## Unsymmetrical Coupling of 1-Chloroalkynes and Terminal Alkynes under Experimental Sonogashira Conditions

Mikkel Andreas Christensen, Morten Rimmen, Mogens Brøndsted Nielsen\*

Department of Chemistry, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen Ø, Denmark

Fax +4535320212; E-mail: mbn@kiku.dk

Received: 23.08.2013; Accepted: 05.09.2013

Abstract: The coupling of a 1-chloroalkyne and a terminal alkyne to furnish a 1,3-butadiyne under experimental Sonogashira conditions is investigated. Through competition experiments, it is found that 1-chloroalkynes provide cross-coupling products as efficiently (or slightly better) in comparison with iodobenzenes, and almost as effectively as vinyl bromides. Yet, in regard to the degree of conversion into various products, chloroalkynes are the most reactive of all the substrates examined under the explored conditions. Optimized conditions for this cross-coupling reaction are presented.

Key words: alkynes, catalysis, copper, cross-coupling, palladium

1-Haloalkynes are precursors for the synthesis of unsymmetrical 1,3-butadiynes. The first use of haloalkynes for the formation of divnes was reported in 1954 by Black and co-workers,<sup>1</sup> who showed that iodoalkynes underwent coupling with alkynyl Grignard reagents in the presence of copper(I) chloride (CuCl) or cobalt(II) chloride (CoCl<sub>2</sub>). In 1955, Cadiot and Chodkiewicz<sup>2</sup> discovered that bromoalkynes and terminal alkynes could be coupled to give a divne using a copper(I) catalyst and an amine base. The first examples of coupling of chloroalkynes under similar conditions were reported 15 years later,<sup>3</sup> but with divne products being obtained in various yields. In the 1990s, the coupling of haloalkynes and terminal alkynes was further refined by the addition of a palladium co-catalyst, usually resulting in improved yields.<sup>4</sup> Alami and Ferri<sup>4e</sup> reported the palladium-catalyzed coupling of a chloroalkyne and a terminal alkyne, but the unsymmetrical 1,3-butadiyne was, however, obtained in rather low yield (20-30%). Subsequently, Nishihara et al.<sup>5</sup> developed a convenient route to unsymmetrical diynes by subjecting a chloroalkyne and a trimethylsilyl-protected alkyne to copper(I) chloride in N,N-dimethylformamide at 80 °C for 48 hours, in the absence of an amine base. They found that addition of a palladium catalyst decreased the yields on account of homocoupling of the chloroalkynes. One disadvantage of the method was the need to heat the reaction mixture for a long time, and for this reason, we became interested in investigating, in more detail, the scope of palladium-catalyzed cross-couplings of chloroalkynes and terminal alkynes under room-temperature Sonogashira conditions<sup>6</sup> [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, CuI, amine], which have proven so useful with aryl or vinyl halides as

*SYNLETT* 2013, 24, 2715–2719 Advanced online publication: 16.10.2013

DOI: 10.1055/s-0033-1339891; Art ID: ST-2013-D0815-L

© Georg Thieme Verlag Stuttgart · New York

substrates.<sup>7</sup> In particular, we wanted to establish the reactivity of chloroalkynes in comparison to traditional Sonogashira substrates.

Chloroalkynes are attractive substrates as they are relatively easily accessed. For example, we have developed a simple method for generating chloroalkynes by treating a trimethylsilyl-protected alkyne precursor with silver nitrate (AgNO<sub>3</sub>) and trichloroisocyanuric acid.<sup>8</sup>

First, we investigated the reactivity of the known chloroalkyne  $1^8$  toward different alkynes under Sonogashira conditions using diisopropylamine as the base (Scheme 1 and Table 1). Using different terminal alkynes (2.5–3.0 mol equiv) provided the corresponding butadiynes **2–5** in good yields (see Table 1) and in short reaction times (2–3 h). The only isolated by-products were the symmetrical diynes resulting from homocoupling of the terminal alkynes. When using only one molar equivalent of terminal alkyne, reduced, but still reasonable, yields were obtained.



