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Catalytic Alkynylation of Ketones and Aldehydes Using Quaternary Ammonium Hydroxide Base

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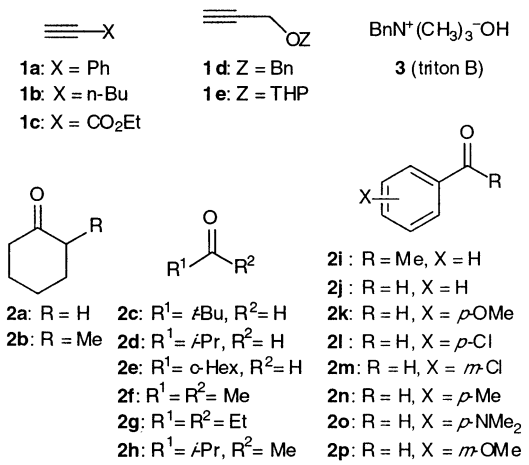
Received October 22, 2002

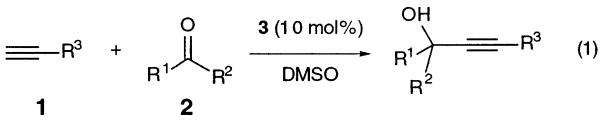
Abstract: Catalytic alkynylation of diverse ketones and aldehydes using nonmetallic benzyltrimethylammonium hydroxide or a basic resin of the hydroxide type in DMSO is described. Aliphatic or alicyclic carbonyl partners gave satisfactory results, whereas aromatic ones afforded products with low yields. When aromatic aldehydes were reacted with phenylacetylene, enones such as chalcone derivatives were obtained in place of ynols. These organobase-catalyzed systems provide a practical nonmetallic protocol for C−C bond formation.

Propargylic alcohols are well-known as versatile building blocks in organic synthesis. Their traditional synthesis through alkynylation of ketones and aldehydes using a stoichiometric amount of bases such as Grignard reagents or alkyllithiums has recently been replaced with a catalytic system. Babler,[1] Knochel,[2] Carreira,[3] Pu,[4] and Chan[5] have made a significant contribution to this important achievement in organic synthesis. They used alkynylides containing potassium,[1] cesium,[2] or zinc[3−5] playing a key role as a nucleophile in C−C bond formation. However, *t*-BuOK-catalyzed alkynylation of enolizable aldehydes led to a complex mixture of products.[1] A CsOH-catalyzed system gave a solution to this problem by means of a syringe pump technique but did not effect alkynylation of aromatic carbonyl compounds.[2] On the other hand, zinc alkynylides are required for asymmetric alkynylation in combination with appropriate chiral ligands to result in a high level of enantiocontrol, but only aldehydes were employed as an electrophile in these cases.[3−5] Therefore, a more general alkynylide with a higher tolerance for substrates, including both enolizable aldehydes or ketones and aromatic carbonyl compounds, is highly desirable.

CHART 1. Alkynes, Ketones, Aldehydes, and Base



In our continuing interest in the development of practical methods for C−C bond formation,[6] we have investigated catalytic alkynylation using a nonmetallic ammonium acetylide anion.[7] Since no effort has been made toward examining the potential of such a cabanion in a catalytic alkynylation process so far, we hoped that there still remains a possibility for the nonmetallic acetylide anion of this class to become a more tolerable alkynylide. In this report, we describe the catalytic alkynylation of diverse ketones and aldehydes (**2**) with a variety of alkynes (**1**) using commercially available benzyltrimethylammonium hydroxide (**3**) as a base (eq 1 and Chart 1). This provided a promising nonmetallic protocol for alkynylation in a practical sense. Some interesting transformations from phenylacetylene (**1a**) and aromatic aldehydes to chalcone derivatives under the given reaction conditions are also presented.



Catalytic alkynylation reactions between alkynes (**1a**−**e**) and carbonyl compounds (**2a**−**n**) were examined by employing method A or B. A typical experimental procedure for method A is as follows. To a solution of **1** (5.0 mmol) and **2** (1.2 equiv) in DMSO (2.5 mL) was added a solution of **3** (10 mol %) in DMSO (2.5 mL) over 10 min at room temperature. The reaction was stirred until the

