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Copper catalyzed regioselective coupling of allylic halides and alkynes promoted by weak inorganic bases

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Abstract—Allylic halides and terminal alkynes couple under CuI catalysis in DMSO or DMF solution. In most cases, sodium carbonate or bicarbonate is sufficient to promote the reaction; less reactive alkynes require catalytic amounts of DBU. Bifunctional alkynes and halides can be reacted selectively according to the stoichiometry used. Trimethylsilyl, hydroxyl, ester and halide groups are tolerated in the alkyne. Most halides react without allylic rearrangement. The method is suitable for the synthesis of functionalized enynes.

Most of C–C bond forming reactions by nucleophilic substitution involve carbanionic species or organometallic reagents and have been performed traditionally in anhydrous organic solvents. Only during the past two decades numerous examples of such transformations have been reported to occur in the presence of water or even in completely aqueous medium.[1] An early precursor of the actual aqueous methodologies was the allylation of terminal alkynes performed in a water/diethyl ether system using tertiary amines as base, but only alkynols and simple allylic and propargylic halides gave interesting preparative yields.[2] A somewhat more general method has made use of triethylamine as solvent and was successful also with phenyl acetylene.[3] The introduction of inorganic bases[4] and aprotic polar solvents[5,6] brought further improvement in the yields, but the scope of these couplings remained restricted to simple allylic halides and mostly unfunctionalized alkynes or alkynols. Other limitations were long reaction times and the need for an inert atmosphere. During our studies on the reactivity of terminal acetylenes towards unusual electrophiles such as diphenyl dichalcogenides[7] or iminium ions[8] under protic conditions we found that the allylation reaction can also be performed under very mild conditions in the presence of moisture and oxygen.

Starting with allyl bromide and phenyl acetylene we observed that the reaction was complete after stirring for 4 h in commercial, undried DMSO at room temperature, using 0.02 equiv of copper iodide as catalyst and potassium carbonate as base (Table 1, entry 1). 1-Hexyne showed much lower reactivity in the same reaction, but addition of a catalytic amount of DBU promoted a quantitative allylation in the same delay (entry 2). Alkynols reacted under similar conditions and with excellent yields, in the case of propargyl alcohol even in pure water as solvent (entries 5–7). Examining other functionalized alkynes, we obtained excellent results with trimethylsilyl acetylene and ethyl propiolate, whose saponification was minimized using potassium bicarbonate as base (entries 3 and 4). In these and the following examples the addition of solid sodium sulfite was useful to suppress some oxidative dimerization and to produce the coupling products in high yield and purity. Under similar controlled conditions, but in DMF as solvent, even propargyl chloride could be allylated at the terminal acetylenic carbon producing a reagent suitable for further substitution reactions (entry 8). Use of 1,4-diethynyl benzene in appropriate stoichiometries allowed selective mono- or diallylation in high yields (entries 9 and 10).

After these encouraging results with allyl bromide, higher allylic halides were used under similar conditions.

Keywords: Allylation; Functionalized alkynes; Aprotic solvent; Inorganic bases; Selectivity.

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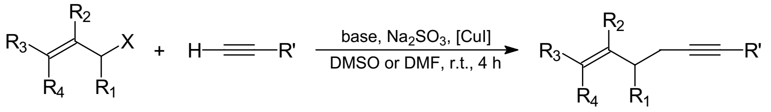
Table 1. Allylation of alkynes[9]