Scheme 1 Synthesis of unsymmetrical butadiynes

Table 1	Coupling of Chloroalkyne <b>1</b> with Different Terminal
Alkynes	under Sonogashira Conditions

Entry	R	Alkyne equiv	Time	Product (yield)
1	SiMe <sub>3</sub>	3	2 h	<b>2</b> (75%)
2	SiMe <sub>3</sub>	1	2 h	2 (44%)
3	Ph	3	2 h	<b>3</b> (72%)
4	Ph	1	2 h	3 (44%)
5	$4-MeOC_6H_4$	3	3 h	4 (58%)
6	$4-MeOC_6H_4$	1	3 h	4 (39%)
7	$4-O_2NC_6H_4$	2.5	3 h	<b>5</b> (58%)
8	$4-O_2NC_6H_4$	1	3 h	<b>5</b> (35%)

Having established that the chloroalkyne 1 undergoes palladium-catalyzed cross-couplings, our next objective was to establish its reactivity in comparison to aryl halides. For this goal we turned to competition experiments9 in which an approximate 1:1:1 mixture of chloroalkyne, aryl halide, and terminal alkyne was subjected to Sonogashira conditions. We used trimethylsilylacetylene as the terminal alkyne in an amount that corresponded roughly to one equivalent. The reaction mixtures, after a standard washing procedure, were analyzed by GC-MS in order to establish the product ratios. First, a competition experiment between chloroalkyne 1 and 4-bromobenzonitrile (6) was conducted (Scheme 2). After two hours, the mixture (following work-up by extraction<sup>9</sup>) was analyzed by GC-MS (see the Supporting Information). Apart from some butadivne generated by homocoupling of trimethylsilylacetylene (indicating that it was present in some excess), only the diyne cross-coupling product 2 was formed. A signal due to unreacted 4-bromobenzonitrile was observed, while no signals corresponding to unreacted chloroalkyne 1 or the cross-coupling product 7 were evident.



**Scheme 2** Competition experiment. *Reagents and conditions*: PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%), CuI (5 mol%), 2 h, r.t.

Next, we studied the reactivity of the parent chloroethynylbenzene 8<sup>8</sup> in comparison to bromo- and iodobenzene (Scheme 3). The conversions after two hours of reaction are shown in Table 2. GC-MS analysis (see the Supporting Information) revealed that, in the presence of bromobenzene, the chloroalkyne underwent conversion into the butadiyne cross-coupling product 9 (but unreacted chloroalkyne was also present after 2 h), while the product 10 was not formed from bromobenzene (Table 2, entry 1). Thus again, this experiment signals the higher reactivity of a chloroalkyne in comparison to bromobenzene. In addition, we identified a product in substantial amount, which we assigned as the butadiyne 11. Formation of this product can be explained by a reductive homocoupling of two chloroalkynes, as previously reported for the coupling of bromo- and iodoalkynes.<sup>4c,d,10</sup> Using instead iodobenzene as the competing coupling partner, we found from two independent experiments (Table 2, entries 2 and 3) that the products 9 and 10 formed in almost equal amounts. To verify the accuracy of the method, a mixture of 9 and 10, prepared from the pure compounds, was analyzed by <sup>1</sup>H NMR spectroscopy and GC–MS; both methods gave similar ratios between the two species (see the Supporting Information). In addition to the product **11**, 1,2-diphenylethyne (**12**) was also formed, corresponding to a reductive cross-coupling of **8** and iodobenzene. With respect to GC–MS evaluation of the contents of the mixtures, it should be noted that both the bromobenzene and iodobenzene starting materials gave lower intensities than expected from reference mixtures with compounds balanced out in known ratios (see the Supporting Information). Moreover, some of these aryl halides were lost in the intermediate work-up procedure (during evaporation of solvents), but this is not relevant for the ratios provided in Table 2 and in the subsequent Tables, that only show relative product distributions [in this regard ignoring the 1,4-bis(trimethylsilyl)buta-1,3-diyne product], and not including unreacted starting materials.



**Scheme 3** Competition experiments. *Reagents and conditions*: PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%), CuI (5 mol%), 2 h, r.t. For product ratios, see Table 2.

 Table 2
 Outcomes of the Competition Experiments (cf. Scheme 3);

 Product Distributions Based on GC–MS Analysis

Entry	Ph–X	<b>9</b> (%)	10 (%)	11 (%)	12 (%)
1	Ph–Br	61	0	39	0
2	Ph–I	34	33	14	19
3	Ph–I	35	31	14	20

The different reactivities of the chloroalkyne and aryl bromide functionalities should allow for selective coupling reactions. Subjecting compound 13 and trimethylsilylacetylene to Sonogashira conditions furnished the diyne product 14 in an isolated yield of 63% (Scheme 4). GC–MS analysis of the crude reaction mixture also revealed the presence of by-products 15 and 16, but only in minor quantities.