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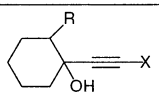
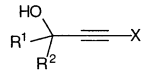
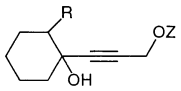
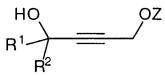
(1) Babler, J. H.; Liptak, V. P.; Phan, N. *J. Org. Chem.* **1996**, *61*, 416−417.
(2) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463−1465.
(3) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688.
(4) Moor, D.; Pu, Lin. *Org. Lett.* **2002**, *4*, 1855−1857.
(5) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636−12637.
(6) Ishikawa, T.; Kadoya, R.; Arai, M.; Takahashi, H.; Kaisi, Y.; Mizuta, T.; Yoshikai, K.; Saito, S. *J. Org. Chem.* **2001**, *66*, 8000−8009.
(7) For quaternary ammonium hydroxide-catalyzed reactions, see: (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355. (b) Arai, S.; Shirai, Y. Ishida, T.; Shioiri, T. *Chem. Commun.* **1999**, 49−50. (c) Corey, E. J.; Bo, Y.; Petersen, J. B. *J. Am. Chem. Soc.* **1998**, *120*, 13000−13001. (d) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228−5229. For other nonmetal organo-catalytic processes, see: (e) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (f) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (g) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371.

10.1021/jo026592g CCC: $25.00
Published on Web 04/04/2003

TABLE 1. Catalytic Alkynylation of Aliphatic Ketones and Aldehydes with 3[a]

entry	1	2	method	time/h	product	yield/%
						
1	**1a**	**2a**	A	2	**4a** (X= Ph, R= H)	95
2		**2b**	A	20	**4b** (X= Ph, R= Me)	85
3	**1b**	**2a**	A	20	**4c** (X= Bu, R= H)	43
4	**1c**	**2a**	B	1	**4d** (X= CO_2Et, R= H)	51
5		**2b**	B	1	**4e** (X= CO_2Et, R= Me)	62
						
6	**1a**	**2c**	A	12	**4f** (X= Ph, R^1= *t*-Bu, R^2= H)	96
7		**2d**	B	1	**4g** (X= Ph, R^1= *i*-Pr, R^2= H)	96
8		**2e**	B	1	**4h** (X= Ph, R^1= c-Hex, R^2= H)	70
9	**1b**	**2c**	A	12	**4i** (X= Bu, R^1= *t*-Bu, R^2= H)	56
10	**1a**	**2f**	B	2.5	**4j** (X= Ph, R^1= R^2= Me)	69
11		**2g**	B	1.5	**4k** (X= Ph, R^1= R^2= Et)	81
12		**2h**	B	2	**4l** (X= Ph, R^1= *i*-Pr, R^2= Me)	73
13	**1c**	**2h**	B	2	**4m** (X= CO_2Et, R^1= *i*-Pr, R^2= Me)	65
14	**1c**	**2e**	B	2	**4n** (X= CO_2Et, R^1= c-Hex, R^2= H)	55
						
15	**1d**	**2a**	A	12	**4o** (Z= Bn, R= H)	84
16		**2b**	A	12	**4p** (Z= Bn, R= Me)	81
17	**1e**	**2b**	A	20	**4q** (Z= THP, R= Me)	46
						
18	**1d**	**2c**	B	12	**4r** (Z= Bn, R^1= *t*-Bu, R^2= H)	92
19		**2d**	A	2.5	**4s** (Z= Bn, R^1= *i*-Pr, R^2= H)	55
20	**1e**	**2f** [b]	B	6	**4t** (Z= THP, R^1= R^2= Me)	89
21		**2g**	B	4	**4u** (Z= THP, R^1= R^2= Et)	90
22	**1d**	**2h**	B	2	**4v** (Z= Bn, R^1= *i*-Pr, R^2= Me)	70

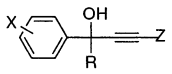
[a] Alkynes **1** (1.2 equiv) and 10 mol % **3** were used unless otherwise indicated. For method A or B, see Experimental Section. Yields are for isolated products. [b] Used 2 equiv of **2f**.

disappearance of **1** on TLC. The usual workup and chromatographic purification afforded the expected propargyl alcohols (**4**). In method B, **1** (5.0 mmol) was added to a solution of base **3** (10 mol %) in DMSO (5 mL) at room temperature, and to this mixture was added **2** (1.2 equiv) over 30 min at room temperature followed by a procedure similar to that of method A. The present system showed a highly critical solvent effect: DMSO[8] is most appropriate, and other solvents (THF, toluene, and DMF) resulted in no reaction or considerably decreased yields of the products. In every entry, no special slow addition of aldehydes using a syringe pump was needed to avoid possible competitive aldol reactions. The results are shown in Tables 1 and 2.

