Direct Copper(I)-Catalyzed Cycloaddition of Organic Azides with TMS-Protected Alkynes

Félix Cuevas,^a Ana I. Oliva,^a Miquel A. Pericàs*^{a,b}

^a Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain Fax +34(977)920222; E-mail: mapericas@iciq.es

^b Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain *Received 4 May 2010*

Abstract: A methodology for the direct use of trimethylsilyl-protected alkynes in the copper(I)-mediated alkyne–azide cycloaddition reaction without the need of a previous deprotection step is reported. This methodology is selective for the trimethylsilyl in front of other silicon-based C(sp)–H protecting groups.

Key words: alkynes, azides, cycloaddition, tandem reaction, click chemistry

The copper-catalyzed alkyne–azide cycloaddition reaction $(CuAAC)^1$ has become the archetypal example of 'click chemistry',² and the process has found application in almost every field of chemistry.³ The efficiency and selectivity of this transformation are a direct consequence of the reactivity of in situ generated copper(I) acetylides, and therefore CuAAC is usually limited to terminal acetylenes, which produce only 1,4-disubstituted triazoles.⁴

Trimethylsilyl-protected alkynes (TMS-alkynes) are very useful intermediates for the synthesis of complex molecules through CuAAC cycloadditions, but a previous deprotection step is required to generate the reactive, terminal alkyne. Methods involving treatment of the TMSalkyne with fluoride⁵ or with silver salts,⁶ or the use of K_2CO_3 in methanol⁷ are most frequently used, and even 'one-pot' deprotection–CuAAC tandem procedures have been reported.⁸

Although the transformation of TMS-alkynes into copper(I) acetylides by the use of Cu(I) salts has been reported,⁹ this methodology has not been studied in connection with CuAAC reactions. In the context of our own research in this domain,¹⁰ we wondered whether TMS-alkynes, when submitted to the usual conditions for the CuAAC reaction, could generate a catalytic amount of the copper(I) acetylide intermediate and this could enter the cycloaddition catalytic cycle, as represented in Scheme 1. This would allow using disubstituted 1-trimethylsilyl-1alkynes as direct substrates for the CuAAC avoiding any previous deprotection step.



Scheme 1 Direct CuAAC reaction with 1-trimethylsilyl-1-alkynes

SYNLETT 2010, No. 12, pp 1873–1877 Advanced online publication: 30.06.2010 DOI: 10.1055/s-0030-1258120; Art ID: G12510ST © Georg Thieme Verlag Stuttgart · New York In this communication we whish to report the successful implementation of a catalytic tandem desilylation–CuAAC of 1-trimethylsilyl-1-alkynes mediated by CuBr.

According to our expectations, when 1-phenyl-2-trimethylsilylacetylene (**1a**) was treated with benzyl azide (**2**) in the presence of CuBr (15 mol%) in DMF at room temperature under argon, the formation of the triazole product **3a** was observed, and this compound could be isolated in 41% yield after 40 hours reaction (Table 1, entry 1). The addition of one equivalent of *N*-methylmorpholine (NMM) to the reaction mixture led to a slightly improved yield (entry 2), much probably by increasing the solubility of the putative Cu(I) acetylide intermediate.¹¹ Yield could be further improved and reaction time very significantly shortened by performing the reaction at 100 °C (entries 3 and 4).

The influence of different amines (entries 5-10) and solvents (entries 11-16) on the course of the reaction was next studied. In general, yield was not importantly affected by the nature of the employed amine, although results obtained in the presence of 1 equivalent of triethylamine (entry 5) were consistently better. Only in the case of using *o*-phenantroline as ligand (entry 10) the cycloaddition yield decreased considerably. This is probably due to the formation of a stable phenantroline–Cu complex, likely less active in the desilylation of the starting alkyne.

The nature of the solvent, in turn, exerted a dramatic influence on the performance of the reaction. While the use of DMF, our initial guess, appears to be optimal, acetonitrile and ethanol gave only moderate yields (entries 11 and 12), and solvents such as toluene, THF, 1,2-dichloroethane, and water had deleterious effects on the course of the reaction (entries 13–16).

