$HgCl_2$-Catalyzed Benzylation of 1-Aryl-1-propynes†

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Formation of C−C bonds is one of the major objectives in organic synthesis. Cross-coupling reaction between an organometallic reagent (RML_n) and R′X (X = leaving group) with or without transition-metal catalysts is very attractive because of the easy availability of both reactants.[1] C−H activation using strong bases (deprotonation), halide−metal exchange, direct reaction of an alkyl halide with a metal, carbometalation (including hydrometalation), and transmetalation are major pathways to organometallic reagents (RML_n). Although alkylation of 1-(trimethylsilyl)-1-propyne using *n*-BuLi and an alkylating agent is well documented,[2] the corresponding lithiation of 1-phenyl-1-propyne was reported to be problematic.[3] During the course of our study on transition-metal-catalyzed intramolecular cyclization reaction, the product from benzylation of 1-aryl-1-propyne was desired. We wish to report here our newly developed novel methodology for benzylation of 1-aryl-1-propynes.

As expected,[3] lithiation of 1-phenyl-1-propyne at −78 °C and subsequent addition of benzyl bromide in THF afforded the expected product **2a** in <5% yield (Scheme 1). After screening several additives, it is interesting to observe that *lithiation of 1-phenyl-1-propyne in the presence of 1.5 mol % $HgCl_2$ at −78 °C followed by the addition of benzyl bromide gave the mono*benzylation product **2a** in desirable 65% yield (Scheme 1). The formation of dibenzylated product **3** was not observed.

This new method is general for benzylic alkylation of 1-aryl-1-propynes. Some results are summarized in Table 1. Several points are noteworthy: (1) the yields are from moderate to good; (2) both chlorides and bromides are effective; (3) while the reactions of benzylic halides with an electron-donating group on the aromatic ring are high yielding, *p*-nitrobenzyl bromide did not afford the expected product in decent yield; and (4) regioisomers, e.g., **2f** and **2g**, were prepared cleanly just by switching the corresponding substituents in the starting alkynes and benzylic halides (compare entries 6 and 7, Table 1).

From retrosynthetic analysis, compounds **2** might be prepared by direct reaction of Ar′CH_2CH_2X with lithium arylacetylide. Indeed, 1-phenyl-1-propyne was synthesized by HMPA-mediated methylation of lithium phenylacetylide with MeI in THF. However, the reaction between lithium phenylacetylide and 2-phenylethyl bromide/iodide in the presence of HMPA afforded only a trace amount of the title compound **2a**. The major reaction was the elimination reaction of 2-phenylethyl halides affording styrene. In both cases, halides are recovered in large amounts (Scheme 2).

In conclusion, we have developed an efficient methodology for the benzylation of 1-aryl-1-propynes and a convenient route to 1,4-diaryl-1-butynes, which are not easily available from known methods. Due to the easy availability of both starting compounds, wide scope, simple operation, and high yield, this reaction will show its utility in organic synthesis. The effect of $HgCl_2$ in this reaction and further synthetic applications are under investigation in our laboratory.

Scheme 1

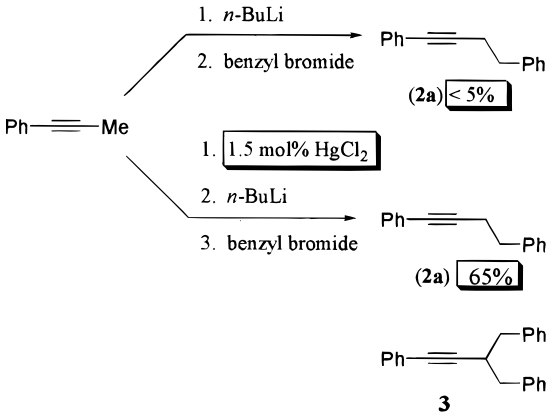
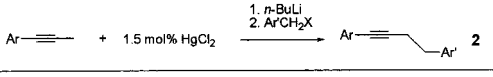
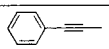
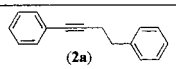
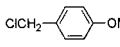
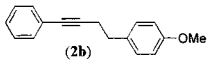
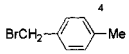
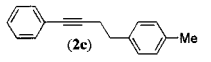
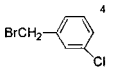
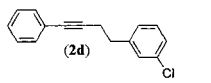
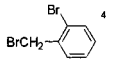
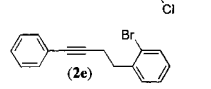
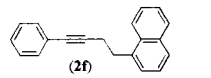
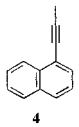
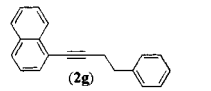