Vinyl bromides are usually more reactive than iodobenzenes in the Sonogashira coupling,<sup>7</sup> and are hence also expected to be more reactive than chloroalkynes. A competition experiment between the bromostyrene **17** and the chloroalkyne **8** was performed (Scheme 5 and Table 3), the outcome of which revealed a ratio (1.2-1.3) between cross-coupling products **18** and **9** in favor of enyne



Scheme 4 Selective cross-coupling reaction

18, from two independent experiments. Yet, when comparing GC–MS and NMR ratios of a preformed mixture of the two compounds, it seems that GC–MS overestimates the content of 18 (see the Supporting Information) (by a factor of ca. 1.2 relative to the ratio found by NMR). Taking this uncertainty in the method into account, the yield of 9 was comparable to that of 18. Again the reductive homocoupling product 11 of the chloroalkyne was observed, along with the envne 19 corresponding to reductive crosscoupling of the chloroalkyne and bromostyrene substrates. It is also noteworthy that no chloroalkyne starting material 8 was observed by GC-MS, while some bromostyrene 17 remained. Although the chloroalkyne may have been lost during work-up (evaporation under reduced pressure), GC-MS showed a higher intensity of the products originating from the chloroalkyne than those derived from the bromostyrene, and it thus seems that the chloroalkyne is more readily converted into different products under the explored conditions.



Scheme 5 Competition experiment. *Reagents and conditions*: PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%), CuI (5 mol%), 2 h, r.t. Compounds 18 and 19 were formed as *cis/trans* mixtures.

© Georg Thieme Verlag Stuttgart · New York

**Table 3** Outcomes of the Competition Experiments (cf. Scheme 5;Two Independent Experiments); Product Distributions Based on GC–MS Analysis

Entry	9 (%)	18 (%)	11 (%)	19 (%)		
1	28	36	14	22		
2	33	39	15	13		

Next, we studied the influence of having an alkyl group instead of an aryl group on the chloroalkyne. Scheme 6 and Table 4 show the results of competition experiments between 1-chloro-1-octyne (20) and aryl halides. It was evident that 20 was significantly more reactive than bromobenzene (product 21 was formed almost exclusively, Table 4, entries 1 and 2). In comparison to iodobenzene, more of the cross-coupled product was obtained from 20, as revealed by the ratio between products 10 and 21 of approximately 1.4 (Table 4, entries 3 and 4). Again it is note-worthy that while both halobenzene substrates were observed by GC–MS after two hours of reaction, no signal from the chloroalkyne 20 was evident.



**Scheme 6** Competition experiments. *Reagents and conditions*: PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%), CuI (5 mol%), 2 h, r.t. For product ratios, see Table 4.

**Table 4** Outcomes of the Competition Experiments (cf. Scheme 6);Product Distributions Based on GC–MS Analysis

Entry	Ph–X	21 (%)	10 (%)	22 (%)	23 (%)
1	Br	67	0.5	32.5	0
2	Br	80	0	20	0
3	Ι	34	25	6	35
4	Ι	33	23	13	31

In order to diminish formation of the homocoupling product from two chloroalkynes, we screened the effect of increasing the copper-to-palladium ratio on the reaction between chloroalkyne 8 and trimethylsilylacetylene. The GC-MS product ratios (9:11) under different conditions are listed in Table 5. The validity of the GC-MS ratios

was ascertained by analyzing two mixtures with known amounts of the two products (see the Supporting Information). The results showed that by using a higher copper:palladium ratio, the yield of the desired crosscoupling product 9 was increased (Table 5, entries 1 vs 2 and 3 vs 4). When using three molar equivalents of the terminal alkyne (Table 5, entry 4), the yield increased to 91%. Further, we found that using tetrakis(triphenylphosphine)palladium(0)  $[Pd(PPh_3)_4]$  as the palladium catalyst instead of bis(triphenylphosphine)palladium(II) dichloride  $[PdCl_2(PPh_3)_2]$  had little influence on the product ratio, but the reaction time was increased significantly (Table 5, entry 5). It seemed that the prolonged reaction time was due to the additional triphenylphosphine  $(Ph_3P)$ ligands. As previously recognized for Sonogashira couplings,<sup>11</sup> this is likely due to the larger equilibrium content of catalytically inactive tris(triphenylphosphine)palladium(0) species at the expense of the catalytically active bis(triphenylphosphine)palladium(0) [Pd(PPh<sub>3</sub>)<sub>2</sub>] species for the oxidative addition step. Indeed, when repeating the reaction with bis(triphenylphosphine)palladium(II) dichloride plus two molar equivalents of triphenylphosphine (relative to the Pd catalyst), no conversion was observed according to TLC analysis after two hours, while a parallel reaction without the additional triphenylphosphine seemed to be complete after this period. According to TLC, it took more than 17 hours for the reaction with added triphenylphosphine to go to completion (Table 5, entry 6). The ratio between 9 and 11 was, however, slightly more beneficial for 9 than that obtained in entry 3. We also tested the influence of leaving out either of the two catalysts. Thus, in the absence of a palladium catalyst, only starting material was observed by GC-MS after 120 hours (Table 5, entry 7). When copper(I) iodide was omitted, some conversion was observed with the bis(triphenylphosphine)palladium(II) dichloride catalyst, but the reaction proceeded very slowly; after 120 hours, GC-MS analysis provided a ratio between starting material 8 and product 9 of 66:34. Using tetrakis(triphenylphosphine)palladium(0) instead (and no CuI), less than 1% conversion was observed after 120 hours. Overall, these experiments show that for optimal coupling conditions both the palladium and copper sources should be present. Thus, palladium plays an active role in the reaction mechanism, although we cannot say whether the mechanism strictly follows the conventional Sonogashira mechanism.

