Available online at www.sciencedirect.com

Tetrahedron Letters 45 (2004) 8281–8283

Tetrahedron Letters

Mild and efficient synthesis of propargylamines by copper-catalyzed Mannich reaction

Lothar W. Bieber* and Margarete F. da Silva

Departamento de Química Fundamental, Universidade Federal de Pernambuco, Cidade Universitária, 50670-901 Recife, PE, Brazil

Received 27 August 2004; revised 8 September 2004; accepted 10 September 2004

Abstract—Terminal alkynes undergo mild and efficient aminomethylation with aqueous formaldehyde and secondary amines under CuI catalysis. In most cases high to nearly quantitative yields of tertiary propargylamines are obtained in DMSO solution at room temperature. Aromatic, aliphatic and silylated acetylenes as well as alkynols can be used. Primary amines are less reactive and satisfactory yields of secondary propargylamines are obtained only with phenylacetylene.

Propargylamines **3** are compounds of interesting biological properties and important synthetic intermediates.[1,2] The most attractive synthetic access is the classical Mannich reaction,[3] a three component procedure between terminal alkynes **1**, formaldehyde and secondary amines **2**; initially restricted to arylacetylenes, the reaction has been extended to some less activated alkynes by the introduction of copper catalysts.[4] However, rather harsh conditions, moderate yields and complex workup and purification procedures still have limited a wider application. Also a recent microwave-enhanced, solventless reaction on alumina does not represent an attractive alternative because of the need of large excess of formaldehyde and copper(I) iodide.[5] In contrast to the lack of efficient Mannich procedures with formaldehyde itself, recently several related reactions starting from aliphatic and aromatic aldehydes via enamines,[6] N,O-acetals,[7] iminium salts and their precursors[8] have been reported, some of them even under asymmetric catalysis.[6,9] Most of these procedures require dry aprotic solvents, but solid-phase methodologies[10] and several aqueous procedures catalyzed by Cu, Ag or Au have also been described.[11]

Recent progress in two different copper(I)-catalyzed reactions, the mild and efficient Barbier-type alkylation of iminium ions[12] and the direct synthesis of phenylselenyl alkynes,[13] prompted us to examine similar conditions for the aminomethylation of terminal alkynes.

$$\underset{\mathbf{1}}{\mathrm{R{-}\!\!\equiv}} + \mathrm{CH_2O} + \underset{\mathbf{2}}{\mathrm{HNR'R''}} \xrightarrow[\text{[CuI]}]{\mathrm{DMSO/H_2O}} \underset{\mathbf{3}}{\mathrm{R{-}\!\!\equiv\!\!{-}CH_2NR'R''}}$$

In our first experiments, phenylacetylene, morpholine and aqueous formaldehyde were reacted at 30 °C in commercial, DMSO in the presence of 0.02 equiv of copper(I) iodide. After 2 h, the alkyne was almost consumed and the desired tertiary amine **3** could be isolated in nearly quantitative yield (Table 1, entry 1). Other copper(I) salts were less effective with yields decreasing from CuCN to CuBr and CuCl; surprisingly, also $CuCl_2$ gave **3**, albeit in moderate yield, probably because of in situ reduction by formaldehyde (entries 2–5). With $CuSO_4$, Cu_2O and metallic copper and in the absence of catalyst no reaction at all occurred (entries 6–9). $AuCl_3$ and AgI, which have been reported to catalyze similar transformations with aromatic and higher aliphatic aldehydes in refluxing water,[11b,c] produced only trace amounts of product under our conditions (entries 10 and 11). Variation of the solvent brought no further improvement: acetonitrile was less efficient than DMSO, water and methanol gave only a few percent of yield and dioxane or carbon tetrachloride did not afford any product at all (entries 12–16). Paraformaldehyde in the absence of additional water can also be used, but required 20 h at room temperature probably because of the slow depolymerization (entries 17 and 18).

Keywords: Aminomethylation; Terminal alkynes; Primary and secondary amines.

