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Synthetic Methods

A Versatile and Highly Efficient Method for 1-Chlorination of Terminal and Trialkylsilyl-Protected Alkynes

Nurbey Gulia, Bartłomiej Pigulski, Marta Charewicz, and Sławomir Szafert*[a]

Abstract: A highly efficient one-pot procedure for the preparation of 1-chloroalkynes and 1-chlorobutadiynes from terminal and trialkylsilyl-protected precursors is reported. This convenient reaction, proceeding under mild conditions, utilizes *N*-chlorosuccinimide as the chlorinating agent and tolerates a range of functional groups.

1-Chloroalkynes are attracting increasing interest in the scientific community owing to their use in organic and organometallic synthesis. Such species have been applied in numerous areas, such as carbon–carbon bond-forming reactions,[1] syntheses of various haloalkene derivatives,[2] and cyclization reactions.[3]

Classically, 1-chloroalkynes are obtained from terminal alkynes by using a strong base and an appropriate chlorinating agent.[4] A typical reaction pathway proceeds through a deprotonated alkyne and prevents the use of some functional groups, for example the hydroxyl group. Other important routes towards the synthesis of 1-chloroalkynes include the chlorination of terminal alkynes by using hypochlorites,[5] the use a AgOAc/NCS (Ac = acetyl, NCS = *N*-chlorosuccinimide) system[6] or a CCl_4/K_2CO_3/TBAF (TBAF = tetrabutylammonium fluoride) system,[7] and the use of phase-transfer catalysis.[8]

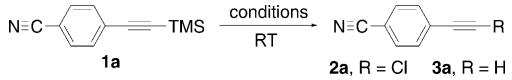
The use of terminal alkynes, although common, can sometimes be problematic because these compounds can be unstable, especially long homologs. Trialkylsilyl end-capped alkynes and polyynes are usually much more stable[9] and are widely used. Therefore, the direct chlorination of silyl-protected alkynes could be a very valuable route towards 1-chloroalkynes.

Although the preparation of 1-bromo- and 1-iodoalkynes from trialkylsilyl-protected acetylenes is well known,[10] the analogous synthesis of 1-chloroalkynes presents a challenge. To the best of our knowledge, there is only one report on such a transformation, which describes the use of TCCA (trichloroisocyanuric acid) as the chlorinating agent.[11] Nevertheless, a long reaction time or microwave heating is required and for some compounds multiple chlorination products and low yields are observed. Additionally, this reaction was only applied to a few compounds.

Herein, we report a new, convenient, and high-yielding procedure that leads to 1-chloroalkynes and 1-chlorobutadiynes from trialkylsilyl-protected compounds, as well as from terminal alkynes. To avoid multiple chlorinations occurring, NCS was selected as the chlorinating agent because of its lower activity, compared with that of TCCA.[12] In search of an effective reaction system, 4-(trimethylsilylethynyl)benzonitrile has been selected as a model compound owing to the ease of its preparation and the low volatility of the corresponding chloride.

The resulting yields for the different reaction systems are shown in Table 1. Conditions analogous to those for bromination and iodination[13] (Table 1, entry 1) did not lead to the corresponding 1-chloroalkyne. The use of AgOTf (OTf = trifluoromethanesulfonate) led to the corresponding terminal alkyne (Table 1, entry 2). $AgNO_3$/KF (Table 1, entry 3) enabled the reaction, but provided the product in low yield, probably because of the limited solubility of KF. A similarly poor result was obtained for the $K_2CO_3/AgNO_3$ system (Table 1, entry 5), whereas the KOH/$AgNO_3$ mixture (Table 1, entry 4) was not effective at all. Finally, the most promising results were obtained by using an $AgNO_3$/TBAF system (Table 1, entry 6), which was then selected for further optimization.

Table 1. Screening of reaction systems.



1a **2a**, R = Cl **3a**, R = H

Entry	Conditions [(equiv)]	Yield [%][a] 2a	3a
1	NCS (1.5), AgF (1.0), acetone, 22 h[b]	0	0
2	NCS (2.0), AgOTf (0.3), acetone, 24 h	0	84
3	NCS (1.2), KF (0.3), $AgNO_3$ (0.3), acetone, 6 h	6	46
4	NCS (1.2), KOH (18), $AgNO_3$ (0.3), DMF, 45 min[c]	0	0
5	NCS (1.2), K_2CO_3 (3.0), $AgNO_3$ (0.3), acetone, 30 h[d]	12	44
6	NCS (2.4), TBAF (1.0), $AgNO_3$ (0.3), DMF, 20 h	65	9

[a] Relative quantities of products were estimated from the NMR spectra and yields were calculated in reference to the starting material. [b] Only starting material was recovered. [c] Decomposition of starting material was observed. [d] Carried out under reflux.