Entry	Halide	R′	Solvent	Base	Yield (%)
1	Allyl-Br	Ph	DMSO	K_2CO_3	100
2		*n*-Bu	DMSO	K_2CO_3/DBU	100
3		$SiMe_3$	DMSO	K_2CO_3/DBU	86
4		CO_2Et	DMSO	$KHCO_3$	82
5		CH_2OH	H_2O	K_2CO_3	100
6		CMe_2OH	DMSO	K_2CO_3/DBU	85
7		CH_2CH_2OH	DMSO	K_2CO_3/DBU	85
8		CH_2Cl	DMF	K_2CO_3	79
9		*p*-C_6H_4CCH[a]	DMSO	K_2CO_3	95
10		*p*-C_6H_4CCH[b]	DMSO	$KHCO_3$	75
11	Crotyl-Br	Ph	DMSO	K_2CO_3	100[c]
12		$SiMe_3$	DMSO	K_2CO_3/DBU	96[c]
13	Prenyl-Cl	Ph	DMF	K_2CO_3/DBU	83
14		$SiMe_3$	DMF	K_2CO_3/DBU	73
15		CO_2Et	DMF	$KHCO_3$	96
16		CH_2OH	DMSO	K_2CO_3/DBU	73
17	Geranyl-Br	Ph	DMF	K_2CO_3	74
18		*n*-Bu	DMF	K_2CO_3/DBU	75
19		$SiMe_3$	DMF	K_2CO_3	83
20		CH_2OH	DMF	K_2CO_3/DBU	66
21		CMe_2OH	DMF	K_2CO_3/DBU	90
22		CH_2CH_2OH	DMF	K_2CO_3/DBU	67
23	Cinnamyl-Br	Ph	DMF	K_2CO_3	80
24		*n*-Bu	DMF	K_2CO_3/DBU	82
25		CO_2Et	DMF	$KHCO_3$	50
26		CH_2OH	DMF	K_2CO_3/DBU	70
27		CMe_2OH	DMF	K_2CO_3/DBU	90
28		CH_2CH_2OH	DMF	K_2CO_3/DBU	89
29		*p*-C_6H_4CCH[a]	DMF	K_2CO_3	90
30		*p*-C_6H_4CCH[b]	DMF	K_2CO_3	75
31	3-Bromocyclohexene	Ph	DMF	K_2CO_3/DBU	85
32		*n*-Bu	DMF	K_2CO_3/DBU	55
33		$SiMe_3$	DMSO	K_2CO_3/DBU	90
34		CO_2Et	DMF	$KHCO_3$/DBU	93
35		CH_2OH	DMF	K_2CO_3/DBU	63
36		CMe_2OH	DMF	K_2CO_3/DBU	50
37		CH_2CH_2OH	DMF	K_2CO_3/DBU	52
38	(*E*)-1,4-Dibromo-2-butene	Ph	DMF	K_2CO_3	73[d]
39[e]		Ph	DMF	K_2CO_3	61
40[e]		$SiMe_3$	DMF	K_2CO_3	65

[a] 0.5 mmol of 1,4-diethynylbenzene was used (diallylation).

[b] 1.5 mmol of 1,4-diethynylbenzene was used (monoallylation).

[c] Regioisomer ratio 4:1 (α:γ) in the crude product.

[d] Mono-substitution.

[e] 0.5 mmol of halide was used (di-substitution).

Crotyl bromide produced excellent overall yields with phenyl and trimethylsilyl acetylene, but a 4:1 ratio of α- and γ-substitution was observed (entries 11 and 12); no important improvement of the regioselectivity could be obtained by modifications of the reaction conditions, a behaviour also reported by Jeffery.[6]

In contrast, prenyl chloride, geranyl and cinnamyl bromide gave only α-substitution in good to excellent yields with phenyl acetylene and several functionalized and unfunctionalized alkynes, most of them in DMF (entries 13–28). Once more, simple or double substitution of a diacetylenic compound was achieved according to the stoichiometry (entries 29 and 30).

3-Bromocyclohexene in general is not prone to give clean and efficient nucleophilic displacement reactions, but under the described conditions preparatively useful yields could be obtained with most of the alkynes used in this work[9] (entries 31–37).

Finally, *trans*-1,4-dibromo-2-butene, a compound possessing two allylic halogens, was also examined. In most cases, the reagent was consumed rapidly even with very mild bases, but the acetylenic compounds remained unchanged. Only in the case of trimethylsilyl acetylene and phenyl acetylene double substitution to the interesting skipped *trans*-oct-4-ene-1,7-diyne system was successful; with the latter alkyne also the simple substitution could be achieved when an excess of halide was used (entries 38–40).

In conclusion, this experimentally simple procedure allows the allylation of functionalized terminal alkynes under very mild conditions using environmentally neutral reagents and solvents without need of inert atmosphere. Selective reactions with bifunctional acetylenes or halides and cleavage of the trimethylsilyl group open an attractive access to complex non-symmetrical enynes.

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9. *General experimental procedure*: A mixture of 1.5 mmol of allylic halide, 1.0 mmol of alkyne, 0.5 mmol of Na_2SO_3, 0.02 mmol of CuI , 1.0 mmol of the base (see Table 1) and 1 drop of DBU (where indicated) were stirred at 30 °C in 1 mL of the indicated solvent for 4 h. After acidic work up and extraction with ether or dichloromethane, the crude products were purified by crystallization or a short column of silica gel.