* Corresponding author. Tel.: +55 81 21268441; fax: +55 81 21268442; e-mail: bieberlothar@hotmail.com

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.079

Table 1. Mannich reaction of phenylacetylene with formaldehyde and morpholine[14]

Entry	Catalyst	Solvent	Time (h)	Yield[a] (%)
1	CuI	DMSO	2	95
2	CuCN	DMSO	2	77
3	CuBr	DMSO	2	60
4	CuCl	DMSO	2	23
5	$CuCl_2$	DMSO	2	59
6	$CuSO_4$	DMSO	2	—
7	Cu_2O	DMSO	2	—
8	Cu^0	DMSO	2	—
9	—	DMSO	2	—
10	$AuCl_3$	DMSO	2	17
11	AgI	DMSO	2	2
12	CuI	MeCN	2	71
13	CuI	H_2O	2	5
14	CuI	MeOH	2	2
15	CuI	Dioxane	2	—
16	CuI	CCl_4	2	—
17[b]	CuI	DMSO	2	4
18[b]	CuI	DMSO	20	93

[a] Determined by ^{1}H NMR in the crude extract (1 mL of CCl_4 containing 0.05 mmol of cyclohexane as internal quantitative reference).

[b] 1 mmol of paraformaldehyde was used in the absence of additional water.

Table 2. Synthesis of propargylamines **3**[14]

Entry	R	R′, R″	Solvent	Time (h)	Yield (%)
1	Ph	Me, Me[a,b]	DMSO	10	95
2	Ph	Et, Et	DMSO	10	98
3	Ph	c-C_6H_{11}, c-C_6H_{11}	DMSO	20	96
4	Ph	$(CH_2)_4$	DMSO	10	92
5	Ph	$(CH_2)_5$	DMSO	10	98
6	Ph	$(CH_2)_2O(CH_2)_2$	DMSO	10	98
7	Ph	Ph, Me	DMSO	20	93
8	Ph	Me, H[a,b,c]	DMSO	20	73
9	Ph	*n*-Bu, H[c]	DMSO	20	70
10	Ph	$PhCH_2$, H[c]	DMSO	20	72
11	*n*-Bu	Me, Me[a,b]	DMSO	72	86
12	*n*-Bu	Et, Et	DMSO	20	98
13	*n*-Bu	c-C_6H_{11}, c-C_6H_{11}	DMSO	72	89
14	*n*-Bu	$(CH_2)_4$	DMSO	20	96
15	*n*-Bu	$(CH_2)_5$	DMSO	20	95
16	*n*-Bu	$(CH_2)_2O(CH_2)_2$	DMSO	20	93
17	*n*-Bu	Ph, Me	DMSO	4[d,e]	83
18	*n*-Oct	Ph, Me	DMSO	4[d]	78
19	CH_2OH	$(CH_2)_4$	H_2O	72	70
20	CH_2OH	$(CH_2)_5$	H_2O	72	96
21	CH_2OH	c-C_6H_{11}, c-C_6H_{11}	DMSO	20	67
22	CMe_2OH	Et, Et	H_2O	72	87
23	CMe_2OH	$(CH_2)_4$	H_2O	72	80
24	CMe_2OH	$(CH_2)_5$	H_2O	72	82
25	CMe_2OH	c-C_6H_{11}, c-C_6H_{11}	DMSO	20	67
26	$SiMe_3$	Me, Me[a,c,f]	DMSO	72	71
27	$SiMe_3$	$(CH_2)_2O(CH_2)_2$[g]	DMSO	72	60

[a] The hydrochloride was used.

[b] 1 mmol of $KHCO_3$ was added as auxiliary base.

[c] 1 mmol of amine was used.

[d] Reaction temperature 80 °C.

[e] Performed in a sealed tube.

[f] 1 mmol of paraformaldehyde and 1 mmol of K_2HPO_4 as auxiliary base were used.

[g] 0.75 mmol of acetic acid were also added.

In the following experiments the procedure was adjusted to different amines and alkynes. Several secondary amines gave excellent yields with phenylacetylene, including the highly hindered dicyclohexylamine; dimethylamine was used as the hydrochloride and potassium bicarbonate was added as auxiliary base (Table 2, entries 1–6). Also the less basic *N*-methylaniline produced a high yield after 20 h (entry 7). Even primary amines, previously found unreactive, gave preparative results of secondary propargylamines **3** (entries 8–10).