Reactions between aliphatic aldehydes and ketones with alkynes smoothly proceeded at room temperature to give the corresponding propargylic alcohols (**4a**−**v**) in moderate to high yields (Table 1). Entry 17 employing **1e** (THP protection) required a rather longer reaction time (20 h) to result in a low yield of **4q** (46%) in marked contrast to entry 16 employing **1d** (benzyl protection), which led to a high yield of **4p** (12 h, 81%). The reason

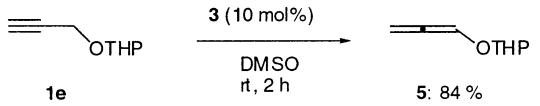
(8) For equilibrium acidity data in DMSO, see: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.

TABLE 2. Catalytic Alkynylation of Aromatic Ketones and Aldehydes with 3[a]

entry	1	2	method	time/h	product	yield/%
						
1	**1a**	**2i**	B	30	**4w** (X= H, Z=Ph, R= Me)	38
2			B [b]	2		71
3	**1d**	**2i**	B	30	**4x** (X= H, Z=CH_2OBn, R= Me)	33
4			B [b]	2		62
5	**1e**	**2i**	B	10	**4y** (X= H, Z=CH_2OTHP, R= Me)	38
6	**1e**	**2j**	A	18	**4z** (X= H, Z=CH_2OTHP, R= H)	26
7	**1d**	**2k**	A	1.5	**4aa** (X= *p*-OMe, Z=CH_2OBn, R= H)	38
8	**1e**	**2l**	A	12	**4bb** (X= *p*-Cl, Z=CH_2OTHP, R= H)	32
9	**1e**	**2m**	A	10	**4cc** (X= *m*-Cl, Z=CH_2OTHP, R= H)	30

[a] Alkynes **1** (1.2 equiv) and 10 mol % **3** were used unless otherwise indicated. For method A or B, see Experimental Section. Yields are for isolated products. [b] Used 100 mol % **3**.

SCHEME 1. Rearrangement of Tetrahydropyranyloxypropyne to Allen Derivative



1e **5**: 84 %

for such a problem for **1e** was revealed by subjecting **1e** to identical reaction conditions for alkynylation without alkyne, where **1e** led to allen derivative (**5**) in high yield over 2 h (Scheme 1).

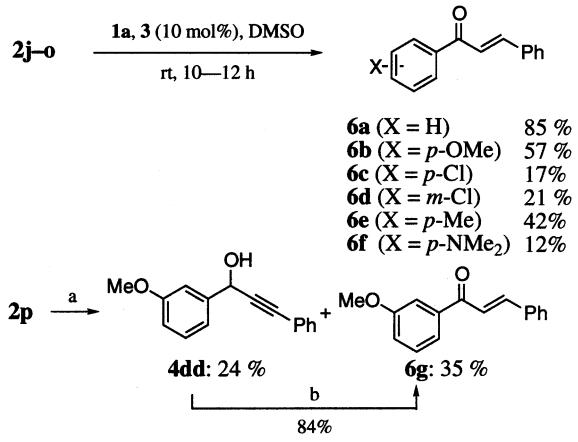
For aromatic ketone (**2i**), the desired adducts were obtained in low yields under catalytic conditions (entries 1, 3, and 5 in Table 2). However, increasing the amount of **3** to 100 mol % led to acceptable product yields (entries 2 and 4, Table 2). On the other hand, aromatic aldehydes furnished propargylic alcohols only in unacceptable yields for every case (26−38% yields; entries 6−9 in Table 2), not only under the catalytic conditions but also under the conditions employing 100 mol % **3**.[9] In light of these results, however, the present system employing **3** deserves consideration when we recall that aromatic aldehydes and ketones are not suited for CsOH-catalyzed systems.[2,10] It was surprising that alkynes bearing a rather long-chain alkyl group such as hexyne (**1b**) exhibited no reactivity toward aromatic aldehydes under the given reaction conditions.[11]

Interestingly, the reaction of phenylacetylene **1a** with aromatic aldehydes (**2j**−**o**) gave not propargyl alcohols but chalcone derivatives (**6a**−**g**)(Scheme 2). The yields depended considerably on the electronic nature of substituents of **2j**−**o** but indicated no explainable, definite

(9) Other products were a mixture of multiple components that were difficult to fractionate, and thus their structures have not been elucidated yet: no starting aldehydes were recovered at all. One definite cause for such low yields observed for aromatic aldehydes should be ascribed to the instability of the products under the given reaction conditions. For example, **4bb** led to a complex mixture when exposed to 10 mol % base in DMSO for 2 h at room temperature, although it was kept unchanged for the initial 20 min. On the other hand, **4a** obtained from cyclohexanone and phenylacetylene was totally stable under the given reaction conditions for 24 h and was recovered unchanged. Use of 100 mol % **3** for the reaction of **2l** with **1d** in DMSO resulted in a complex mixture after several minutes at room temperature, from which 23% yield of 4-*O*-benzyl-1-(*p*-chlorophenyl)-2-butyne-1,4-diol was obtained through very careful chromatographic purification.

