A Facile Alkylation of Aryl Aldehyde Tosylhydrazones with Trialkylboranes

George W. Kabalka,* John T. Maddox, and Ekaterini Bogas

Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996-1600

Received June 20, 1994®

Summary: Trialkylboranes readily alkylate aryl aldehyde tosylhydrazones to produce either the corresponding arylalkane or aryl alcohol in excellent yields.

Alkylation of carbonyl compounds by organometallic reagents is one of the most useful reactions in synthetic organic chemistry. Typically, only active alkylmetal reagents such as organomagnesium,[1] organolithium,[2] or organozinc[3] can be utilized to achieve this transformation but their basicity limits their reactions to nonfunctionalized alkyl groups. Organoboranes tolerate a wide variety of functional groups, and their use in carbonyl addition reactions would make it possible to transfer a wide selection of alkyl groups.[4] Trialkylboranes, however, do not routinely alkylate carbonyl compounds, although a few exceptions are known.[5]

We wish to report an alkylation reaction utilizing trialkylboranes that is equivalent to the overall 1,2-addition of an alkyl group to a carbonyl compound. Tributylborane reacts with aryl aldehyde tosylhydrazones in the presence of base to produce a new trialkylborane, **1** (Scheme 1).[6] This trialkylborane is readily protonolyzed to the corresponding alkane **2** or oxidized to the corresponding alcohol **3** depending upon the reaction conditions chosen.

Use of a strongly nucleophilic base, such as Bu_4NOH, affords excellent yields of arylalkanes **2** (Table 1). The reaction is based on an observation made by Brown in 1966 that trialkylboranes capable of yielding stable carbanions when deboronated, e.g., **1**, are readily protonolyzed.[7] As anticipated based on the proposed mechanism, Scheme 1, electron-withdrawing groups increase the yield of product. Ortho-, meta-, or para-substituted starting materials produce comparable yields of products (Table 1, entries 5–7).

Oxidation of intermediate **1** produces alcohol **3** if a nonnucleophilic base such as DBU is used. The use of a nonnucleophilic base minimizes the deboronation of **1** and subsequent protonolysis to **2**. The classical hydrogen peroxide–base oxidation procedure cannot, therefore, be used since benzylboranes, **1**, are easily protonolyzed under strongly basic conditions.[7] Use of the milder sodium perborate ($NaBO_3{\cdot}4H_2O$) procedure[8] produces the aryl alcohols, **3**, in good yields (Table 2). Electron-withdrawing substituents, however, activate the ring to the extent that significant protonolysis occurs with the sodium perborate procedure (Table 2, entry 5). The use of peracetic acid as the oxidant[9] increases the yield of alcohol (Table 2, entry 6) and is the oxidant of choice

Scheme 1

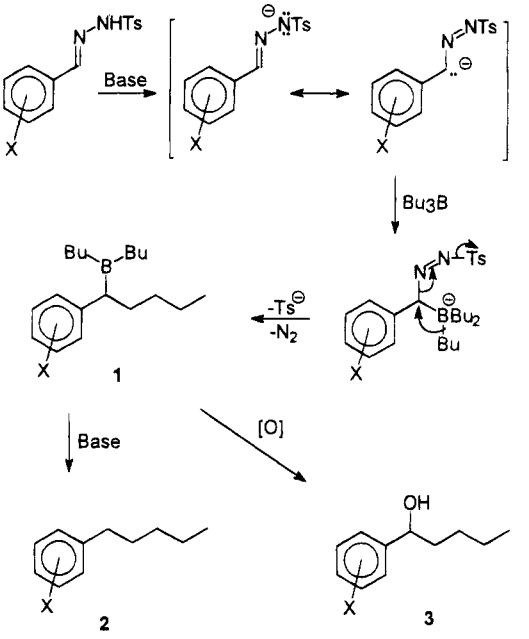


Table 1. Synthesis of Arylalkanes 2

entry	X	mp of tosylhydrazone (°C)	time (h)	% yield[a] of **2**
1	H	125.0–128.0[b]	1	80
2	4-methyl	147.7–149.8[c]	1	90
3	4-methoxy	110.0–112.0[d]	1.5	83
4	4-chloro	163.8–164.0[e]	1	94
5	4-bromo	172.0–176.0[f]	1	94
6	3-bromo	114.5–117.5[g]	1	89
7	2-bromo	165.0–167.5[h]	1	92
8	3-nitro	159.1–160.2[i]	1	91
9	4-nitro	156.8–158.2[j]	1	98