1-Hexyne was less reactive with secondary amines and needed longer reaction times to achieve complete transformation (entries 11–16). No reaction was observed with *N*-methylaniline at 30 °C, but a satisfactory yield was obtained at 80 °C in a sealed tube; the less volatile decyne gave similar results at atmospheric pressure (entries 17 and 18). Alkynols too showed good reactivity (entries 19–25). Especially when both substrates **1** and **2** were hydrophilic (entries 19 and 20), water instead of DMSO improved the yields by a factor of 2–3. Under careful pH-control, the reaction was also successful with the acid and base-sensitive trimethylsilyl acetylene. This was achieved by the addition of a weak inorganic base (K_2HPO_4) in the case of the hydrochloride of dimethylamine (entry 26) or by buffering free morpholine with 1.5 equiv of acetic acid (entry 27).

The described reactions can be regarded as examples of the Mannich reaction, which involves enols or carbanions as intermediates in the classical version. In the present study, a terminal acetylene is used as CH-acidic component under weakly basic conditions. However, in view of the need for a copper catalyst and the exceptionally mild reaction conditions, a radical intermediate should also be considered. A radical addition of phenyl, acetyl and alkyl radicals to iminium ions has been postulated before in the Zn-Barbier reaction[12] and in the $TiCl_3$-promoted reaction with diazonium salts or *tert*-butyl hydroperoxide.[15]

In summary, the method allows the easy, mild and efficient synthesis of a large number of differently substituted propargylamines characterized by high atom economy, low environmental impact and use of nontoxic solvents and reagents. The possibility to react unprotected primary amines and alkynols allows further reactions on these sites. Present studies with suitable benzyl, allyl or silyl-protected secondary amines are underway and can open an easy access also to primary propargylamines.

Acknowledgements

We gratefully acknowledge financial support from CNPq.

References and notes

1. (a) Karlén, B.; Lindere, S.; Svensson, K.-G.; Dahlbom, R. *J. Med. Chem.* **1970**, *13*, 1351–1356; (b) Huffman, M. A.;

Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590–1594; (c) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716.

2. (a) Nilsson, B.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285–294; (b) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151–1152; (c) Jenmalm, A.; Berts, W.; Li, Y. L.; Luthman, K.; Csoregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139–1148; (d) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999–5004.
3. Mannich, C.; Chang, F. T. *Ber.* **1933**, *66*, 418–420.
4. (a) Tramontini, M. *Synthesis* **1973**, 703–775; (b) Tramonitini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791–1837, and references cited therein.
5. Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676–678.
6. (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535–2538; (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2003**, *9*, 2797–2811.
7. Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171–4174.
8. (a) Ukhin, L. Y.; Komissarov, V. N.; Orlova, Z. I.; Tokarskaya, O. A.; Yanovskii, A. I.; Struchkov, Y. T. *Zh. Org. Khim.* **1987**, *23*, 1323–1325; (b) Katritzki, A. R.; Nair, S. K.; Qiu, G. F. *Synthesis* **2002**, 199–202; (c) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731–5733.
9. Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766.
10. (a) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967–970; (b) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647–3650.
11. (a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001–1003; (b) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473–4475; (c) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585.
12. Estevam, I. H. S.; Bieber, L. W. *Tetrahedron Lett.* **2003**, *44*, 667–670.
13. Bieber, L. W.; Silva, M. F.; Menezes, P. H. *Tetrahedron Lett.* **2004**, *45*, 2735–2737.
14. Typical procedure: Alkyne (0.5 mmol), amine (0.6 mmol), aqueous formaldehyde (35%, 0.2 mL) and catalyst (2 mg) were dissolved in 1 mL of commercial DMSO and stirred for the indicated time at 30 °C. After basic aqueous workup and extraction with chloroform or ether, the product was purified by short path distillation or crystallization with picric acid.
15. Clerici, A.; Porta, O. *Gazz. Chim. Ital.* **1992**, *122*, 165–166.