkynylation of carbonyl compounds using an indium(III) halide and Lewis base. We report herein that a novel $InBr_3$–Et_3N reagent system effectively promotes the alkynylation of aldehydes leading to the corresponding propargylic alcohols under relatively mild conditions. We also disclose herein that, unlike conventional alkynylations using enamines,[12] aminals,[13] and imines,[9a,14] this reagent system can be used in alkynylation reaction of *N,O*-acetals, which function as imine equivalents, directly producing propargylic amines in excellent yields.

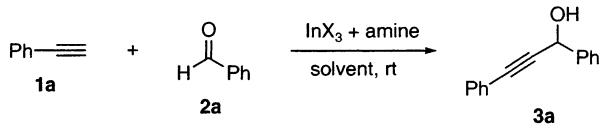
We initially examined the reaction of phenylacetylene (**1a**) with benzaldehyde (**2a**) in the presence of indium trichloride. Thus, when the acetylene (1.5 equiv.) was treated with Et_3N (1.5 equiv.) and $InCl_3$ (1.5 equiv.) at room temperature for an hour, followed by the addition of benzaldehyde, the corresponding propargyl alcohol **3a** was produced in 21% yield (run 1).[15] To optimize the alkynylation, we then ran the reaction using several different solvents and other indium trihalides. The results are summarized in Table 1. Consequently, we found that when Et_2O was used instead of CH_2Cl_2, the product yield was improved to 50% yield (run 3). In contrast, in the cases of THF and PhMe, the yields decreased (runs 4 and 5). It is particularly noteworthy that, when $InBr_3$ was used as a promoter, the reaction proceeded smoothly and the yield of **3a** was dramatically improved to a near quantitative yield (run 7). On the other hand, an amine, such as trihexylamine, and InI_3 were not effective for this reaction (runs 6 and 8). It was also found that 2 equiv. of these reagents

Keywords: indium tribromide; alkynylation; propargylic alcohol; propargylic amine; *N,O*-acetal.

* Corresponding author. Tel.: +81-4-7124-1501; fax: +81-4-7123-9890; e-mail: sakachem@rs.noda.tus.ac.jp

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00931-6

Table 1. Examination of indium trihalide and reaction conditions[a]



Run	InX_3 (equiv.)	Amine (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	$InCl_3$ (1.5)	Et_3N (1.5)	CH_2Cl_2	24	21
2	$InCl_3$ (2)	Et_3N (2)	CH_2Cl_2	24	33
3	$InCl_3$ (2)	Et_3N (2)	Et_2O	24	50
4	$InCl_3$ (2)	Et_3N (2)	THF	24	4
5	$InCl_3$ (2)	Et_3N (2)	PhMe	24	Trace
6	$InCl_3$ (2)	Hex_3N (2)	Et_2O	18	11
7	**$InBr_3$ (2)**	**Et_3N (2)**	**Et_2O**	**3**	**98** (94)[c]
8	InI_3 (2)	Et_3N (2)	Et_2O	24	26
9	$InBr_3$ (1.2)	Et_3N (1.2)	Et_2O	6	61
10	None	Et_3N (2)	Et_2O	10	ND[d]

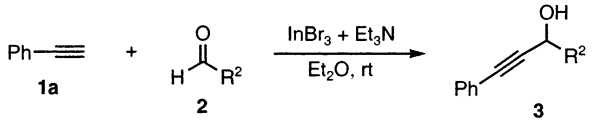
[a] Reaction was carried out using phenylacetylene **1a** (1.2–2 equiv. per **2a**), benzaldehyde **2a** (0.4 mmol), and indium trihalide (1.2–2 equiv. per **2a**). See Typical procedure in Ref. 15.
[b] NMR yields based on benzaldehyde **2a**.
[c] Isolated yield was in parenthesis.
[d] ND = not detected.

(acetylene, $InBr_3$, and amine) per aldehyde **2** was required for this reaction; if not, the product yield is reduced and the reaction time is prolonged (run 9). Needless to say, in the absence of indium trihalide, no alkynylation took place (run 10).