[a] Isolated yields based on tosylhydrazone. [b] Lit.[12] mp = 127–128 °C. [c] Lit.[13] mp = 115–116 °C. [d] Lit.[14] mp = 112–114 °C. [e] Lit.[15] mp = 148–151 °C. [f] Anal. Calcd for $C_{14}H_{13}N_2O_2SBr$: C, 47.60; H, 3.71; N, 7.93. Found: C, 47.68; H, 3.77; N, 7.98. [g] Anal. Calcd for $C_{14}H_{13}N_2O_2SBr$: C, 47.60; H, 3.71; N, 7.93. Found: C, 47.79; H, 3.81; N, 8.01. [h] Anal. Calcd for $C_{14}H_{13}N_2O_2SBr$: C, 47.60; H, 3.71; N, 7.93. Found: C, 47.77; H, 3.76; N, 8.00. [i] Lit.[16] mp = 160–161 °C. [j] Lit.[16] mp = 158 °C.

® Abstract published in *Advance ACS Abstracts,* September 1, 1994.

(1) (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954. (b) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18. (c) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; pp 553–567.

(2) (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: New York, 1988. (b) Reference 1c.

(3) (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 103. (c) Reference 1c.

(4) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.

(5) (a) Miyaura, N.; Itoh, M.; Suzuki, A.; Brown, H. C.; Midland, M. M.; Jacob, P., III. *J. Am. Chem. Soc.* **1972**, *94*, 6549. (b) Okada, K.; Hosoda, Y.; Oda, M. *Tetrahedron Lett.* **1986**, 27, 6213. (c) Mikhailov, B. M.; Baryshnikova, T. K.; Shashkov, A. S. *J. Organomet. Chem.* **1981**, *219*, 301. (d) Negishi, E.; Chiu, K.; Yosida, T. *J. Org. Chem.* **1975**, 40, 1676.

(6) The mechanism of this reaction is similar to that postulated for the reaction of functionally substituted diazo compounds with trialkylboranes. See: (a) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 5936. (b) Hooz, J.; Linke, S. *J. Am. Chem. Soc.* **1968**, *90*, 6891. (c) Hooz, J.; Morrison, G. F. *Can. J. Chem.* **1970**, *48*, 868. (d) Hooz, J.; Gunn, D. M. *J. Am. Chem. Soc.* **1969**, *91*, 6195.

(7) (a) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1966**, *88*, 5851. (b) See also: Weinheimer, A. J.; Marsico, W. E. *J. Org. Chem.* **1962**, 27, 1926.

(8) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

(9) Kidwell, R. L.; Murphy, M.; Darling, S. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 918–921.

0022-3263/94/1959-5530$04.50/0

Table 2. Synthesis of Aryl Alcohols 3

entry	X	time (h)	oxidant	% yield[a] of 3	% yield[a] of 2
1	H	0.5	$NaBO_3$	73	15[b]
2	4-methoxy	3	$NaBO_3$	71	5[b]
3	4-methyl	2	$NaBO_3$	80	8[b]
4	2,4,6-trimethyl[c]	1	$NaBO_3$	90	0
5	4-bromo	1	$NaBO_3$	30	70
6	4-bromo	1	peracetic acid	80	17
7	3-bromo	1	peracetic acid	78	18
8	2-bromo	1	peracetic acid	80	17[b]
9	4-chloro	0.5	peracetic acid	80	15[b]
10	3-nitro	1	peracetic acid	62	23
11	4-nitro	1	peracetic acid	0	84
12	4-nitro	1	$NaBO_3$	0	87
13	4-nitro	1	TMANO	0	84

[a] Isolated yields based on tosylhydrazone except where noted. [b] GC yields. [c] Mp of tosylhydrazone = 162.8–166.0 °C lit.[17] mp = 158.0–160.0 °C.

