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New Method Based on 1-(Trimethysilyl)alk-1-yne To Prepare 1,4-Skipped Diynes

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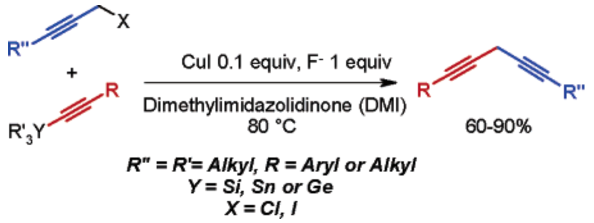
ABSTRACT



We have developed a novel reaction between a terminal TMS-alkyne and a propargyl halide in the presence of a fluoride source and a catalytic amount of copper iodide to prepare 1,4-skipped diynes with good yields and in mild conditions. We have shown that this reaction also works very well with germanium and tin derivatives as an alternative to silicon. This new method can be useful for the synthesis of polyunsaturated fatty acids.

PUFAs (polyunsaturated fatty acids) are widespread in nature, especially the ω-3 fatty acids DHA (docosahexaenoic acid, 22:6) and EPA (eicosapentaenoic acid, 20:5). These highly unsaturated fatty acids are sought after as synthetic targets for therapeutic drugs and food additives.[1,2] A large number of polyunsaturated fatty acids were synthesized using 1,4-diene units through two subsequent Wittig reactions[3] or by using 1,4-skipped diynes[4] as intermediates[5] followed by a catalytic Lindlar partial hydrogenation step. Two major methods are used to prepare 1,4-skipped diynes. The first one is based upon the use of magnesium−copper acetylide systems and a primary propargyl electrophile (halides or sulfonic ester groups).[6] Alternatively, the use of a primary propargyl halide with a terminal acetylene in the presence of a copper(I) salt and an inorganic or organic base is used.[7] In both cases, the key intermediate is a copper acetylide. These reactions are not always chemoselective, and/or the use of base can be limiting with base-sensitive substrates.[8,9]

These observations led us to look for an alternative mild method for the generation of the copper acetylide reagent which induced suitable experimental conditions for these

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[5] Voss, A.; Reinhart, M.; Sankarappa, S.; Sprechter, H. *J. Biol. Chem.* **1991**, *266*, 19995−20000 and ref 1.

[6] Ege, S. N.; Wolovsky, R.; Gensler, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 3080−3085. For a general coverage, see: Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam: 2003 and references therein.

[7] Sevin, A.; Chodkiewicz, W.; Cadiot, P. *Bull. Soc. Chim. Fr*. **1974**, *5−6*, 913−917. Sevin, A.; Chodkiewicz, W.; Cadiot, P. *Tetrahedron Lett.* **1965**, *24*, 1953−1959. Jeffery, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett*. **1992**, *33*, 5757−5760. Lapitskaya, M. A.; Vasiljeva, L. L.; Pivnitsky, K. K. *Synthesis* **1993**, *1*, 65−66.

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sensitive substrates. In this paper, we report the direct use of 1-TMS-alk-1-ynes in copper-catalyzed coupling reactions with propargylic halides to form 1,4-skipped diynes. We also show that the same reaction can be applied to germanium acetylide and tin acetylide derivatives.

TMS-protected acetylenes are frequently used as intermediates in organic synthesis, with a deprotection step required before copper-coupling protocols.[10] In addition, within a total synthesis the orthogonal protection of two terminal acetylenes could be advantageous.[11] The formation of copper acetylide via a 1-TMS-alk-1-yne is a practical method described originally by Hosomi et al.[12] in 1997. The authors prepared ynones by starting with 1-TMS-alk-1-ynes and acyl chlorides (Figure 1).

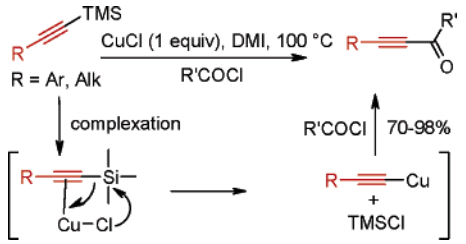

Figure 1. Preparations of ynones from 1-TMS-alk-1-ynes and acyl chlorides.[12]

It should be noted that the reaction of copper acetylides generated by this method was also used with other electrophiles such as chloroethynyls[13] and vinylic iodides.[14]

We thought that it would be possible to obtain 1,4-skipped diynes by applying this method, replacing the acyl chloride by a propargyl halide (Figure 2).

