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Reduction of Benzylic Halides with Diethylzinc Using Tetrakis(triphenylphosphine)palladium as Catalyst

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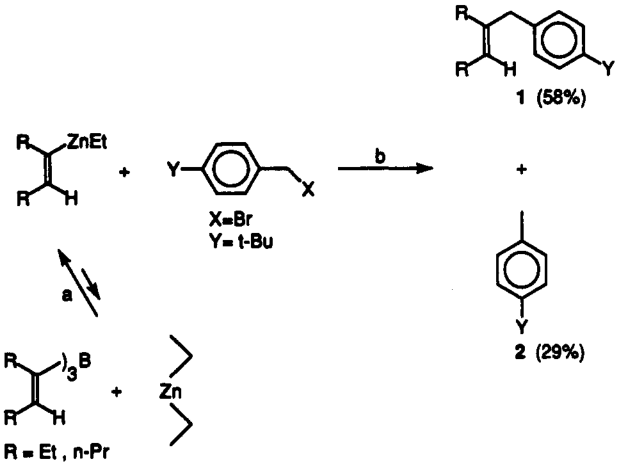
Reduction of organic compounds is important synthetically both in the laboratory and in industry.[1] In the course of our investigation on the chemistry of alkenyl(ethyl)zincs,[2,3] generated *in situ* from the corresponding alkenylboranes by transmetalation, we found that in their reactions with benzylic halides, in addition to the coupling product 1, a significant amount of the reduction product 2 was obtained unexpectedly (Scheme I). Our initial thought was that the dialkylzinc species, in particular diethylzinc, might be responsible for the reduction of the benzylic halides, which indeed proved to be the case.

Benzylic halides and related compounds have been reduced to the corresponding hydrocarbons, although in some cases coupled, dimeric products are also obtained. This type of reduction has been accomplished in the past with several reducing agents. Historically, primary, secondary, and tertiary benzylic halides have been cleaved with zinc dust in acetic acid or under basic conditions.[4,5] Hydrogenolysis over Raney nickel has also been used effectively.[6] The repertoire of reducing agents used for this type of reduction also includes several metal hydrides such as $LiAlH_4$[7] and $NaBH_4$.[8] The former is not chemoselective at all, since it can also affect several other reducible groups, e.g., -COOH, -COOR, -CN, -CO-, and -CHO, while the latter in dipolar aprotic solvents, such as DMSO and sulfolane, effectively reduces primary, secondary, and tertiary benzylic halides to alkanes, leaving nitro, ester, and carboxylic acid groups untouched. Addition of $ZnCl_2$ to $NaCNBH_3$ produced a reagent which is stable in aqueous media and can reduce a variety of benzylic and allylic functional groups.[9]

The preparation of diethylzinc by Frankland in 1848 is generally associated with the start of organometallic chemistry.[10] Since then diethylzinc has been proven to be a valuable organometallic reagent for a variety of organic transformations.[11]

Scheme I



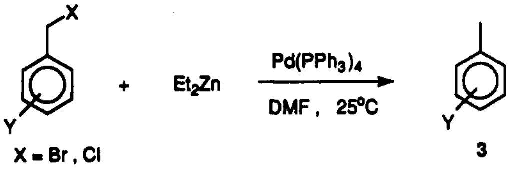
[a] Key: (a) hexanes; (b) $Pd(PPh_3)_4$, DMF, rt.

Table I. **Reduction of Benzylic Halides with Diethylzinc in the Presence of $Pd(PPh_3)_4$[a]**

entry	benzylic halide	% isold yield of redctn product 3
1	α-bromo-*m*-toluonitrile	98
2[b]	2-methoxy-5-nitrobenzyl bromide	56
3[b]	3-nitrobenzyl bromide	63
4	3-bromobenzyl bromide	76
5	4-methoxybenzyl chloride	95
6	4-*tert*-butylbenzyl bromide	70
7[c]	α-bromo-*p*-toluic acid	24
8[d]	α-bromo-*p*-toluic acid ethyl ester	76
9	4-nitrobenzyl bromide	0
10[e,f]	α-bromo-*p*-toluonitrile	63