Table 1. Benzylation of 1-Ary-l-propynes[a]



Entry	1-Aryl-1-propyne	benzylic halide	time(h)	product (2)	yield(%)[b]
1	 (1)	$PhCH_2Br$	4	 (2a)	65
2	1		8	 (2b)	61
3	1		6	 (2c)	71
4	1		7	 (2d)	65
5	1		6	 (2e)	70
6	1		4	 (2f)	79
7	 4	$PhCH_2Br$	48[c]	 (2g)	73

[a] Alkyne (1.0 mmol), $HgCl_2$ (1.5 mol %), *n*-BuLi in *n*-heptane (1.0 mmol), and benzylic halide (1.2 mmol) were used. [b] Isolated yield. [c] 1.4 equiv of *n*-BuLi was used.

† Dedicated to Professor Xiyan Lu on the occasion of his 70th birthday.

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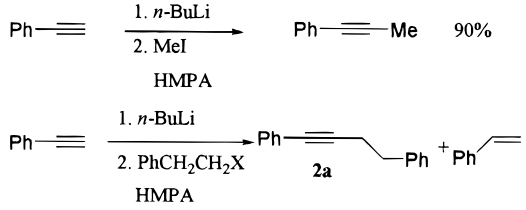
Scheme 2



	2a	styrene	$PhCH_2CH_2X$
X=Br	trace	21%	57%
X=I	trace	23%	43%

Experimental Section

Materials. *n*-BuLi (from Fluka, 2.7 M in *n*-heptane), phenylacetylene (from Fluka), 1-(chloromethyl)naphthalene (from TCI), 1-bromonaphthalene (from TCI), and 4-methoxybenzyl chloride (from Aldrich) are commercially available and used as it is. 4-Methylbenzyl bromide, 2-bromobenzyl bromide, and 3-chlorobenzyl bromide were prepared from the BPO-catalyzed benzylic bromination reactions of the corresponding methyl-substituted arenes with NBS in CCl_4.[4]

1-Naphthylacetylene was prepared by the $Pd(PPh_3)_4$-catalyzed coupling reaction of ethynylzinc chloride with 1-iodonaphthalene in THF at room temperature in 73% yield.[5] The ^1H NMR data were the same as reported in ref 6.

1-Phenyl-1-propyne and 1-(1′-naphthyl)-1-propyne were prepared according to a published procedure[7] in 90% and 63% yield, respectively. After the addition of MeI and HMPA, the reaction was carried out at room temperature and under reflux, respectively. The ^1H NMR data were the same as reported in refs 8 and 9.