To clarify the general applicability of this alkynylation, the reaction of various benzaldehyde derivatives and aliphatic aldehydes with phenylacetylene (**1a**) was carried out under the above optimized conditions, the results of which are listed in Table 2. The use of benzaldehyde derivatives having an electron-withdrawing substituent, such as halogens, cyano, and nitro groups required only a short for a complete reaction, and the corresponding propargyl alcohols **3b–e** were produced in excellent yields ranging from 87 to 97% (runs 1–4). Similarly, benzaldehydes containing an electron-donating group also underwent the expected alkynylation in good yields (runs 5 and 6). In the case of *p*-methoxybenzaldehyde, however, reflux conditions were required to obtain a satisfactory yield (run 5). This is due to the low electrophilicity of *p*-methoxybenzaldehyde. When aliphatic aldehydes were used, the alkynylation of bulky aldehydes such as pival- and isobutyraldehyde gave the corresponding alcohols in good to moderate yields (runs 7 and 8). However, an easily enolizable aldehyde, such as butyraldehyde produced a small amount of the alkynylated product **3j** along with a 22% yield of the side-reaction product, formed by aldol condensation of the aldehyde (run 9). This result shows that the abstraction of an α-hydrogen on the aldehyde by the in-situ formed anionic intermediate proceeds faster than the nucleophilic addition of the intermediate to the aldehyde, thus leading to enolization of the aldehyde.

Table 3 shows some results of reactions of other 1-alkynes with aromatic aldehydes leading to various propargylic alcohol derivatives. Consequently, the present method could be applied to alkynylation reactions using aromatic aldehydes other one with a benzene skeleton (runs 1–9). In particular, unlike previous reports,[2–5,7,8] when acetylene **1a** was treated with heteroaromatic aldehydes containing pyridine, thiophene, and furan skeletons, the corresponding heterocyclic propargylic alcohols were also obtained in satisfactory yields. In contrast, the alkynylation of ketones, such as cyclohexanone was rather sluggish (48 h), and the product yield (48%) was low. Furthermore, a reaction using acetophenone and acetone was not successful, due to enolization of the ketone.

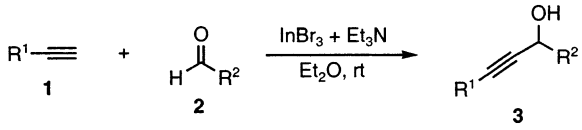
Table 2. Reaction of phenylacetylene with various aldehydes leading to propargylic alcohols



Run	Aldehyde **2**		Time (h)	Yield of **3** (%)[a]	
	R_2				
1	*p*-Cl-Ph	**2b**	5	**3b**	90
2	*p*-F-Ph	**2c**	5	**3c**	92
3	*p*-CN-Ph	**2d**	1.5	**3d**	97
4	*p*-NO_2-Ph	**2e**	0.5	**3e**	87
5	*p*-MeO-Ph	**2f**	24	**3f**	70[b]
6	*p*-Me-Ph	**2g**	15	**3g**	80
7	*t*-Bu	**2h**	24	**3h**	88[b]
8	*i*-Pr	**2i**	24	**3i**	44
9	*n*-Pr	**2j**	24	**3j**	11

[a] Isolated yields based on aldehyde **2**.
[b] Reaction was carried out at 40°C (bath temperature).

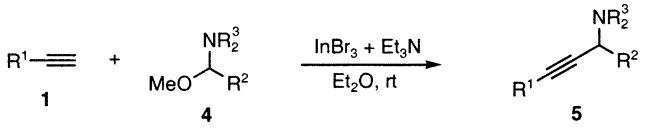
Table 3. Reaction of terminal alkynes with aldehydes leading to propargylic alcohols



Run	Acetylene **1**		Aldehyde **2**		Time (h)	Yield of **3** (%)[a]	
	R^1		R^2				
1	C_6H_{13}	**1b**	*p*-CN-Ph	**2d**	18	**3k**	99
2	*t*-Bu	**1c**	Ph	**2a**	24	**3l**	67
3	Me_3Si	**1d**	*p*-CN-Ph	**2d**	24	**3m**	93[b]
4	Ph	**1a**	1-Naphthyl	**2k**	24	**3n**	61
5	Ph	**1a**	PhCH=CH	**2l**	20	**3o**	46
6	Ph	**1a**	3-Pyridyl	**2m**	1	**3p**	99
7	C_6H_{13}	**1b**	3-Pyridyl	**2m**	12	**3q**	40
8	Ph	**1a**	2-Thienyl	**2n**	24	**3r**	57
9	Ph	**1a**	2-Furyl	**2o**	12	**3s**	93

[a] Isolated yields based on aldehyde **2**.
[b] Reaction was carried out at 40°C (bath temperature).