In an attempt to reduce the amounts of CuBr and triethylamine employed in the reaction, some additional experiments were performed. When 15 mol% of CuBr and 30 mol% of triethylamine were used, a slight decrease of the yield of the reaction was observed (entry 17). This yield was maintained when only 5 mol% of CuBr and 10% of triethylamine were used, although a longer reaction time (5 h) was required (entry 18). Even working with only 2 mol% of catalyst and 4 mol% of triethylamine, the reaction took place in synthetically acceptable yield (entry 19). Finally, the use of microwave irradiation was studied under the optimal reaction conditions (15 mol% CuBr, 100 mol% triethylamine, 100 °C) to reduce reaction time. Gratifyingly, the reaction can carried out to completion in 30 minutes under these conditions with practically no decrease in yield (entry 20).

 Table 1
 Screening of Reaction Conditions for the Tandem Desilylation–CuAAC of 1-Trimethylsilyl-1-alkynes

Ph-TMS		
1a	CuBr (15 mol%) amine (1 equiv)	N=N / }, Ph
+	solvent	Ph
Ph N ₃		3a
2		

-				
Entry	Solvent	Conditions	Amine	Yield (%
1	DMF	r.t., 40 h	_	41
2	DMF	r.t., 40 h	NMM	68
3	DMF	100 °C, 1.5 h	-	63
4	DMF	100 °C, 1.5 h	NMM	83
5	DMF	100 °C, 2 h	Et ₃ N	94
6	DMF	100 °C, 2 h	DIPEA	86
7	DMF	100 °C, 2 h	benzylamine	88
8	DMF	100 °C, 2 h	TMEDA	83
9	DMF	100 °C, 2 h	piperidine	86
10	DMF	100 °C, 2 h	o-phenantroline	31
11	MeCN	100 °C, 2 h	Et ₃ N	70
12	EtOH	100 °C, 2 h	Et ₃ N	53
13	toluene	100 °C, 2 h	Et ₃ N	11
14	THF	100 °C, 2 h	Et ₃ N	11
15	1,2-DCE	100 °C, 2 h	Et ₃ N	7
16	H_2O	100 °C, 2 h	Et ₃ N	9
17 ^a	DMF	100 °C, 3.5 h	Et ₃ N	78
18 ^b	DMF	100 °C, 5 h	Et ₃ N	79
19 ^c	DMF	100 °C, 5 h	Et ₃ N	68
20 ^d	DMF	100 °C, 0.5 h	Et ₃ N	84

^a Conditions: 15 mol% of CuBr, 30 mol% of Et₃N.

^b Conditions: 5 mol% of CuBr, 10 mol% of Et₃N.

^c Conditions: 2 mol% of CuBr, 4 mol% of Et₃N.

^d Conditions: under MW irradiation.

The scope of the tandem desilylation–CuAAC of 1-trimethylsilyl-1-alkynes was studied with a family of alkynes featuring triple bonds with different electronic characteristics (Table 2), using in all cases the previously optimized reaction conditions [method A: CuBr 15 mol%, Et₃N (1 equiv) in DMF at 100 °C].¹² As it can be seen, the process is compatible with the presence of different funtional groups in the alkyne, and good yields are obtained in all cases (entries 1–7, method A). The example in entry 5 illustrates another advantage of the use of this methodology: compound **3e** could not be easily prepared through the traditional CuAAC methodology given the gaseous nature of propyne.

It is noteworthy that when bis(trimethylsilyl)acetylene was used as starting material the reaction product was 4-trimethylsilyltriazole **3h** (entry 8, method A). This fact indicates that only one trimethylsilyl group is removed before the reaction takes place, and that trimethylsilyltriazoles are stable under the reaction conditions involved in the tandem desilylation–CuAAC reaction. In full agreement with these observations, when trimethylsilylacetylene was used as starting material, **3h** was again obtained in high yield (entry 9, method A), and the same stands for the preparation of **3j** from triisopropylsilylacetylene (entry 10, method A). Thus, whenever a C(sp)–H bond is present in the starting alkyne, a direct CuAAC takes place, irrespective of the presence on the substrate of a C(sp)–TMS unit.