[a] The reaction takes place at rt and goes to completion in a short period of time (0.5-1 h), using 1 equiv of diethylzinc, DMF as solvent, and 1 mol % of $Pd(PPh_3)_4$ as catalyst. [b] Addition of diethylzinc was conducted at 0 °C. [c] 2 equiv of diethylzinc were used. [d] A small amount of dimeric product 6c was also formed (see Experimental Section). [e] Galvinoxyl free radical (2 mol %) was used in the reaction. [f] The dimeric product 6a was also isolated in 11% yield.

We report the efficient reduction of benzylic halides to the corresponding hydrocarbons with diethylzinc, using $Pd(PPh_3)_4$ as catalyst (eq 1).[12] One equiv of diethylzinc is required, and the solvent of choice is DMF. The reaction takes place at room temperature and goes to completion in a short period of time (0.5-1 h) using 1 mol % of palladium catalyst. This new reduction method is compatible with several functional groups on the aromatic ring, including reducible groups such as $-NO_2$, -CN, and -COOEt (Table I). The benzylic halide carrying a carboxyl group yielded the corresponding hydrocarbon in very low yield. This was expected since it is known that diethylzinc reacts with carboxylic acids to form ethylzinc carboxylates which exist as trimers in benzene solution.[10] The presence of a nitro group on the aromatic ring also seems to affect the yield of the reduction product. In noncoordinating solvents such as CH_2Cl_2 the reaction was found to proceed very slowly. Thus, the reduction of α-bromo-*m*-toluonitrile

 (1)

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(12) This work was presented in part at the 205th ACS National Meeting, Denver, CO, March 28-April 2, 1993.

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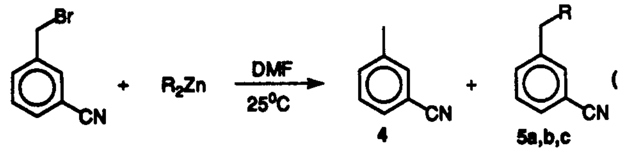
Table II. Competitive Reduction of Benzyl Bromide with $Et_2Zn/Pd(PPh_3)_4$ in the Presence of Other Reducible Compounds[a]

compd	% yield of toluene[b]
benzaldehyde	82
cyclohex-2-enone	87
cyclohexene oxide	87
acetophenone	92
iodobenzene	25[c]

[a] For reaction conditions, see Experimental Section. [b] All yields are GC yields, calculated based on an internal standard. [c] The remainder included ethylbenzene, diphenylmethane, and 1,2-diphenylethane.

in CH_2Cl_2 resulted in only 5% conversion under standard conditions after 1 h. The use of $Ni(PPh_3)_4$ as catalyst altered the course of this reaction. The attempted reduction of benzyl bromide with Et_2Zn, under our standard conditions, using $Ni(PPh_3)_4$ as catalyst, yielded toluene in 13% yield only. The remainder included *n*-propylbenzene (56%) and 1,2-diphenylethane (31%).

To further test the chemoselectivity of this new reducing system, we performed the reduction of benzyl bromide under our standard conditions in the presence of a variety of other reducible structures (Table II). All reactions were conducted at room temperature using 1 equiv of diethylzinc, DMF as solvent, and 1 mol % of $Pd(PPh_3)_4$ as catalyst. In all cases except one, toluene was the only organic product detected by GC analysis. This shows that diethylzinc allows highly chemoselective palladium-catalyzed reductions of benzylic halides, even in the presence of aldehydes, ketones, α,β-unsaturated ketones, and epoxides.[13] In the case of benzaldehyde, this was somewhat surprising, since transition metals are known to catalyze the addition of diethylzinc to aldehydes.[14] In the presence of iodobenzene, the reduction of benzyl bromide gave toluene in 25% yield, while the remainder included ethylbenzene, diphenylmethane and 1,2-diphenylethane.