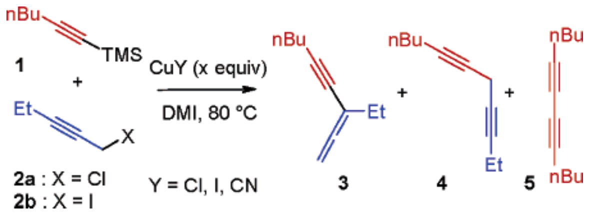

Figure 2. Preparation of 1,4-skipped diynes from 1-TMS-hex-1-yne and 1-chloropent-2-yne.

Initially, we used the conditions described by Hosomi et al. (Table 1, entry 1). Based on GC/MS analysis, the reaction of the 1-TMS-hex-1-yne **1** and the 1-chloropent-2-yne **2a** in the presence of a stoichiometric amount of copper chloride in DMI (1,3-dimethylimidazolidin-2-one) gave the desired 1,4-skipped diyne **4**, the allene **3** resulting from the S_N2' addition and the homocoupling product **5**.

Table 1. First Results under Hosomi's Conditions[a]

entry	X	time (days)	CuCl (equiv)	GC ratio[15] **3/4/5**	isolated yields (%) of **3/4/5**
1	Cl	1	1	traces/0.7/1	nd/nd/15
2	Cl	2	0.1	0/0/1	nd/nd/20
3	I	1	1	0.5/1/0.4	nd/20/10

[a] nd: not detected (may be a consequence of the volatility of the product). Reactions conducted with 1.0 equiv of **2** at 80 °C in nondegassed DMI (c = 0.5 M).

The use of catalytic amounts of CuCl gave compound **5** resulting from homocoupling (entry 2) as the only product (Table 1, entry 2). However, we were successful in isolating the 1,4-skipped diyne in 20% yield using the 1-iodopent-2-yne **2b** as starting material (Table 1, entry 3). This is the first time that a 1,4-skipped diyne has been obtained by using this method.

Encouraged by this result, we turned our attention to further optimize this reaction. Oxidative homocoupling of acetylene derivatives is well-known in the literature.[16] To avoid this side reaction, we carefully degassed the starting materials and the solvent. Use of degassed reaction mixture did not increase the yield of 1,4-skipped diyne **4**. However, it did inhibit the formation of the undesired homocoupling compound **5**. Next, we tested various copper(I) salts and/or additives in order to investigate their contributions to this transformation (Table 2).

Table 2. Coupling with Different Copper Salts and Additives[a]

entry	X	time (days)	CuX (equiv)	additive (equiv)	isolated yield of **4** (%)
1	Cl	0.75	CuCl (1)	NaI (0.2)	40
2	Cl	0.75	CuCl (1)	TBAI (0.2)	35
3	Cl	4	CuI (1)		40
4	Cl	4	CuCN (1)		20

[a] Reactions conducted with 1.0 equiv of **2** at 80 °C in degassed DMI (c = 0.5 M). No allenes and homcoupling product were isolated.

The addition of NaI or TBAI (tetrabutylammonium iodide, 0.2 equiv) increased the yield to 40% and 35%, respectively

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(8) Mel'nikova, V. I.; Pivnitskii, K. K. *Zh. Org. Khim.* **1990**, *26*, 78−82. Mathai, I. M.; Taniguchi, H.; Miller, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 115−120. Taniguchi, H.; Mathai, I. M.; Miller, S. I. *Tetrahedron* **1966**, *22*, 867−78.

(9) Florian Montel, Pierre, M. J. Jung unpublished results: during our synthesis of DHA with classical coupling conditions, we discovered that the intermediate 1-chloro-2,5-octadiyne and the product 2,5,8-undecatriyn-1-ol were not stable in the presence of K_2CO_3 in DMF (after 16 h at rt: 66% of degradation for the 1-chloro-2,5-octadiyne and 50% for the 2,5,8-undecatriyn-1-ol). The use of a catalytic amount of copper for this reaction slows down the rate of the coupling reaction and allows the degradation of the intermediate and the final product.

(10) For recent examples, see: Romanov, S. G.; Ivanov, I. V.; Shevchenko, V. P.; Nagaev, I. Y.; Pushkov, A. A.; Myasoedov, N. F.; Myagkova, G. I.; Kuhn, H. *Chem. and Phys. Lip.* **2004**, *130*, 117−126. Teply, F.; Stara, I. G.; Stary, I.; Kollarovic, A.; Saman, D.; Vyskocil, S.; Fiedler, P. *J. Org. Chem.* **2003**, *68*, 5193−5197.

(11) For example, see: Ernst, A.; Gobbi, L.; Vasella, A. *Tetrahedron Lett.* **1996**, *37*, 7959−7962.