Keeping in mind the possibility of developing chemoselective cycloaddition processes on differently protected poliynes, the possible participation in the tandem desilylation–CuAAC reaction of 1-silyl-1-alkynes bearing bulkier trialkylsilyl substituents was studied (entries 11 and 12). Very interestingly, 1-triisopropylsilyl-1-alkynes and 1-*tert*-butyldimethyl-silyl-1-alkynes do not react at all, being quantitatively recovered upon reaction workup, while the corresponding triazole products are not detected. It is thus confirmed that trialkysilyl substituents other than trimethylsilyl are not cleaved under the studied reaction conditions and, hence, that the direct CuAAC reaction with 1-silyl-1-alkynes is selective for trimethylsilyl substituted acetylenes.

As a consequence of this behavior, the protection of two or more terminal triple bonds in a molecule with trimethylsilyl and other trialkylsilyl groups becomes orthogonal towards the tandem desilylation-CuAAC of 1trimethylsilyl-1-alkynes. This fact can be used, in practice, for the ready control of triple-bond reactivity. We illustrate this concept in Scheme 2, where the preparation of a molecule containing two differently substituted 1,2,3triazole moieties is presented. Starting from an orthogonally protected diyne 4, it is possible to use the tandem desilylation-CuAAC of 1-trimethylsilyl-1-alkynes to obtain selectively a monotriazole intermediate at the trimethylsilyl-protected alkyne moiety 5 without affecting the triisopropylsilyl-protected one. Then, the desilylation with tetrabutylammonium fluoride in THF of the TIPS group and the subsequent CuAAC reaction afforded the bistriazole derivative 6 in excellent yield (Scheme 2).

To trace the origin of the hydrogen atom at C-5 in the triazole products and the fate of the trimethylsilyl group on the starting alkyne, the reaction was performed in a NMR tube in DMF- d_7 under the optimal reaction conditions [CuBr (15 mol%), Et₃N (1 equiv), 100 °C] with **1a** and **2**. By monitoring the progress of the reaction, the formation of the nondeuterated triazole **3a** could be observed

R - TMS 1 $+$ Ph 2	CuBr (15 mol%) Et ₃ N (1 equiv) DMF, 100 °C 3			
Entry	Alkyne	Product	Time (h)	Yield (%) A ^a /B ^b
1	TMS 1a	N=N N_Ph	2	94/97
2		H N=N N Ph h	2.5	82/93
3		N=N N_Ph	2.5	82/84
4		3c	2.5	76/85
5	10 TMS 1e	N=N N=N N N Ph 3e	2.5	69/56
6	→ TMS	N=N N N Ph	1.5	94/87
7	тмс	$3f \qquad \qquad$	2.5	85/76
8	Ig TMS— —— TMS 1h	sg TMS N=N Ph	2.5	57/43
9	──TMS 1i	$\frac{N=N}{MS} \xrightarrow{N=N} Ph$	2.5	77/37
10	TIPS 1j	TIPS N Ph	2.5	91/88
11		Ph Ph Ph Ph $3a$	2.5	n.d. ^c
12		Ph Ph Ph 3a	2.5	n.d. ^c

 Table 2
 Scope of the Tandem Desilylation–CuAAC of 1-Trimethylsilyl-1-alkynes

^a Method A: in DMF.

^b Method B: in DMF–H₂O (2 equiv).

^c n.d.: not detected.



Scheme 2 Selective synthesis of differently substituted bistriazoles

(Figure 1). Interestingly, when conversion of the starting material reached ca. 50%, the reaction importantly slowed down. We interpreted that traces of water present in the deuterated solvent had been completely consumed by the reacting system at that point. In fact, addition of a small amount of D₂O to the reaction mixture led to immediate reactivation, the formation of **3a** deuterated at the triazole ring being observed from this moment on. In a parallel experiment the reaction was performed in DMF- d_7 containing 2 equivalents of D₂O. In this case, the reaction cleanly progressed to 90% conversion in 2 hours, partially deuterated **3a** being formed.