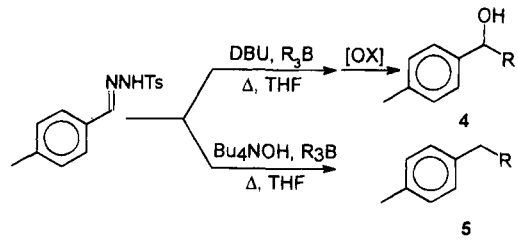
when electronegative substituents are present in the molecule. A *p*-nitro group activates the intermediate, **1**, to the extent that no alcohol is produced under any oxidizing conditions, including the anhydrous trimethylamine *N*-oxide (TMANO) procedure.[10]

Both the protonolysis and oxidation reactions appear to be general for a variety of aryl substituents. The reaction also appears to be insensitive to steric effects present in the tosylhydrazone. Thus, the sterically hindered 2,4,6-trimethyl derivative (Table 2, entry 4) leads to an excellent yield of alcohol.

Organoboranes have been particularly useful in organic synthesis because of their exceptional tolerance of a wide variety of functional groups.[4] The new alkylation reaction permits use of functional groups which are not compatible with traditional alkylmetal reagents. For example, alkyl groups containing nitrile, ester, or halo functionalities are readily transferred (Table 3). Secondary alkyl groups such as cyclohexyl and *sec*-butyl are also transferred.

The following procedure is representative for the synthesis of alcohol **3**. In a dry, argon-flushed, round-bottomed flask equipped with a side arm, reflux condenser, and stirring bar, 3.0 mmol of aryl aldehyde tosylhydrazone was dissolved in 17 mL of dry THF.

Table 3. Reaction of *p*-Tolualdehyde Tosylhydrazone with Various Trialkylboranes



alkene	R	4[a] (%)	5[a] (%)
5-chloro-1-pentene	$-CH_2(CH_2)_3CH_2Cl$	76	91[b]
5-cyano-1-pentene	$-CH_2(CH_2)_3CH_2CN$	72	98
methyl 10-undecenoate	$-CH_2(CH_2)_9COOCH_3$	75	89
cyclohexene	−Chx[c]	68	71
2-butene	$-CH(CH_3)CH_2CH_3$	51	62

[a] Isolated yields. [b] Two equiv of Bu_4NOH used. [c] Chx = cyclohexyl.

Tributylborane (3.0 mmol, 3.0 mL of a 1.0 M solution in THF) was added via syringe. DBU (3.0 mmol, 0.45 mL) was then added and the reaction slowly heated to gentle reflux. Gas evolution was noticeable as the mixture was heated. The reaction was continued until TLC indicated the absence of starting material. The reaction was then cooled and oxidized according to published procedures.[8-10] The product was extracted into ether (3 × 10 mL), the solvent removed, and the product purified by flash chromatography.[11] For the synthesis of alkane **2**, the same procedure is followed except that Bu_4NOH (3.0 mmol, 3.0 mL of a 1.0 M solution in methanol) is used as the base and water (10 mL) is added prior to workup. All reaction products exhibit physical and spectral characteristics in accord with literature values.

We are currently investigating the synthetic utility of this new alkylation reaction.

Acknowledgment. This study was supported by grants from the Department of Energy.

(10) Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330.
(11) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(12) Kabalka, G. W.; Summers, S. T. *J. Org. Chem.* **1981**, *46*, 1217.
(13) Closs, G. L.; Moss, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4042.
(14) Farnum, D. G. *J. Org. Chem.* **1963**, *28*, 870.
(15) Sayer, J. M.; Peskin, M.; Jencks, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 4277.
(16) Davies, H. W.; Schwarz, M. *J. Org. Chem.* **1965**, *30*, 1242.
(17) Nozaki, H.; Noyori, R.; Sisido, K. *Tetrahedron* **1964**, *20*, 1125.