In Situ Generation of 1-Propyne: A Useful Introduction of 1-Propyne on Unsaturated Halogenated Compounds through the Sonogashira Reaction

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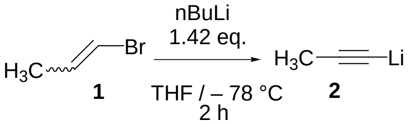
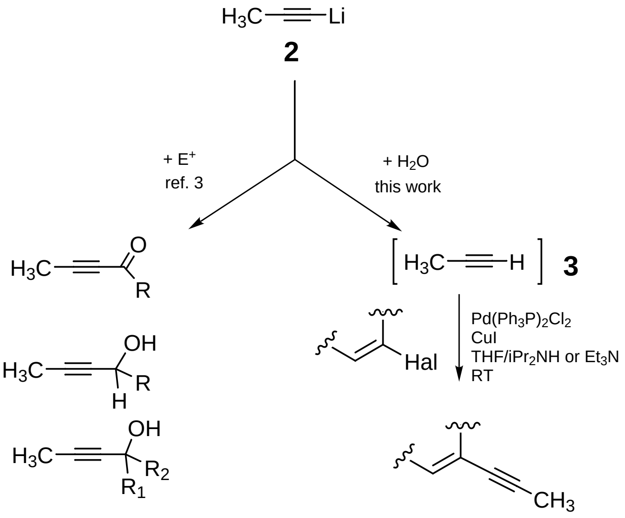
Abstract: Reaction of (*E*/*Z*)-1-bromopropene with exactly 1.42 equivalents of *n*BuLi followed by addition of water produces in situ a THF solution of propyne. Addition of a vinylic or aromatic halogenated substrates, $Pd(PPh_3)_2Cl_2$, CuI and an amine to this solution give high yield of the corresponding coupling product bearing a propyne moiety. This practical procedure avoids the use of expensive and inflammable propyne gas which need a special apparatus for bubbling it into the reaction flask.

Key words: alkyne, palladium, catalysis, cross-coupling

It is of general interest to find new protocols in preparative organic synthesis for the reaction of reagents, which have several disadvantages for laboratory purposes. Propyne gas is one of those compounds, it is only sold in steel bottles, is very expensive and very flammable. In addition it needs special equipment to be introduced in the reaction vessel. There are many reports in the literature on the reaction of propyne with halogenated organic compounds in the presence of a palladium catalysis intermediates for the preparation of biologically active compounds.[1] Mainly these compounds are synthesized from propyne gas by bubbling the gas directly in the reaction mixture containing the substrate, the catalyst and the co-catalyst. In some cases propyne gas has been replaced by the cheap welding gas mixture MAPP,[2] (methylacetylene, propanediene, propene) which contains up to 13.5% of propyne in the preparation of propynyllithium. Unfortunately this mixture of gas is not useful in the Sonogashira type reaction because of the small percentage of propyne. In a recent publication[3] we have proposed a new and very efficient preparation of propynyllithium from simple, inexpensive commercially available starting material. In this way propynyllithium **2** can be generated in anhydrous THF in high yield by reaction at –78 °C of the commercially available mixture of *Z*/*E* 1-bromopropene **1** with *n*BuLi This reaction is related to the well known Fritsch-Buttenberg-Wiechell[4] rearrangement (Scheme 1). Herein, we report that propyne **3** can be generated in situ in anhydrous THF solution at -78 °C and smoothly reacts through a Sonogashira[5] coupling reaction with vinyl or aromatic halogenated starting material in the presence of a palladium catalyst and CuI to give in high yields the corresponding product substituted with a propyne moiety. When a solution of (*Z*/*E*)-1-bromopropene in anhydrous THF at –78 °C is treated with 1.42 equivalents of *n*BuLi, propynyllithium is quantitatively formed and reacts either with electrophiles such aldehydes, ketones, Weinreb amides and acid chlorides or, when quenched at low temperature by 2.2 equivalent of H_2O, produces a solution of propyne in the reaction mixture (Scheme 2). This THF solution of propyne can be directly used in Sonogashira coupling reaction by introduction of an appropriate substrate and a palladium catalyst.