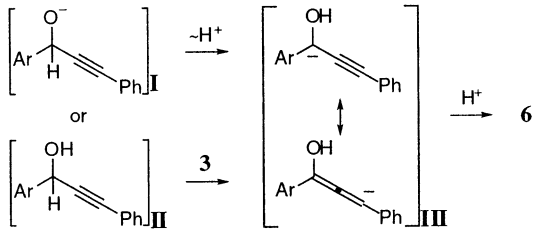
(10) Aromatic aldehydes and ketones have been reported to undergo side reactions when CsOH was employed: see ref 2.

SCHEME 2. Formation of Chalcones from Phenylacetylene (1A) and Aromatic Aldehydes[a]



[a] Conditions: (a) **1a**, **3** (10 mol %)/DMSO/rt, 12 h; (b) **3** (10 mol %)/DMSO/rt, 2 h.

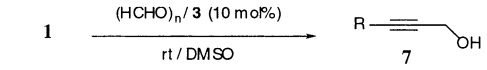
SCHEME 3. Plausible Mechanism for Chalcone Formation



trend.[12] On the other hand, the mechanistic evidence for this transformation was furnished by the reaction of 3-methoxybenzaldehyde (**2p**) with **1a** to give a mixture of propargylic alcohol (**4dd**, 24%) and chalcone derivative **6g** (35%): the isolated **4dd** could be converted to **6g** in 84% yield by treatment with the same base **3**. These results clearly indicate that the formation of **6** may be explained as the result of the formation of carbanion species (**III**) from the initial alkynylation intermediate (**I**) through proton transfer from carbon to oxygen or from the product propargylic alcohol (**II**) via deprotonation and eventual protonation of **III** as shown in Scheme 3.[13] Thus, a phenylethynyl group is functioning as an anion-stabilizing group in this instance, similar to a nitrile group in the benzoin condensation.[14]

Hydroxymethylation of **1** using paraformaldehyde by means of the present catalytic system was successful, and

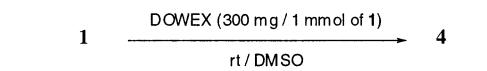
TABLE 3. Catalytic Hydroxymethylation of Alkynes[a]



entry	1	time/h	product	yield/%
1	**1a**	1.5	**7a** (R = Ph)	82
2	**1b**	24		
3	**1c**	0.5	**7c** (R = CO_2Et)	25
4	**1d**	0.5	**7d** (R = CH_2OBn)	80

[a] Method C: to a solution of **1** (5 mmol) and paraformaldehyde (1.2 equiv) in DMSO (2.5 mL) was added **3** in DMSO (2.5 mL) over 10 min. Yields are for isolated products.

TABLE 4. Catalytic Alkynylation Using Basic Resin (DOWEX)[a]



entry	1	2	time/h	4	yield/%
1	**1a**	**2a**	24	**4a**	68
2		**2c**	12	**4f**	75
3		**2d**	24	**4g**	39
4	**1d**	**2a**	65	**4o**	49 (64)
5	**1e**	**2j**	29	**4y**	38 (59)

[a] Method D: to a suspension of Dowex (1.5 g) and molecular sieves (1.5 g) in DMSO (5 mL) was added a mixture of **1** (5 mmol) and **2** (1.2 equiv). Yields in parentheses are based on consumed **1**.

representative results are summarized in Table 3. Alkynes **1a**,**c**,**d** afforded 3-substituted propargyl alcohols **7a**,**c**,**d**, respectively. The extremely low yield for entry 3 is due to hydrolysis of the ester function during or after the reaction (see also entries 4, 5, 13, and 14 in Table 1). Again, long-chain **1b** exhibited no reactivity toward paraformaldehyde (entry 2 in Table 3), similar to the case of aromatic aldehydes (vide supra).[11]