Figure 1

It can be concluded from these results that the presence of traces of water in the solvent (DMF) is necessary for the reaction to proceed. According to the results obtained with D_2O , water is responsible for the protonation of the triazolyl–copper intermediate, where the catalytic Cu(I) species regenerates. It is interesting to note that this exper-

Synlett 2010, No. 12, 1873–1877 © Thieme Stuttgart · New York

iment represents an additional argument in favor of the intermediacy of copper acetylides in the CuAAC reaction.^{1c,4a,13} The different events required for the catalytic cycle to operate are included in the simplified mechanistic proposal presented in Scheme 3.



Scheme 3 Proposed catalytic cycle for the tandem desilylation– CuAAC of 1-trimethylsilyl-1-alkynes

Although conventional dry grade DMF usually contains enough water as to allow the achievement of high conversions under the standard reaction conditions used in this work (Table 2, method A), the reaction was also studied in the presence of a slight excess (2 equiv) of water (Table 2 and Scheme 2, method B). In general, yields recorded with method B are higher. As an exception, alkynes bearing hydrolysis-prone substituents, such as TMS (entries 8 and 9, method B), or those leading to volatile species upon hydrolysis (entry 5, method B) are more efficiently converted under the reaction conditions of method A. Much probably, the presence of excess water favors hydrolysis of the starting alkynes or of cycloaddition intermediates in detriment of yield.

In conclusion, we have described a catalytic, tandem desilylation–CuAAC of 1-trimethylsilyl-1-alkynes that avoids a previous deprotection step. Under the reaction conditions reported, the intermediate copper(I) acetylide is formed in situ from the copper(I) species used as catalyst, and subsequently undergoes the cycloaddition reaction with the azide counterpart. From a practical perspective, this methodology avoids the isolation and manipulation of the often volatile terminal alkynes, leading in general to substantially improved yields. Moreover, this process is selective for trimethylsilyl-protected alkynes [vs. alkynes bearing bulkier silyl-based C(sp)–H protecting groups], and this allows using this methodology for the controlled synthesis of molecules bearing two or more differently substituted triazoles.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was funded by MICINN (Grant CTQ2008-00947/BQU), DIUE (Grant 2009SGR623), Consolider Ingenio 2010 (Grant CSD2006-0003), Laboratorios del Dr. Esteve, S. A., and ICIQ Foundation.

References and Notes

- (a) Meldal, M.; Christensen, C.; Tornoe, C. W. J. Org. Chem. 2002, 67, 3057. (b) Sharpless, K. B.; Fokin, V. V.; Green, L. G.; Rostovtsev, V. V. Angew. Chem. Int. Ed. 2002, 114, 2708. (c) Meldal, M.; Tornoe, C. W. Chem. Rev. 2008, 108, 2952.
- (2) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew. Chem. Int. Ed. 2001, 40, 2004.
- (3) (a) Macromol. Rapid. Commun. 2008, 29, 943; special thematic issue. (b) QSAR Comb. Sci. 2007, 26, 1110; special thematic issue. (c) Angell, Y. L.; Burgess, K. Chem. Soc. Rev. 2007, 36, 1674. (d) Moses, E.; Moorhouse, A. D. Chem. Soc. Rev. 2007, 36, 1249. (e) Lutz, J.-F. Angew. Chem. Int. Ed. 2007, 46, 1018. (f) Wu, P.; Fokin, V. V. Aldrichimica Acta 2007, 40, 7.
- (4) (a) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* 2005, *127*, 210. For two examples of CuAAC involving the use of internal alkynes, see: (b) Candelon, N.; Lastécouères, D.; Diallo, A. K.; Ruiz-Aranzaes, J.; Astruc, D.; Vincent, J.-M. *Chem. Commun.* 2008, 741. (c) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* 2006, *12*, 7558.
- (5) (a) Fujino, T.; Marine, G.; Nakamura, E.; Isobe, H. *Nucleic Acids Symp. Ser.* 2007, *51*, 267. (b) Gadzikwa, T.; Farha, O. K.; Malliakas, C. D.; Kanatzidis, M. G.; Hupp, J. T.; Nguyen, S. T. *J. Am. Chem. Soc.* 2009, *131*, 13613.
- (6) Valverde, I. E.; Delmas, A. F.; Aucagne, V. *Tetrahedron* 2009, 65, 7597.
- (7) Montagnat, O. D.; Lessene, G.; Hugues, A. B. *Tetrahedron Lett.* 2006, 47, 6971.
- (8) (a) Aucagne, V.; Leigh, D. A. Org. Lett. 2006, 8, 4505.
 (b) Hu, M.; Li, J.; Yao, S. Q. Org. Lett. 2008, 10, 5529.
 (c) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. Tetrahedron 2009, 10573. (d) Beltrán, E.; Serrano, J. L.; Sierra, T.; Giménez, R. Org. Lett. 2010, 12, 1404.
- (9) Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. Tetrahedron Lett. 1997, 38, 3977.
- (10) (a) Font, D.; Jimeno, C.; Pericàs, M. A. Org. Lett. 2006, 8, 4653. (b) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. Org. Lett. 2007, 9, 1943. (c) Bastero, A.; Font, D.; Pericàs, M. A. J. Org. Chem. 2007, 72, 2460. (d) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. Org. Lett. 2007, 9, 3717. (e) Font, D.; Sayalero, S.; Bastero,