Scheme 1



Scheme 2

Typically, addition of 1 equivalent of the halogenated starting compound followed by addition of 5% $Pd(Ph_3P)_2Cl_2$, 10% of copper iodide and an excess of amine (*i*Pr_2NH or Et_3N depending of the halogenated substrate) furnished the corresponding propynylated products in high yields (see Table). The reaction proceeded efficiently at room temperature with a variety of bromides and iodides.[6]

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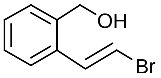
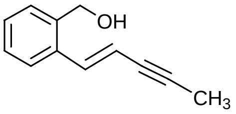
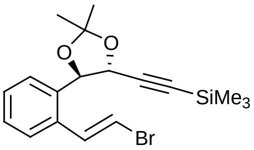
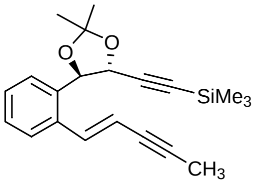
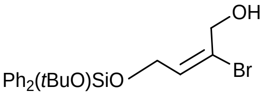
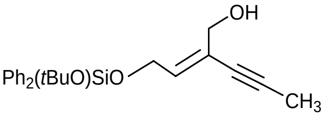
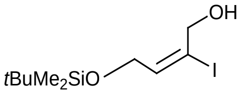
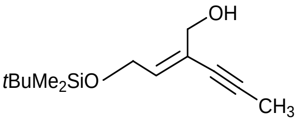
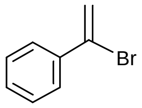
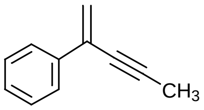
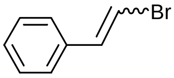
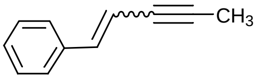
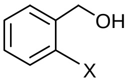
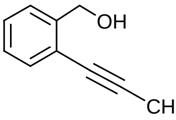
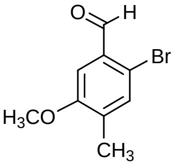
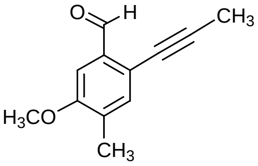
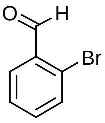
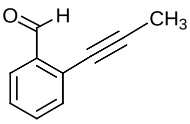
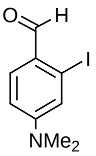
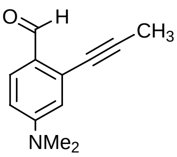
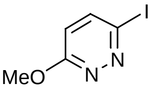
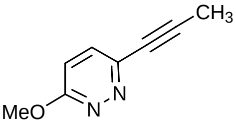
Table Pd-Catalysed Propynylation of Halogenated Compounds[a]

Entry	Aryl or vinyl halide	Product	Yield
1			93[d]
2			98[d]
3			96[d]
4			82[d]
5			75[d]
6			77[d]
7 8	 X = Br X = I		0[b] 98[d]
9			64[c]
10			73[c]
11			92[c]
12			61[d]

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[a] Reaction conditions: $Pd(PPh_3)_2Cl_2$ CuI, 10%, THF/$i$$Pr_2NH$ or Et_3N, r.t.

[b] Experiment repeated 3 times.

[c] Et_3N used as a base.

[d] $i$$Pr_2NH$ used as a base.

