96110-21-3; *sec*-BuC(O)C(NHPr)=NHPr, 96110-22-4; EtN=C=NEt, 693-29-8; PrN=C=NPr, 821-79-4; CH_2=$CHCH_2$N=C=NCH_2CH=CH_2, 693-50-5; *t*-BuLi, 594-19-4; *sec*-BuLi, 598-30-1; CO, 630-08-0.

Ortho Allylation of Benzyl Alcohols

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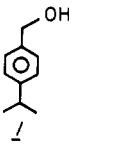
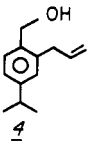
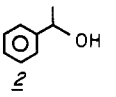
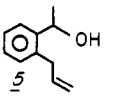
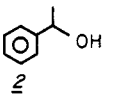
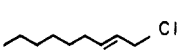
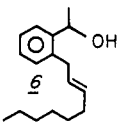
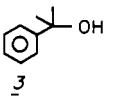
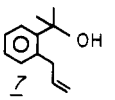
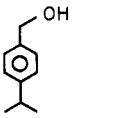
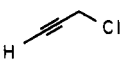
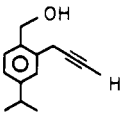
A variety of different activating groups[4,5] have been used to direct ortho lithiation of an aromatic ring. While methylation, silylation, and hydroxyalkylation of the resultant aryllithium species are straightforward, alkylation is usually not. We report herein a brief study that has led to an efficient procedure for the ortho allylation of benzyl alcohols.

This investigation was motivated by our need to attach a long-chain alkyl moiety ortho to a functional group that could become a methyl ketone. It was already known[6] that benzyl alcohols are readily ortho lithiated. While efficiency of ortho lithiation could be demonstrated in our hands by quantitative methylation, attempted alkylation with longer chain alkylating agents (chlorides, bromides, iodides, tosylates) gave low conversion.[7]

After some experimentation in other directions, we essayed formation of a mixed cuprate,[8] using the benzylic lithium alkoxide as one of the ligands on copper. While we have no evidence that such a species in fact is formed, we have found that addition of 0.5 mol equivalent of $Cu_2(CN)_2$ to the lithiated benzyl alcohol followed by an allylic halide effects quantitative (TLC) conversion to the monoallylated product (Table I).

The procedure has limitations. The product allylbenzenes are exceptionally prone toward autoxidation, especially in the presence of Cu(II) during aqueous workup.[9] The acetylenic product from alkylation with propargyl bromide partially isomerizes to the allene during isolation. Nevertheless, this procedure, proceeding directly from commercially available benzyl alcohols, could be the method of choice for the preparation of many simple alkylated benzene derivatives.[10]

Table I

starting alcohol	alkylating agent	product	% yield[a]
 1		 4	67
 2		 5	87
 2		 6	60
 3		 7	53
 1		 8	56[b]

[a] Yield of material isolated by column chromatography and fully characterized. [b] A 3:1 mixture of acetylene to allene was isolated.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were determined on a Bruker WM-250 spectrometer as solutions in $CDCl_3$. Chemical shifts are reported in δ units downfield from the internal reference tetramethylsilane. The couplings (J) are in hertz (Hz). Carbon multiplicities were assigned by a J-modulated spin echo technique. The infrared (IR) spectra were determined on a Perkin-Elmer 180 spectrometer as solutions in CCl_4 and are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) were taken at 70 eV on a DuPont 21-492B mass spectrometer and are reported as mass per unit charge (m/z), with intensities (as a percentage of the peak of greatest ion current having $m/z \geq 100$) in parentheses. Organic chemicals were purchased from Aldrich Chemical Co. *n*-Butyllithium was obtained from Alfa Inorganics and was titrated before use. Cuprous cyanide was azeotropically dried with toluene. The solvent mixtures used for chromatography (e.g., 5% ethyl acetate/hexane) are volume/volume mixtures. R_f values indicated refer to thin-layer chromatography on Analtech 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF. Column chromatography was carried out with TLC-mesh silica

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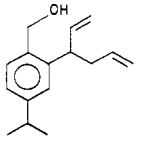
(4) For a detailed review of aromatic metalation, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(5) For more recent developments in aromatic metalation, see: Mills, R. J.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737 and references cited therein.
(6) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521.
(7) Attempted alkylation with allyl bromide gave partial conversion to what was apparently (^1H NMR) i, the product of allylation followed by proton transfer.



i

(8) Other investigators have also noted the beneficial effects of Cu(I) on some such alkylations: (a) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564. (b) Comins, D. L.; Brown, J. D.; Mantlo, N. B. *Tetrahedron Lett.* **1982**, *23*, 3979.
(9) Use of a mildly reductive workup might minimize this autoxidation.
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0022-3263/85/1950-1987$01.50/0

gel, following the procedure we have described.[11]