(2)

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5a,b,c

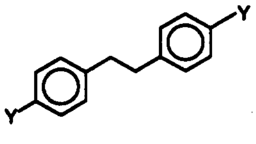
5a: R= Me
5b: R= Et
5c: R= nBu

The attempted reduction of α-bromo-*p*-toluonitrile and 4-nitrobenzyl bromide under our standard conditions gave us an early mechanistic insight into this new type of reduction. Initially, both substrates yielded the corresponding dimeric products **6a,b** exclusively, but in the presence of 2 mol % galvinoxyl free radical (a known free-radical inhibitor), we were able to isolate *p*-toluonitrile in 63% yield along with the dimeric product (11%). Unfortunately, a similar attempt in the case of 4-nitrobenzyl bromide proved unsuccessful. The dimeric product was also obtained exclusively, even when 1,4-dinitrobenzene (a known free-radical anion scavenger) was used in the reaction. These results lead us to believe that in part a radical species is involved in this new type of reduction.[15]

Table III. Reduction of α-Bromo-*m*-toluonitrile with Various Dialkylzincs in the Presence or Absence of $Pd(PPh_3)_4$[a]

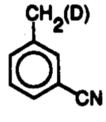
			% yield of products[b]	
	R_2Zn	$Pd(PPh_3)_4$	4	5a–c
1[c]	Me	no	1	6
2	Me	yes	23	17
3	Et	no	70	30
4	Et	yes	98	0
5	*n*-Bu	no	74	26
6	*n*-Bu	yes	54	0

[a] Same reaction conditions as in Table I. The reactions shown in entries 1–3 and 5 were quenched after a period of 24 h, while in entries 4 and 6, they were quenched after 1 h. [b] Reported yields are GC yields, calculated based on an internal standard. [c] The remainder was α-bromo-*m*-toluonitrile.



6a,b,c

6a: Y= -CN
6b: Y= -NO₂
6c: Y= -COOEt



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Looking further into this new reaction from a mechanistic point of view, we carried out the reduction of α-bromo-*m*-toluonitrile under the same conditions, using three different dialkylzincs (having or lacking β-hydrogens) in the presence or absence of the palladium catalyst (Table III). We would like to point out here that our initial mechanistic consideration was that diethylzinc serves as a hydride transfer agent and that a Pd–hydride species is involved in this particular reaction.[16] The results of this study, without rejecting this mechanistic pathway, show at least that this is not the only possible pathway in this reduction process. This conclusion is supported by the following data: (a) Diethylzinc is able to reduce α-bromo-*m*-toluonitrile to the corresponding hydrocarbon in the absence of the palladium catalyst, even though the reaction time on this occasion is much longer and a certain amount of the corresponding coupling product **5b** is obtained. (b) Dimethylzinc (an organometallic reagent lacking β-hydrogens) can reduce the same substrate, even though in a significantly lower yield under palladium catalysis. (c) When the reaction shown in entry 1, Table I was quenched with DCl instead of aqueous HCl, ^{2}H NMR analysis of the hydrocarbon **7** revealed 32% incorporation of deuterium at the benzylic carbon.[17]

This new methodology, using diethylzinc and $Pd(PPh_3)_4$ as catalyst, represents an alternative simple way of reducing benzylic halides with high chemoselectivity.

Experimental Section

Glassware, syringes, and needles were oven dried at 120 °C, assembled while hot, and dried under a flow of Ar. All reactions were done under a positive pressure of Ar.[18] Diethylzinc was purchased from Ethyl Corp. A 2 M solution of diethylzinc in

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(13) For a discussion on the reactivity of dialkylzinc compounds towards carbonyl compounds see refs 10 and 11c.

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(16) For a discussion on β-elimination in organometallic systems see: Cross, R. J. *The Chemistry of Functional Groups*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, Chapter 8.

(17) The ^{2}H NMR spectrum of **7** ($CDCl_3$ served as an internal standard) showed a triplet at 2.34 ppm (J = 2.2 Hz).