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The use of THF as the solvent allowed a rapid elimination/metallation reaction of 2-bromopropene with *n*BuLi and a rapid quenching of the lithio species by H_2O. Use of ether as the solvent for the metallation does not give any traces of propynyllithium. $Pd(PPh_3)_2Cl_2$ was found to be the best source of palladium. The choice of the amine is crucial for the reaction to proceed cleanly. For aldehydes (entry 9–11) only Et_3N is suitable to give good yields of products, while *i*Pr_2NH gave mainly decomposition. Surprisingly the *o*-bromobenzylic alcohol did not give a single trace of the corresponding propynylated product (entry 7). This lack of reactivity has been observed in only one case on such an electron rich aromatic ring. In contrast, the iodide (entry 8) furnished the expected compound with an excellent 98% yield. Only 1.55 equiv of (*Z*/*E*)-1-bromopropene are necessary for the completion of the reaction while the use of propyne gas needs a large excess of the gas.

In summary, we have found a practical alternative to efficiently replace propyne gas by 2-bromopropene for an easy introduction of a propynyl group on aromatic and vinylic halogenated compounds. We are currently applying this methodology for the synthesis of unsaturated polycyclic substrates.

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(6) Representative Procedure (Table, Entry 2): [2,2-Dimethyl-5-(2-pent-1-en-3-ynyl-phenyl)-[1,3]dioxolan-4-ylethynyl]-trimethyl-silane: A solution of *n*BuLi (1.8 mL, 1.54 M in hexane, 2.73 mmol, 2.2 equiv) was slowly added to a cooled solution of (*Z*/*E*)-1-bromopropene (0.233 g, 1.92 mmol, 1.55 equiv) in anhydrous THF (2.5 mL) under argon. This solution was stirred at -78 °C during 2 hours. H_2O (0.05 mL, 2.73 mmol, 2.2 equiv) was then added in one portion at -78 °C via syringe and the reaction mixture warmed to 0 °C. The halogenated substrate (0.470 g, 1.24 mmol, 1 equiv) dissolved in THF (2 mL) was added via syringe to the propyne solution, followed by $Pd(Ph_3P)_2Cl_2$ (43.5 mg, 0.062 mmol, 0.05 equiv), CuI (23.6 mg, 0.124 mmol, 0.1 equiv) and *i*Pr_2NH (2.2 mL). The temperature was raised to 20 °C and the reaction followed by TLC. Then the reaction was quenched with 20 mL of a saturated NH_4Cl in water and extracted with the appropriate solvent (3×10 mL). The organic phase was dried over Na_2SO_4, decolored by charcoal, filtered and the solvent was removed under reduce pressure. The crude propynylated product was purified by flash chromatography (1:99, ether–hexane) on silica gel to give the desired compound (0.418 g 98%). ^1H NMR (200 MHz, $CDCl_3$) δ 0.21 (s, 9 H, $Si(CH_3)_3$); 1.61 (s, 3 H,); 1.62 (s, 3 H); 2.01 (d, 3 H, $J = 2.4$ Hz); 4.38 (d, 1 H, $J = 7.9$ Hz); 5.38 (d, 1 H, $J = 7.9$ Hz); 6.05 (dq, 1 H, $J_{trans} = 16$ Hz, $^5J = 2.4$ Hz); 7.25–7.38 (m, 2 H, arom. H); 7.47 (d, 1 H, $J_{trans} = 16$ Hz); 7.43–7.57 (m, 2 H, arom. H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 0.44 [$Si(CH_3)_3$]; 4.5, 26.3, 26.8, 73.1, 79.2, 79.4, 88.5, 93.3, 100.8, 110.4, 111.5, 125.6, 126.2, 128.4, 128.5, 134.0, 135.6, 137.2. IR ($CHCl_3$, cm^{-1}) 3668 (w); 3026 (m, CH); 2991 (m, CH); 2962 (s); 2918 (m); 2217 (m); 2177 (m, $C\equiv C$); 1600 (m); 1453 (m); 1383 (w); 1255 (w); 1210 (w); 1163 (w); 1100 (w); 1052 (w); 990 (w); 956 (m).

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