Preparation of Alcohol 4. A flame-dried two-neck 50-mL round-bottom flask was flushed with N_2 and charged with 305 mg (2 mmol) of *p*-isopropylbenzyl alcohol (**1**), 930 mg (8 mmol) of TMEDA, and 14 mL of ether. The mixture was magnetically stirred in an ice/water bath and then *n*-BuLi (8 mmol) was added, the first half slowly, the last half all at once. After stirring in the ice bath 5 min, the mixture was warmed to reflux for 1 h.[12] The flask was then immersed in a saturated NaCl/dry ice bath, and 200 mg (1.1 mmol) of dried $Cu_2(CN)_2$ was added. After another 30 min of stirring, allyl chloride (765 mg, 10 mmol, in 2 mL of Et_2O) was added. After an additional 10 min of stirring, the reaction was quenched with aqueous NH_4Cl/NH_4OH solution and extracted with Et_2O. The combined organic layers were dried over anhydrous K_2CO_3 and concentrated in vacuo. The residue was chromatographed on 50 g of silica gel with 3.5% EtOAc/petroleum ether. The first 90 mL was discarded. The next 450 mL was concentrated in vacuo to give 250 mg (1.3 mmol, 67%) of **4** as a pale yellow oil, R_f (30% EtOAc/hexane) 0.55. Repeated runs on 5 times the scale, with 2 equiv of alkylating agent, worked equally well. ^{1}H NMR δ 1.25 (d, J = 7 Hz, 6 H), 1.7–1.9 (br s, 1 H), 2.8–3.0 (m, 1 H), 3.5 (d, J = 7 Hz, 2 H), 4.6 (s, 2 H), 4.9–5.1 (m, 2 H), 5.9–6.1 (m, 1 H), 7.0–7.4 (m, 3 H); ^{13}C NMR 24.0 (q), 33.9 (d), 37.0 (t), 63.1 (t), 115.8 (t), 124.6 (d), 128.2 (d), 128.7 (d), 136.2 (d), 137.8 (d), 148.9 (s) ppm IR 3610, 3420 (br), 3070, 2955, 1627, 1600, 1450, 990, 905 cm^{-1}; MS, 190 m/z (8), 172 (53), 157 (100), 147 (30), 129 (77), 117 (28), 115 (25).

Alcohol 5: R_f (30% EtOAc/hexane) 0.50; ^{1}H NMR δ 1.4 (d, J = 6.5 Hz, 3 H), 2.9–3.0 (br s, 1 H), 3.4 (d, J = 6.5 Hz, 2 H), 4.9–5.1 (m, 3 H), 5.9–6.1 (m, 1 H), 7.1–7.6 (m, 4 H); ^{13}C NMR 24.5 (q), 36.7 (t), 66.2 (d), 115.9 (t), 125.3 (d), 127.0 (d), 127.6 (d), 130.0 (d), 136.0 (s), 137.7 (d), 143.9 (s); IR 3610, 3380 (br), 3070, 2975, 1630, 1440, 1245, 1065, 990, 905, 795 cm^{-1}; MS, m/z 162 (2), 147 (29), 145 (17), 144 (64), 130 (11), 129 (100), 119 (12), 107 (13).

Alcohol 6: R_f (30% EtOAc/hexane) 0.59; ^{1}H NMR δ 0.9 (t, J = 6.5 Hz), 1.3 (br s, 10 H), 1.4 (d, J = 6.5 Hz, 3 H), 2.2–2.4 (br s, 1 H), 3.4 (d, J = 6 Hz 2 H), 5.0–5.2 (m, 1 H), 5.3–5.6 (m, 2 H), 7.1–7.6 (m, 4 H); ^{13}C NMR 14.1 (q), 22.6 (t), 24.3 (q), 28.9 (t), 29.4 (t), 31.7 (t), 32.6 (t), 35.6 (t), 66.2 (d), 125.1 (d) 126.8 (d), 127.4 (d), 128.8 (d), 129.8 (d), 132.2 (d), 137.1 (s), 143.6 (s); IR 3600, 3060, 3010, 2920, 2845, 1475, 1440, 1065, 990, 960 cm^{-1}; MS, m/z 246 (1), 231 (11), 230 (29), 229 (100), 228 (36), 157 (10), 143 (59), 131 (24), 117 (13).