A.; Jimeno, C.; Pericàs, M. A. Org. Lett. 2008, 10, 337.
(f) Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.;
Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.;
Pericàs, M. A. Org. Lett. 2008, 10, 1617. (g) Popa, D.;
Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A.
Adv. Synth. Catal. 2009, 351, 1539. (h) Özçubukçu, S.;
Özkal, E.; Jimeno, C.; Pericàs, M. A. Org. Lett. 2009, 11, 4680. (i) Alza, E.; Rodriguez-Escrich, C.; Sayalero, S.;
Bastero, A.; Pericàs, M. A. Chem. Eur. J. 2009, 15, 10167.
(j) Alza, E.; Pericàs, M. A. Adv. Synth. Catal. 2009, 351, 3051.

- (11) A precipitate forms upon mixture of **1** with CuBr in DMF. In the presence of NMM, precipitation is much less intense.
- (12) General Procedure for the Tandem Desilylation-CuAAC Reaction of 1-Trimethylsilyl-1-alkynes Method A

A mixture of the alkyne (0.24 mmol), CuBr (0.04 mmol, 15 mol%), benzylazide (0.26 mmol), and Et_3N (0.24 mmol) in DMF (0.5 mL) was stirred at 100 °C for the time indicated in Tables 1 and 2. The reaction mixture was cooled at r.t., a sat. solution of NH₄Cl was added and extracted with EtOAc. The organic layer was washed with H₂O, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography, silica gel, gradient hexane to EtOAc.

Method B

As described in method A, but additional $\rm H_2O$ (2 equiv) was added.

1-Benzyl-4-phenyl-1*H*-1,2,3-trizole (3a)

From 1-phenyl-2-trimethylsilylacetylene (**1a**, 27 mg, 30 µL, 0.15 mmol), CuBr (3.3 mg, 0.02 mmol), benzylazide (22 mg, 21 µL, 0.17 mmol), and Et₃N (16 mg, 22 µL, 0.16 mmol) in DMF (0.5 mL), afforded the titled compound (method A: 34 mg, 94% yield; method B: 97%) as a white solid; mp 134–136 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.82 (d, *J* = 7.2 Hz, 2 H), 7.69 (s, 1 H), 7.37 (m, 5 H), 7.33 (m, 2 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 148.35, 134.95, 130.78, 129.31, 129.01, 128.93, 128.34, 128.22, 125.88, 119.86, 54.34 ppm. HRMS (ESI⁺): *m/z* calcd for [M + Na]⁺: 258.1007; found: 258.1001.

(13) (a) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. Angew. Chem. Int. Ed. 2005, 44, 2210. (b) Nolte, C.; Mayer, P.; Straub, B. F. Angew. Chem. Int. Ed. 2007, 46, 2101.
(c) Ahlquist, M.; Fokin, V. V. Organometallics 2007, 26, 4389. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.