Following this result, the influence of the solvent and the quantity of reactants (Table 2) were investigated. The results showed that a TBAF/$AgNO_3$ ratio of 2:1 (Table 2, entries 1–6)

[a] *Dr. N. Gulia,[+] B. Pigulski,[+] M. Charewicz, Dr. S. Szafert*
Department of Chemistry, University of Wrocław
14 F. Joliot-Curie, 50-383 Wrocław (Poland)
E-mail: slawomir.szafert@chem.uni.wroc.pl

[+] *These authors contributed equally to this work.*

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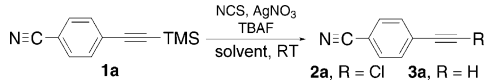
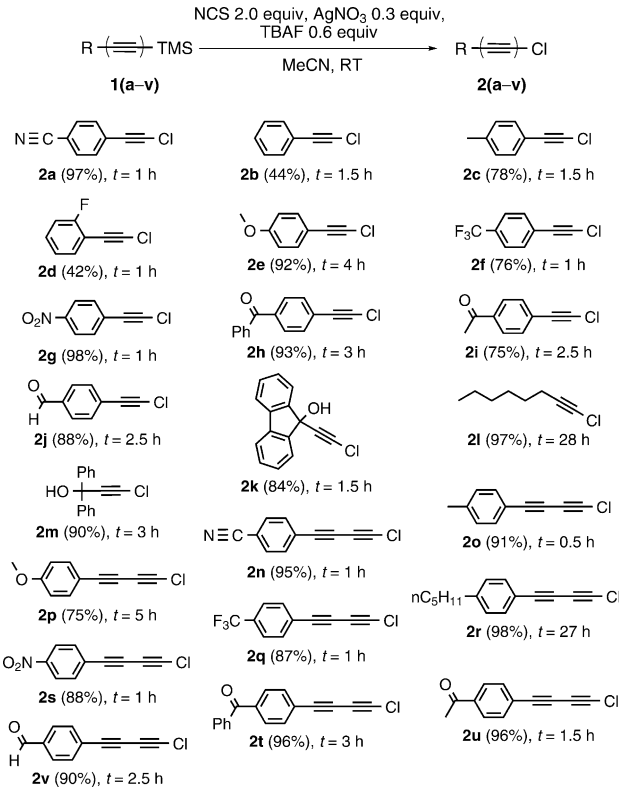
Table 2. Optimization of chlorination conditions.



1a **2a**, R = Cl **3a**, R = H

Entry[a]	$AgNO_3$ [equiv]	TBAF [equiv]	Solvent	Time [h]	Yield [%][b] 1a	2a	3a
1	0.3	1.0	DMF	0.7	0	**75**	0
2	0.3	0	DMF	24	0	**0**	55
3	0.3	0.1	DMF	0.7	0	**0**	79
4	0.3	0.2	DMF	16	30	**22**	25
5	0.3	0.3	DMF	1	18	**81**	0
6	0.3	0.6	DMF	1	0	**79**	5
7	0	0.6	DMF	22	0	**67**	31
8[c]	0.3	0.6	DMF	24	0	**66**	22
9	0.1	0.2	DMF	1.2	46	**41**	trace
10	0.1	0.2	acetone	23	62	**21**	9
11	0.1	0.2	CH_2Cl_2	23	37	**23**	6
12	0.1	0.2	MeCN	22	69	**26**	2
13	0.3	0.6	acetone	3.2	0	**94**	2
14	0.3	0.6	CH_2Cl_2	3	15	**78**	7
15	0.3	0.2	MeCN	22	42	**22**	28
16	0.3	0.6	MeCN	1	0	**97**	0

[a] 2.0 equivalents of NCS were used. [b] Relative quantities of products were estimated from the NMR spectra and yields were calculated in reference to the starting material; [c] 1.0 equivalent of NCS was used.