(18) For details on working with air-sensitive materials using syringe techniques see: Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Synthesis via Organoboranes*; Wiley: New York, 1975.

hexanes was prepared and used in all the reactions. DMF was dried by azeotropic distillation from benzene and distilled prior to use. Tetrakis(triphenylphosphine)palladium(0) and all the benzylic halides[19] were purchased from Aldrich. GC analysis was done on a SE-30 (0.25-mm i.d.) capillary column. ^{1}H and ^{13}C NMR spectra are of $CDCl_3$ solutions. TMS served as an internal standard. Mass spectra were obtained on a GC/MS fitted with a 25 m methylsilicone capillary column.

General Procedure for the Reduction of Benzylic Halides (Table I). Preparation of *m*-Toluonitrile. To a 50-mL round-bottom flask fitted with a side arm, Teflon-lined stirring bar and gas-regulating valve was added 2.94 g (15 mmol) of α-bromo-*m*-toluonitrile followed by the addition of 12.5 mL of DMF. To the solution was added 171 mg (1 mol %) of $Pd(PPh_3)_4$ while maintaining a positive pressure of Ar. Finally, 15 mmol of a 2 M hexanes solution of diethylzinc was added. The reaction mixture was stirred at 25 °C for 1 h. Then it was quenched with HCl(aq) and extracted with ether. The organic phase was washed with H_2O twice and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Distillation of the residue under reduced pressure (99–101 °C/20 mmHg) afforded 1.73 g (98%) of *m*-toluonitrile: ^{1}H NMR ($CDCl_3$) δ 7.46–7.45 (2H, m), 7.41 (1H, d, J = 7.9 Hz), 7.35 (1H, t, J = 7.8 Hz), 2.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 139.2, 133.6, 132.5, 129.3, 129.0, 119.0, 112.2, 21.2; GCMS (*m/z*) 117 (M^+), 90.

2-Methoxy-5-nitrotoluene. 2-methoxy-5-nitrobenzyl bromide (2.46 g, 10 mmol) was used in this reaction. The reaction was conducted under our standard conditions except that the 2 M hexanes solution of Et_2Zn was added at 0 °C: yield 0.94 g (56%); ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, dd, J = 9.0, 2.9 Hz), 8.04 (1H, d, J = 2.9 Hz), 6.86 (1H, d, J = 8.9 Hz), 3.94 (3H, s), 2.27 (3H, s); ^{13}C NMR ($CDCl_3$) δ 162.8, 141.0, 127.8, 126.0, 123.6, 109.2, 56.0, 16.3; GCMS (*m/z*) 167 (M^+), 137, 121, 109, 91, 77, 28.

3-Nitrotoluene. 3-Nitrobenzyl bromide (1.77 g, 8.2 mmol) was used in this reaction. The 2 M hexanes solution of Et_2Zn was added at 0 °C. Pure product was obtained by flash chromatography using ether/hexanes (5:95): yield 0.71 g (63%); ^{1}H NMR ($CDCl_3$) δ 8.04–8.02 (2H, m), 7.50 (1H, d, J = 7.4 Hz), 7.42 (1H, dd, J = 7.7 Hz), 2.47 (3H, s); ^{13}C NMR ($CDCl_3$) δ 148.3, 139.8, 135.3, 129.1, 123.9, 120.7, 21.3; GCMS (*m/z*) 137 (M^+), 107, 91, 79, 65, 28. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.30; H, 5.23; N, 10.09.

3-Bromotoluene. The standard procedure was followed using 2.50 g (10 mmol) of 3-bromobenzyl bromide: yield 1.3 g (76%); ^{1}H NMR ($CDCl_3$) δ 7.33–7.28 (2H, m), 7.13–7.08 (2H, m), 2.32 (3H, s); ^{13}C NMR ($CDCl_3$) δ 140.2, 132.1, 129.7, 128.4, 127.7, 122.3, 21.1; GCMS (*m/z*) 172 / 170 (M^+), 91.