We turned our attention to the use of a solid-supported reagent containing an ammonium hydroxide base in the hope of repeated use of base and, thus, of making the present catalytic system more practical. Preliminary results for this idea using a commercially available basic resin such as DOWEX (550A OH form) are shown in Table 4, although no effort was made to establish optimal reaction conditions.[15] The reactions were very slow under the conditions indicated as compared to **3**, but the alkynylation proceeded as expected. It should be noted that yield for the reaction of **2j** with **1e** was higher [38% (59% based on consumed **1e**): entry 5 in Table 3] than that for the case of **3** (26%, entry 6 in Table 2). This result indicates the advantage of DOWEX (550A OH form) in reducing undesired side reactions arising when aromatic aldehydes were employed.[9]

In conclusion, we have demonstrated that a highly popular, commercially available quaternary ammonium hydroxide such as **3** can catalyze alkynylation of diverse carbonyl compounds when DMSO is employed as a solvent. This new metal-fee process deserves consider-

(11) For example, reactions of **1b** with **2j**,**k** did not occur at all under the given reaction conditions, and neither was pentyne. The origin of this unexpected faint reactivity of hexyne or pentyne is unclear. An NMR experiment using a solution of **1b** and **3** in DMSO-d_6 showed very slow deprotonation from **1b** at ambient temperature, whereas a similar experiment exhibited very rapid deprotonation from **1a**. Although we have no distinctive idea at present about the surprising difference of **1b** in reactivity toward **2a** and **2j** or paraformaldehyde, these interesting observations might suggest that there exists a significant difference in kinetic acidity between **1a** and **1b**.

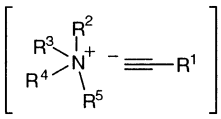
(12) We should have included results for more systematic experiments using acetylides bearing substituents on the aromatic ring of **1a**, which will be done in the near future and reported elsewhere.

(13) For the formation of chalcone derivatives from propargylic alcohols of type II (Scheme 3) under the Sonogashira coupling conditions (Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627), see: Müller, T. J.; Ansorge, M.; Aktah, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1253−1256.

(14) *t*-BuOK-catalyzed system afforded similar results (unpublished observation). The formation of **6** might be pertinent at least partly to the observed low yields of propargylic alcohols for aromatic aldehydes (entries 6−9 in Table 2).

(15) Commercially available resin was used as received. Although the amount and kind of resin might affect the reactivity or the product yield, no effort was made in this context.

ation due to its practicality. In addition, the possible structural diversity of quaternary ammonium hydroxide will lead to the further development of this system into asymmetric synthesis by means of chiral quaternary ammonium hydroxide, which is currently one of our major concerns. Although no physical evidence has been obtained yet, the present results are indicative of the formation of an ammonium acetylide as a reactive intermediate (**8**)[16] that is open to further investigation.



8

Experimental Section

General. All reactions were conducted under a nitrogen or argon atmosphere. Organic extracts were concentrated by evaporation with a rotary evaporator evacuated at around 60 mmHg. Column chromatography was performed with an open column using an appropriate ratio of ethyl acetate−hexane mixed solvent. Materials were obtained from commercial suppliers, and reagent-grade materials were used without further purification. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 under argon.

General Alkynylation Procedure: Method A. To a solution of **1** (5.0 mmol) and **2** (6.0 mmol) in DMSO (2.5 mL) was added a solution of **3** (0.5 mmol) in DMSO (2.5 mL) over 10 min at room temperature. The reaction was stirred until the disappearance of **1** as indicated by TLC. To the reaction mixture was added water (20 mL), and the mixture was extracted with ethyl acetate−hexane (1:3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give a crude residue, which was purified by column chromatography on silica gel using ethyl acetate−hexane to afford **4**.

Method B. To the solution of **3** (0.5 mmol) in DMSO (5 mL) was added **1** (5.0 mmol) at room temperature. Then, **2** (6.0 mmol) was added to the mixture over 30 min at that temperature, followed by a procedure similar to method A.

Method C. To a solution of **1** (5.0 mmol) and paraformaldehyde (6.0 mmol) in DMSO (2.5 mL) was added a solution of **3** (0.5 mmol) in DMSO (2.5 mL) over 10 min at room temperature, followed by a procedure similar to method A.

Method D. To a suspension of Dowex (1.5 g) and molecular sieves (1.5 g) in DMSO (5 mL) was added a mixture of **1** (5.0 mmol) and **2** (6.0 mmol) at room temperature. The reaction mixture was stirred, and the reaction was monitored by TLC analysis. The resin and molecular sieves were removed by filtration and rinsed with ethyl acetate−hexane. The combined organic solutions were concentrated to give a crude product, which was purified by column chromatography on silica gel using ethyl acetate−hexane.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Spectroscopic and some analytical data for **4**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026592G

(16) Physical evidence for the existence of long-lived quaternary ammonium acetylides has not been obtained yet in terms of an NMR probe.