Scheme 1. Preparation of 1-chloroalkynes and 1-chlorobutadiynes from TMS-protected compounds. Yield of isolated product shown in parentheses.

was the most effective. A 1:1 ratio also gave a high yield of product, but a large amount of the starting material was also recovered (Table 2, entry 5). The absence of $AgNO_3$ (Table 2, entry 7), or a smaller quantity of NCS (Table 2, entry 8) led to the formation of significant amounts of the terminal alkyne. This finding proved that both $AgNO_3$ and an excess of NCS were necessary for the desired reaction to occur.

Also, the stoichiometry of the system appeared to strongly influence the yield. Reducing the amount of $AgNO_3$/TBAF from $AgNO_3$ (0.3 equivalents), TBAF (0.6 equivalents) to $AgNO_3$ (0.1 equivalents), TBAF (0.2 equivalents), in different solvents, gave only 21–41% of the desired product (Table 2, entries 9–12) compared with 78–97% for entries 6, 13, 14, and 16. It appears that, in general, polar solvents favor the formation of the desired product. Acetonitrile gave the best results; however, acetone and DMF can be used as alternatives when acetonitrile is an inappropriate solvent for the reaction. Finally, we managed to obtain **2a** almost quantitatively (Table 2, entry 16) by using acetonitrile, 0.3 equivalents of $AgNO_3$, 0.6 equivalents of TBAF, and 2.0 equivalents of NCS. These conditions were chosen for further investigations.

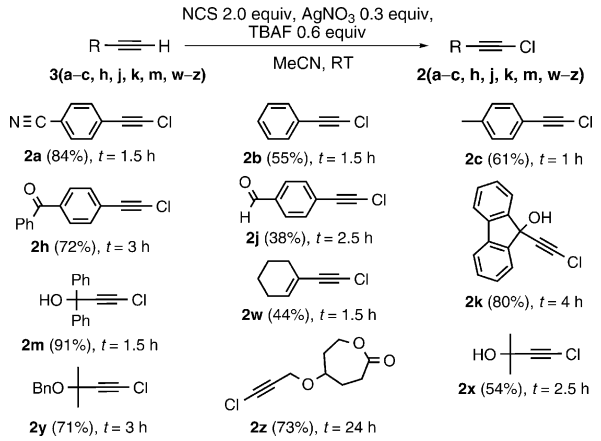
It was found that a critical element of this reaction is the order of addition of the reagents. 1-Chloroalkyne was obtained only when TBAF was added as the last component of the system. The addition of TBAF before the addition of NCS led to decomposition of the starting material and the desired product was not observed.

Next, the procedure was tested by using a series of trimethylsilyl- (TMS-) protected alkynes and butadiynes, as shown in Scheme 1. The desired products were usually obtained with good to excellent (75–98%) yields. Only for the two most volatile 1-chloroalkynes (**2b** and **2d**) were the yields markedly lower (42–44%). All reactions were monitored by TLC and were quenched after consumption of the starting material. In most cases the reaction time was under 5 h, however, the reaction to produce **2r** and **2l** needed over 24 h to reach completion.

This research shows high versatility of the designed protocol and a great tolerance towards many functional groups (only for 4-[(trimethylsilyl)ethynyl]aniline and acetylene-substituted benzoxazine did the reaction give an unresolved mixture of unidentified products). The great advantage of this method is the easy synthesis of 1-chlorobutadiynes (Scheme 1) from the stable TMS-protected precursors. To the best of our knowledge very few syntheses of such compounds have been reported.[14]

Whereas the 1-chloroalkynes synthesized in this study are quite stable, the 1-chlorobutadiynes usually decomposed at room temperature within hours, in accordance with the properties of 1-chlorobutadiynes already described in the literature.[14b] The two liquid butadiynes (**2o** and **2r**) are extremely unstable, becoming dark in color a few minutes after isolation. Nevertheless, all of the synthesized compounds can be stored at low temperatures (−30 °C) for months, both in solid and in solution form.

Next, we tried to discover the role of TBAF in the reaction system. Because TBAF is mainly used for the deprotection of silyl-protected alkynes and alcohols,[15] we wanted to verify if, in this case, it acts as an deprotecting agent or whether it also has an additional role in the chlorination process. Towards this end, a room-temperature reaction of terminal 4-ethynylbenzonitrile with 0.3 equivalents of $AgNO_3$ and 2.0 equivalents of



Scheme 2. Preparation of 1-chloroalkynes from terminal alkynes. Yield of isolated product shown in parentheses.