In conclusion, chloroalkynes readily undergo cross-coupling reactions with terminal alkynes under experimental Sonogashira conditions. From competition experiments, we can place chloroalkynes in the following sequence when it comes to furnishing the cross-coupling product: vinyl bromide  $\geq$  chloroalkyne  $\geq$  aryl iodide >> aryl bromide. However, when it comes to general reactivity, with conversions not only providing the desired cross-coupling product, chloroalkynes seem to be the most reactive substrates under the explored conditions. Finally, it should be emphasized that our primary aim in this work was to es-

LETTER

 Table 5
 Optimization of the Conditions for the Reaction between 8

 and Trimethylsilylacetylene; Product Distributions from GC–MS

 Analysis

Entry	Pd cat. (mol%) <sup>a</sup>	CuI (mol%)	Alkyne (equiv)	Time (h)	9 (%)	11 (%)
1	5	5	1	3	61	39
2	1	10	1	3	75	25
3	5	5	3	3	81	19
4	1	10	3	3	91	9
5	5 <sup>b</sup>	5	3	24	77	23
6	5°	5	3	24	87	13
7	0	5	3	120	0	0

<sup>a</sup> Pd cat. = PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> unless otherwise stated.

<sup>b</sup> Pd cat. =  $Pd(PPh_3)_4$ .

<sup>c</sup> PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> + PPh<sub>3</sub> (2 equiv).

tablish which substrates provide Sonogashira cross-coupling products most readily under similar experimental conditions, which is particularly important when aiming at selective cross-coupling reactions on multifunctional molecules, but this does not imply that the investigated substrates necessarily follow the exact same mechanism of coupling.

## Acknowledgment

The University of Copenhagen is gratefully acknowledged for financial support. We thank Mr. Dennis Larsen for recording HRMS spectra.

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

## References

- Black, H. K.; Horn, D. H. S.; Weedon, B. C. L. J. Chem. Soc. 1954, 1704.
- (2) Cadiot, P.; Chodkiewicz, W. C. R. Hebd. Seances Acad. Sci. 1955, 241, 1055.
- (3) Philippe, J.-L.; Chodkiewicz, W.; Cadiot, P. *Tetrahedron* Lett. **1970**, 1795.
- (4) (a) Wityak, J.; Chan, J. B. Synth. Commun. 1991, 21, 977.
  (b) Elbaum, D.; Nguyen, T. B.; Jorgensen, W. L.; Schreiber, S. L. Tetrahedron 1994, 50, 1503. (c) Alzer, J.; Vasella, A. Helv. Chim. Acta 1995, 78, 177. (d) Cai, C.; Vasella, A. Helv. Chim. Acta 1995, 78, 2053. (e) Alami, M.; Ferri, F. Tetrahedron Lett. 1996, 37, 2763.
- (5) (a) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075. (b) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. J. Org. Chem. **2000**, *65*, 1780.
- (6) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* 1975, 4467.
- (7) Chinchilla, R.; Nájera, C. Chem. Soc. Rev. 2011, 40, 5084.
- (8) Vilhelmsen, M. H.; Andersson, A. S.; Nielsen, M. B. Synthesis 2009, 1469.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

## (9) Competition Experiments; General Procedure

The chloroalkyne (0.7 mmol) and the appropriate aryl or vinyl halide (0.7 mmol) were dissolved in THF (10 mL) and disopropylamine (2 mL). To this solution was added  $PdCl_2(PPh_3)_2$  (26 mg, 0.037 mmol), CuI (7 mg, 0.04 mmol), and trimethylsilylacetylene (ca. 72 mg, ca. 0.7 mmol). After stirring the mixture at r.t. for 2 h, sat. aq NH<sub>4</sub>Cl solution (25

mL) was added, and the mixture was extracted with  $CH_2Cl_2$  (50 mL), washed with brine (25 mL), dried over  $Na_2SO_4$ , filtered and concentrated under reduced pressure. The residue was analyzed by GC–MS.

- (10) Weng, Y.; Cheng, B.; He, C.; Lei, A. Angew. Chem. Int. Ed. 2012, 51, 9547.
- (11) Amatore, C.; Jutand, A. Acc. Chem. Res. 2000, 33, 314.

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.