(Table 2, entries 1 and 2). This yield increase presumably is due to the in situ formation of CuI, which is more soluble and leads to a more efficient reaction. The in situ formation of propargyl iodide is also possible but was shown not to contribute to the yield increase (Table 1, entry 3). Noteworthy, an opposing effect was observed by Hosomi et al.[12] Effectively, CuI gives a lower yield than CuCl in the addition of TMS-acetylenes on acyl chlorides via Cu-catalyzed reaction.

A further yield improvement was realized through the addition of a fluoride source, presumably by favoring the copper−silicon exchange (Table 3).[17]

Table 3. Influence of the Fluoride Source and the Temperature[a]

entry	XF	solvent	T (°C)	CuI (equiv)	product **4** (%)
1	CsF	DMI	80	1	68
2	CsF	DMF	80	1	64
3	KF	DMI	80	1	60
4	TBAF	DMI	80	1	82
5	NaF	DMI	80	1	
6	LiF	DMI	80	1	
7	CsF	DMI	80		3
8	TBAF	DMI	80		5
9	CsF	DMI	80	0.1	56
10	TBAF	DMI	80	0.1	72
11	CsF	DMI	rt	1	
12	CsF	DMI	50	1	<10
13	NaF	DMI	90	1	43
14	LiF	DMI	110	1	38

[a] Reactions conducted with 1.0 equiv of **2** and 1.0 equiv of XF at 80 °C in degassed DMI ($c = 0.5$ M). No allenes and homcoupling product were isolated.

Consequently, the reaction of the 1-TMS-hex-1-yne **1** and the 1-chloropent-2-yne **2a** in the presence of a stoichiometric amount of copper iodide and 1 equiv of cesium fluoride gave the desired 1,4-skipped diyne **4** in a respectable 68% yield. The use of TBAF further improved the yield to 82%. We postulate the formation of a pentavalent silicon species[18] **6** which facilitates the silicon−copper exchange reaction (Figure 3). In support of this, the existence of a similar intermediate has been proposed by Scheidt et al.[19]

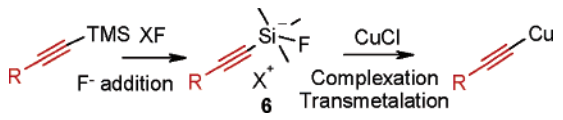

Figure 3. Mechanism proposed for the formation of the copper acetylide intermediate via a pentavalent silicon species.

Detailed investigation (Table 3) of this reaction showed that it is strongly solvent and fluoride source dependent. Of the solvents tested, only DMF or DMI (Table 3, entries 1 and 2) is suitable for this reaction; all others yield no identifiable product.[20] The addition of a fluoride source decreases the reaction time from 18 to 2 h, and no homocoupling product **5** could be detected even when solvents and reagents were not degassed.

As fluoride sources, cesium fluoride, potassium fluoride, and TBAF (tetrabutylammonium fluoride) could be used. However, when sodium or lithium fluoride were used, product **4** was only formed at higher temperatures and with lower yields (Table 3, entries 5 and 6 vs 13 and 14). The yields follow the classical scale of the nucleophilicity of fluoride from TBAF to LiF (82% to 0% at 80 °C. Table 3, entries 1 and 3−6).

For this transformation, we confirmed that copper iodide was crucial for an efficient coupling reaction (Table 3, entries 7 and 8). In addition, we found that copper iodide could be used in catalytic quantity, with a reduction in yield of around 10% when we used 10 mol % of copper iodide rather than 1 equiv (Table 3, entries 9 and 10). To support our proposed mechanism, we conducted the control reaction between the hex-1-yne and 1-chloropent-2-yne with TBAF at rt or at 50 °C, giving no product as expected.[21]

Attempts to improve the yield of the reaction by lowering or increasing the temperature gave varying results as a function of the fluoride source. A reaction temperature of 80 °C appears to be optimal for most reactions, even though the use of NaF or LiF required higher temperature for the formation of the desired products (Table 3, entries 11−14).

We next explored the scope of the reaction (Table 4). Different 1-TMS-alk-1-ynes were reacted with 1-chloropent-2-yne **2a** in the presence of 1 equiv of cesium fluoride and 10 mol % of copper iodide in DMI at 80 °C. In most cases, the reactions proceeded in good yields. But, the reaction was found to be incompatible with functional groups containing a basic nitrogen, presumably because of a competitive complexation of the copper species (Table 4, entries 5 and 6).

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(12) Ito, H.; Arimoto, K.; Sensui, H.-O.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 3977−3980.

(13) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075−4078.

(14) Marshall, J.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107−4110.