NCS (in the absence of TBAF) in acetonitrile was carried out. After 48 h only the starting material was detected and the chlorinated product was not observed, even in trace amounts. As shown in Scheme 2, the same reaction carried out in the presence of TBAF (0.6 equivalents) gave the desired product in 84% yield. This result suggests that TBAF is required, not only to remove the silyl substituent, but also for the chlorination step. Although we made no attempts to investigate the mechanism of the activation of the terminal SiR_3 moiety, or H atom, by catalytic amounts of F^- ions, this mechanism has already been discussed in the literature.[7a,16]

Next, the chlorination procedure was tested for a series of terminal alkynes, as shown in Scheme 2. Products were obtained with good to excellent yields, proving that these conditions are also useful for H-terminated alkynes.

Bulky trialkylsilyl-protected alkynes were then tested. Such sterically hindered groups are widely used in acetylene chemistry because these bulky alkynes are far more stable than TMS-protected alkynes.[15] Moreover, in coupling reactions, acetylenes with bulkier groups can sometimes provide higher yields of product than the corresponding TMS-protected acetylenes.[17]

As shown in Table 3, TES-, TBDMS-, and TIPS-protected **4a**, **5a**, and **6a** were successfully transformed into the corresponding 1-chloroalkyne with good to excellent yields (69–96%). Bulkier silanes are more stable under the reaction conditions, therefore, longer reaction times were needed (Table 3).

Finally, selective desilylation–chlorination was investigated. Several simple compounds, containing bulky (trialkylsilyl)ethynyl groups, were used. These groups were TES (**1aa**), TBDMS (**1ab**), and TIPS (**1ac**). The corresponding products (**2aa**–**ac**) were obtained in 43–64% yield, but the reaction was selective only when TBAF was added dropwise over approximately 0.5 h. The same reaction under standard conditions (TBAF added in one portion) also gave products **2aa** (42%) and **2ac** (53%), but was not selective, 1,4-bis(chloroethynyl)benzene was obtained in 14 and 12%, respectively.

In summary, a new and high-yielding method for the chlorination of trialkylsilyl-protected acetylenes has been developed. Owing to the mild conditions required, this reaction has a broad tolerance towards different functional groups and has successfully been utilized to obtain a series of 1-chlorobutadiynes rarely seen in the literature. The procedure has proven effective towards bulkier silyl end groups (TES, TBDMS, and TIPS) and showed selectivity against different silyl substituents. This was achieved by slow and controlled addition of TBAF, which appeared to play not only the role of a deprotecting agent, but also an active role in the chlorination process.

Experimental Section

General procedure

The alkyne (1 equivalent) was dissolved, under N_2, in acetonitrile and $AgNO_3$ (0.3 equivalents) and *N*-chlorosuccinimide (NCS, 2.0 equivalents) were added. Tetrabutylammonium fluoride (TBAF, 0.6 equivalents) was then added and the mixture was stirred at room temperature (0.5–24 h). The solvent was then removed under reduced pressure and the crude product was purified by passing the mixture through a short silica-gel plug (yield: 38–98%).

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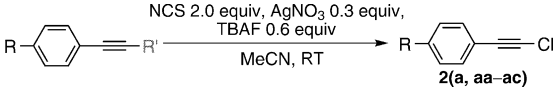
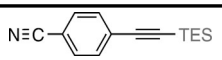
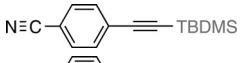
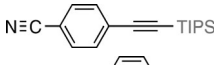
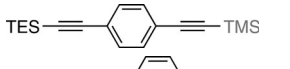
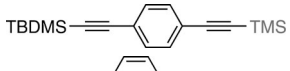
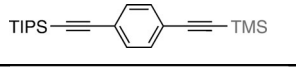
Table 3. Chlorination of sterically hindered trialkylsilyl-protected alkynes.[a]



Starting material		Product	Time [h]	Yield [%][b]
4a		**2a**	4.5	69
5a		**2a**	23	83
6a		**2a**	4	96
1aa[c]		**2aa**	2	43
1ab[c]		**2ab**	2	54
1ac[c]		**2ac**	2	64

[a] TES = triethylsilane; TBDMS = *tert*-butyldimethylsilane; TIPS = triisopropylsilane. [b] Yield of isolated product. [c] Slow addition of TBAF (over 0.5 h).

Keywords: 1-haloalkynes · chlorine · halogenation · silanes · synthetic methods

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