Alcohol 7: R_f (30% EtOAc/hexane) 0.69; ^{1}H NMR δ 1.6 (s, 6 H), 2.0–2.2 (br s, 1 H), 3.7–3.8 (m, 2 H), 4.9–5.1 (m, 2 H), 5.95–6.1 (m, 1 H), 7.1–7.5 (m, 4 H); ^{13}C NMR 31.7 (q), 38.3 (t), 73.8 (s), 115.3 (t), 125.5 (d), 125.9 (d), 127.1 (d), 132.3 (d), 137.9 (s), 139.5 (d), 145.6 (s) ppm; IR 3600, 3060, 2970, 1630, 1120, 900 MS, cm^{-1}; m/z 176 (11), 175 (28), 159 (100), 158 (96), 143 (67), 128 (93), 115 (33), 117 (41).

Alcohol 8: R_f (30% EtOAc/hexane) 0.48; IR 3610, 3300, 3010, 2955, 1930, 1600, 1450, 995, 840 cm^{-1}; allene MS, m/z 188 (6.9), 150 (81.3), 135 (100), 132 (22.8), 119 (32.2), 117 (24.9), 107 (38.7), 105 (38.6); allene ^{1}H NMR δ 1.25 (dd, J = 3, 8 Hz, 6 H), 2.0 (s, 2 H), 2.8–2.95 (m, 1 H), 3.0–3.2 (br s, 1 H), 4.5 (d, J = 2 Hz, 2 H), 5.1 (d, J = 7.5 Hz, 2 H), 6.4 (t, J = 6 Hz, 1 H), 7.0–7.4 (m, 3 H). Anal. (allene/acetylene). Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.98; H, 8.61.

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Registry No. 1, 536-60-7; 2, 98-85-1; 3, 617-94-7; 4, 96096-44-5; 5, 82315-95-5; 6, 96096-45-6; 7, 96096-46-7; 8, 96096-47-8; BuLi, 109-72-8; Cu(CN), 544-92-3; allyl chloride, 107-05-1; 1-chloro-2-nonene, 41792-06-7; 3-chloro-1-propyne, 624-65-7; 4-(1-methylethyl)-2-propa-1,2-dienylbenzenemethanol, 96109-60-3.

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(12) Metalation conditions are optimized. Alternative metalation procedures were evaluated by quenching with CH_3I, followed by ^{1}H NMR analysis.

Prosthetic Group Radioiodination at "No-Carrier Added" Levels of Carbonyl-Containing Molecules

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Indirect radioiodination by attachment of prelabeled prosthetic groups of drugs, enzymes, proteins, and other biologically important molecules is a useful synthetic method.[1,2] Examples in the literature include radioiodinated aryl diazonium ions, imidates, and esters which attach to amino functions on the target molecule[3-5] or radioiodinated phenolic amines and acyl hydrazines which attach to carbonyl loci.[6,7] Many of these are difficult to use at no-carrier added radioiodine levels or, in the case of those which are iodinated phenolics, undergo rapid in vivo deiodination.[8] There is need of a nonmetabolized, prosthetic radioiodination moiety which can be prepared in high specific activity.[9,10]

A logical prosthetic group would be an acyl hydrazide directly iodinated on an aryl ring. We therefore attempted the preparation of iodobenzyl hydrazide by reaction of benzoyl hydrazide with both iodine monochloride in acetic acid and iodide/iodic acid reaction. No product was obtained even when the potential iodinating electrophiles were in excess, a condition which, even if it had been successful, would have been inconsistent with radioiodination at no-carrier added levels.

Our earlier studies with the Sandmeyer/Wallach reaction (Scheme I) showed it to be operable at no-carrier added levels of radioiodine.[11,12] Such diazotizations would, of course, be impossible on a hydrazide, and the latter function was thus protected as an oxidazole (**2**). Acid catalysis hydrolyzes the triazene and the oxadiazole to 3-iodobenzoyl hydrazide which can be prepared in 30% chemical yield and 12% radiochemical yield at no-carrier added levels (Scheme II). The meta-substituted (triazenophenyl)oxadiazole was selected because previous studies of electronic effects indicated that electron-withdrawing groups on the aryl ring in conjugation with the triazene site reduce the yield of aryl iodide.[11,12]

Three model hydrazones (3a–c) were prepared in excellent conversions at both mass level (with Na^{127}I, in 69–89% chemical yields) and at tracer level (with Na^{125}I in radiochemical yields of 58–72% based on [^{125}I]-3-iodobenzoyl hydrazide) (Scheme III). A pharmacologically important substrate, doxorubicin, was prosthetically labeled with the benzoyl hydrazide without cleavage of the aglycone residue. Acylhydrazones of anthracycline antitumor antibiotics have demonstrated impressive cytotoxic activity.[13-15] Many antitumor agents after labeling with

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