(15) See the Supporting Information for the method. Retention time: **1** (6.71 min), **2a** (4.19 min), **2b** (7.10 min), 3 (8.21 min), **4** (8.51 min), **5** (9.25 min).

(16) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon: Oxford, U.K. 1991; Vol. 5, p 1543. Ikegashira, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Chem. Commun.* **1997**, *11*, 1039−1040.

(17) Stadnichuk, M. D.; Aleksandrova, E. A. *Russ. J. Gen. Chem.* **1993**, *63*, 1662. Stadnichuk, M. D.; Komissarova, E. V. *Russ. J. Gen. Chem.* **1994**, *64*, 629.

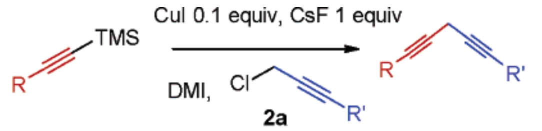
(18) Chuit, C.; Corriu, R. J. P.; Reye, C. **1999**, *81*, 146, Holmes, R. R. *Chem. Rev.* **1996**, *96*, 927−950, Kost, D. Kalikhman, I. *Chem. Org. Silicon Comput.* **1998**, *2*, 1339−1445.

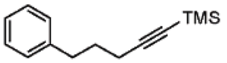
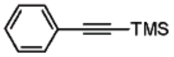
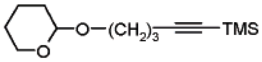
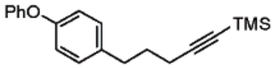
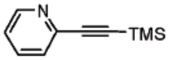
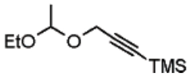
(19) For example: Lettan, R. B., II; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227−3230.

(20) It should be noted that use of a THF/DMI (1/1) mixture gives the same yield as with pure DMI. The others solvents tested were hexane, toluene, THF, [Bmim][PF$_6$] (1-butyl-3-methylimidazolium hexafluorophosphate), and water.

(21) The reaction of 1-hexyne and 1-chloropent-2-yne **2a** in the presence of a stoichiometric amount of copper iodine in DMI and a stoichiometric amount of TBAF at rt or 50 °C gave no products. At 80 °C, we isolated only the corresponding allene in 4% yield.

Table 4. Copper Salt Catalyzed Alkynylation of 1-Chloropent-2-yne **2a** and 1-Chloroocto-2,5-diyne[a]



entry	R'	nucleophile	yield (%)
1	Et		72
2	Et		62
3	Et		54
4	Et		71
5	Et		-[b]
6	Et		-[b]
7			64

[a] Reactions conducted with 1.0 equiv of **2** at 80 °C, 0.1 equiv of CuI, and 1.0 equiv of CsF in degassed DMI. No allenes and homcoupling product were isolated. [b] Only degradation or complex mixtures were obtained.

However, we were pleased to observe that these experimental conditions are suitable for base sensitive products, as exemplified by the reaction of the 1-chloroocta-2,5-diyne and the 1-ethoxyethyl-1-(trimethylsilyl)-1-propyn-3-yl ether which affords, with good yield (64%), the sensitive triyne system (Table 4, entry 7).

The above reaction conditions were also applied to the coupling of germanium or tin acetylides with a propargyl chloride. Gratifyingly, the reaction of tributyl(phenylethynyl)stannane **7a** or trimethyl(5-phenypent-1-ynyl)germane **7b** in the presence of copper iodide and cesium fluoride in DMI gave the desired product **8a** or **8b** in 70% and 90% yield, respectively (Figure 4). To the best of our knowledge, germanium or tin acetylides in such coupling reactions have not been previouly described.

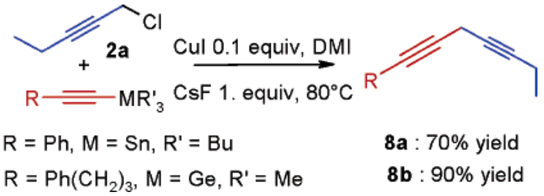


Figure 4. Coupling reaction with tin and germanium acetylides.

In summary, we have developed a novel and efficient method for the preparation of 1,4-skipped diynes via copper acetylides generated directly using a trimethylsilylalkyne, trimethylgermanylalkyne, or tributylstannylalkyne derivative in the presence of a fluoride source and a catalytic amount of copper. The method described here should be valuable for the discrimination of terminal diacetylenic compounds.[11,21] Moreover, these experimental conditions can be applied to base sensitive substrates and open new ways to prepare polynes for the synthesis of natural products.

Acknowledgment. We would like to thank Dr. Tammo Winkler and Johan Drapel for their help in compound analysis.

Supporting Information Available: General experimental data and characterization data for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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