Table 4. Reaction of terminal alkynes with *N*,*O*-acetals leading to propargylic amines



Run	Acetylene **1**		*N*,*O*-Acetal **4**			Time (min)	Yield of **5** (%)[a]	
	R^1		R^2	R^3				
1	Ph	**1a**	Ph	Et	**4a**	<5	**5a**	94
2	C_6H_{13}	**1b**	Ph	Et	**4a**	<10	**5b**	78
3	Me_3Si	**1d**	Ph	Et	**4a**	10	**5c**	54
4	Ph	**1a**	H	$SiMe_3$	**4b**	<60	**5d**	68 (R^3 = H)

[a] Isolated yields based on *N*,*O*-acetal **4**.

Finally, on the basis of our previous work,[16] we applied the present reaction to the preparation of propargylic amine derivatives, the skeletons of which were widely distributed in natural products and biologically active substances,[1] with *N*,*O*-acetals.[17] Thus, the reaction of three types of 1-alkynes with appropriate *N*,*O*-acetals was carried out under optimized conditions and the results are shown in Table 4. It should be especially noted that the alkynylation of *N*,*O*-acetals proceeds faster than that of aldehydes to produce the expected propargylic amines in good to excellent yields, demonstrating the generality of this procedure.

Although, there is no clear explanation for the reaction intermediate at present, we assume that a nucleophilic intermediate such as a dibromoindium acetylide, which is similar to that reported by Baba et al.[11] would be formed.

Thus far, we have demonstrated that the $InBr_3$–Et_3N reagent system promotes the facile reaction of 1-alkynes with a variety of aldehydes under mild conditions leading to the corresponding propargylic alcohols in good to excellent yields. In addition, we also found that, unlike conventional alkynylations using Al and Ga, this reagent system can be used in alkynylation reaction of heteroaromatic aldehydes producing the corresponding heterocyclic propargylic alcohols in excellent yields, and can be applied to the smooth preparation of propargylic amine derivatives with *N*,*O*-acetals. Further investigation into the mechanism of this reaction is now in progress.

Acknowledgements

This work was partially supported by a grant from the Japan Private School Promotion Foundation and a grant for High Technology Research Centers of Private Universities.