$HgCl_2$-Catalyzed Benzylation of 1-Aryl-1-propynes. Synthesis of 1,4-Diphenyl-1-butyne (2a). Typical Procedure. To a solution of 1-phenyl-1-propyne (232 mg, 2.0 mmol) and $HgCl_2$ (8 mg, 1.5 mol %) in THF (5 mL) was added *n*-BuLi (2.7 M in *n*-heptane, 0.74 mL, 2.0 mmol) at −78 °C. After 1 h, benzyl bromide (2.4 mmol) was added at −78 °C, and the reaction was allowed to warm to room temperature naturally. After 4 h at room temperature, the reaction was quenched with saturated NH_4Cl. Extracting with petroleum ether (60−90 °C), washing with saturated NaCl, drying over $MgSO_4$, and chromatography on silica gel (petroleum ether) afforded 267 mg (65%) of **2a**: liquid; ^1H NMR δ 2.65 (t, J = 7.39 Hz, 2 H), 2.90 (t, J = 7.39 Hz, 2 H), 7.10−7.50 (m, 10 H); ^{13}C NMR 21.833, 35.370, 89.572, 96.298, 124.046, 127.700, 128.292, 128.516, 128.642, 131.666, 132.434, 140.808; MS *m/e* 206 (M^+, 100); IR (neat) 2226 cm^{-1}. Anal. Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 92.75; H, 7.08.

The following compounds were prepared similarly.

1-Phenyl-4-(4′-methoxylphenyl)-1-butyne (2b): liquid; yield 61%; ^1H NMR δ 2.58 (t, J = 7.32 Hz, 2 H), 2.82 (t, J = 7.32 Hz, 2 H), 3.70 (s, 3 H), 6.75 (d, J = 8.55 Hz, 2 H), 7.15 (d, J = 8.55 Hz, 2 H), 7.15∼7.40 (m, 5 H); MS *m/e* 236 (M^+, 12.08), 121 (100); IR (neat) 2346 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.59; H, 6.92.

1-Phenyl-4-(4′-methylphenyl)-1-butyne (2c): liquid; yield 71%; ^1H NMR δ 2.30 (s, 3 H), 2.65 (t, J = 7.49 Hz, 2 H), 2.85 (t, J = 7.49 Hz, 2 H), 6.95−7.40 (m, 9 H); MS *m/e* 220 (M^+, 27.37), 105 (100); IR (neat) 2252 cm^{-1}. Anal. Calcd for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 93.06; H, 7.12.

1-Phenyl-4-(3′-cholorophenyl)-1-butyne (2d): liquid; yield 65%; ^1H NMR δ 2.65 (t, J = 7.39 Hz, 2 H), 2.95 (t, J = 7.39 Hz, 2 H), 6.95−7.60 (m, 9 H); MS *m/e* 242 (M^+(^{37}Cl), 10.08), 240 (M^+-(^{35}Cl), 27.19), 115 (100); IR (neat) 2228 cm^{-1}; HRMS calcd for $C_{16}H_{13}Cl(^{35}Cl)$ 240.0704, found 240.0703.

1-Phenyl-4-(2′-bromophenyl)-1-butyne (2e): liquid; yield 70%; ^1H NMR δ 2.75 (t, J = 7.40 Hz, 2 H), 3.05 (t, J = 7.40 Hz, 2 H), 7.02−7.60 (m, 9 H); MS *m/e* 286 (M^+(^{81}Br), 0.62), 284 (M^+-(^{79}Br), 0.78), 205 (100); IR (neat) 2318 cm^{-1}. Anal. Calcd for $C_{16}H_{13}Br$: C, 67.39; H, 4.59. Found: C, 66.92; H, 4.60.

1-Phenyl-4-naphthyl-1-butyne (2f): liquid; yield 79%; ^1H NMR δ 2.85 (t, J = 7.53 Hz, 2 H), 3.45 (t, J = 7.63 Hz, 2 H), 7.10−8.25 (m, 12 H); MS *m/e* 256 (M^+, 29.59), 141 (100); IR (neat) 2228 cm^{-1}. Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.74; H, 6.72.

1-Naphthyl-4-phenyl-1-butyne (2g): solid; mp 49−51 °C; yield 73%; ^1H NMR δ 2.85 (t, J = 7.26 Hz, 2 H), 3.05 (t, J = 7.26 Hz, 2 H), 7.10−8.20 (m, 12 H); MS *m/e* 256 (M^+, 50.39), 165 (100); IR (neat) 2225 cm^{-1}. Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.92; H, 6.48.

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Supporting Information Available: The ^1H NMR spectrum of compound **2d** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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