References

1. *Encyclopedia of the Alkaloids*; Glasby, J. S., Ed.; Plenum Press: New York, 1975.
2. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett*. **1984**, *25*, 4233.
3. Brown, H. C.; Molander, G. A.; Singh, S. M.; Racherla, U. S. *J. Org. Chem*. **1985**, *50*, 1577.
4. Hirao, T.; Misu, D.; Agawa, T. *Tetrahedron Lett*. **1986**, *27*, 933.
5. (a) Ahn, J. H.; Joung, M. J.; Yoon, N. M.; Oniciu, D. C.; Katritzky, A. R. *J. Org. Chem*. **1999**, *64*, 488; (b) Ahn, J. H.; Joung, M. J.; Yoon, N. M. *J. Org. Chem*. **1995**, *60*, 6173.
6. Hurdlik, P. F.; Hurdlik, A. M. In *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; John Wiley and Sons: New York, 1978; p. 256.
7. (a) Yamaguchi, M.; Hayashi, A.; Minami, T. *J. Org. Chem*. **1991**, *56*, 4091; (b) Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett*. **1992**, 2479.
8. Han, Y.; Huang, Y.-Z. *Tetrahedron Lett*. **1995**, *36*, 7277.
9. (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc*. **1999**, *121*, 11245; (b) Jiang, B.; Si, Y.-G. *Tetrahedron Lett*. **2002**, *43*, 8323.
10. For selected reviews and papers for indium-promoted or catalyzed reactions, see: (a) Marshall, J. A. In *Lewis Acids in Organic Synthesis*, Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 1, p. 453; (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem*. **2002**, 1578; (c) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (d) Ranu, B. C. *Eur. J. Org. Chem*. **2000**, 2347; (e) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem*. **1995**, *60*, 1920.
11. Baba et al. have already reported that the smooth reaction of indium acetylides, which are generated by transmetalation between alkynyl tins and indium chloride, with aldehydes. See: Yasuda, M.; Miyai, T.; Shibata, I.; Baba, A.; Nomura, R.; Matsuda, H. *Tetrahedron Lett*. **1995**, *36*, 9497.
12. Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed*. **2002**, *41*, 2535.
13. (a) Katritzky, A. R.; Nair, S. K.; Qiu, G. *Synthesis* **2002**, 199; (b) Gommermann, N.; Koradin, C.; Knochel, P. *Synthesis* **2002**, 2143; (c) Xu, Y.; Dolbier, W. R., Jr. *J. Org. Chem*. **2000**, *65*, 2134.
14. (a) Li, C.-J.; Wei, C. *Chem. Commun*. **2002**, 268; (b) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett*. **1998**, *39*, 967; (c) Ukhin, L. Y.; Komissarov, V. N.; Orlova, Z. I.; Tokarskaya, D. A.; Yanovskii, A. I.; Struchkov, Y. T. *J. Org. Chem. USSR*. **1987**, *23*, 1323.
15. **Typical procedure**: An indium tribromide (0.08 mmol), phenylacetylene (0.08 mmol), and triethylamine (0.08 mmol) were successively added to Et_2O (3 mL) at room temperature with stirring under an argon atmosphere. After 1 h, the aldehyde (0.04 mmol) (or *N*,*O*-acetal) was added, and the reaction mixture was stirred until the reaction reached completion, as evidenced by TLC (hexane/AcOEt = 9/1) or GC. After the usual work-up, the residue was separated by silica gel chromatography (hexane–AcOEt) to afford the corresponding products. All new compounds were fully characterized. Spectral data for **5a**: colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, 3H, J = 7.0 Hz), 2.57 (q, 2H, J = 7.0 Hz), 2.67 (q, 2H, J = 7.0 Hz), 5.08 (s, 1H), 7.27–7.37 (m, 6H), 7.51 (q, 2H, J = 7.5 Hz), 7.71 (t, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 44.6, 57.1, 86.1, 87.5, 123.3, 127.3, 127.8, 128.0, 128.3, 128.4, 131.8, 139.8; MS(FAB) m/z 264 (M^++H, 61%), 191 (M^+–NEt_2, 100%); HR-MS (FAB, M^++H) calcd for $C_{19}H_{22}N$: 264.1764. Found: 264.1757. **5b**: colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, 3H, J = 7.0 Hz), 1.03 (t, 6H, J = 7.0 Hz), 1.32 (m, 4H), 1.44 (m, 2H), 1.54 (m, 2H), 2.31 (m, 2H), 2.45 (q, 2H, J = 7.0 Hz), 2.55 (q, 2H, J = 7.0 Hz), 4.8 (s, 1H), 7.23–7.26 (m, 1H), 7.30–7.33 (m, 2H), 7.61–7.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 14.0, 18.8, 22.6, 28.6, 29.1, 31.3, 44.4, 56.5, 76.0, 87.5, 127.0, 127.8, 128.4, 140.5; MS(EI) m/z 271 (M^+, 21%), 194 (M^+–Ph, 100%); HR-MS (FAB) calcd for $C_{19}H_{29}N$: 271.2300. Found: 271.2302.
16. (a) Sakai, N.; Hirasawa, M.; Konakahara, T. *J. Org. Chem*. **2003**, *68*, 483; (b) Sakai, N.; Hamajima, T.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett*. **2002**, *43*, 4821.
17. A few papers dealing with the preparation of propargylic amines using alkynyl metals and *N*,*O*-acetals have been reported, see: (a) Fleming, J. J.; Flori, K. W.; Du Bois, J. *J. Am. Chem. Soc*. **2003**, *125*, 2028; (b) Barluenga, J.; Campos, P. J.; Canal, G. *Synthesis* **1989**, 33; (c) Mensnard, D.; Miginiac, L. *J. Organomet. Chem*. **1989**, *373*, 1; (c) Courtois, G.; Miginiac, P. *Bull. Soc. Chim. Fr*. **1983**, *1–2*, 21.