4-Methylanisole. The standard procedure was followed using 1.34 g (8.6 mmol) of 4-methoxylbenzyl chloride: yield 1.0 g (95%); ^{1}H NMR ($CDCl_3$) δ 7.08 (2H, d, J = 8.6 Hz), 6.80 (2H, d, J = 8.6 Hz), 3.78 (3H, s), 2.28 (3H, s); ^{13}C NMR ($CDCl_3$) δ 157.4, 129.8, 129.8, 113.6, 55.2, 20.4; GCMS (*m/z*) 122 (M^+), 107, 91, 79.

4-*tert*-Butyltoluene. The standard procedure was followed using 1.85 g (8.1 mmol) of 4-*tert*-butylbenzyl bromide. Pure product was obtained by distillation under reduced pressure (85–87 °C/20 mmHg): yield 0.85 g (70%); ^{1}H NMR ($CDCl_3$) δ 7.29 (2H, d, J = 8.2 Hz), 7.12 (2H, d, J = 8.1 Hz), 2.32 (3H, s), 1.31 (9H, s); ^{13}C NMR ($CDCl_3$) δ 148.1, 134.8, 128.7, 125.1, 34.3, 31.4, 20.8; GCMS (*m/z*) 148 (M^+), 133.

***p*-Toluic Acid.** α-Bromo-*p*-toluic acid (2.15 g, 10 mmol) was used in this reaction. To the reaction mixture was added 20 mmol of a 2 M hexanes solution of Et_2Zn at 0 °C: yield 0.33 g (24%); ^{1}H NMR ($CDCl_3$) δ 8.00 (2H, d, J = 8.1 Hz), 7.27 (2H, d, J = 8.3 Hz), 2.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 171.4, 144.5, 130.2, 129.2, 128.6, 21.7.

***p*-Toluonitrile.** α-Bromo-*p*-toluonitrile (0.59 g, 3 mmol) was used in this reaction, which was conducted in the presence of 30 mg (2 mol %) of galvinoxyl free radical. After the reaction mixture was quenched with aqueous HCl, it was extracted with $CHCl_3$. Pure product was obtained by flash chromatography using ether/hexanes (10:90): yield 0.22 g (63%); ^{1}H NMR ($CDCl_3$) δ 7.54 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.1 Hz), 2.42 (3H, s); ^{13}C NMR ($CDCl_3$) δ 143.6, 132.0, 129.8, 119.1, 109.2, 21.8; GCMS (*m/z*) 117.25 (M^+).

The dimeric product **6a** was also eluted, using $CHCl_3$: yield 75 mg (11%).

***p*-Toluic Acid Ethyl Ester.** The standard procedure was followed using 0.90 g (3.7 mmol) of α-bromo-*p*-toluic acid ethyl ester. Pure product was obtained by flash chromatography using ether/hexanes (5:95): yield 0.46 g (76%); ^{1}H NMR ($CDCl_3$) δ 7.94 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 2.40 (3H, s), 1.38 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 143.3, 129.5, 129.0, 127.7, 60.7, 21.6, 14.3; GCMS (*m/z*) 164 (M^+), 136, 119, 91.

A small amount of the dimeric product **6c** was also formed. According to the ^{1}H NMR spectrum of the crude product, the reduction product was formed in favor of the dimeric product in an 8:1 ratio.

General Procedure for Competitive Experiments (Table II). Reduction of Benzyl Bromide with $Et_2Zn/Pd(PPh_3)_4$ in the Presence of Benzaldehyde. To a 50-mL round-bottom flask fitted with a side arm, Teflon-lined stirring bar, and gas-regulating valve were transferred 0.787 g (4.6 mmol) of benzyl bromide, 0.419 g (4.0 mmol) of benzaldehyde, and 0.567 g (4.4 mmol) of nonane (internal standard) followed by the addition of 13 mL of DMF. Minute aliquots were withdrawn from this solution and analyzed in the gas chromatograph in order to calculate the response factors of benzyl bromide and benzaldehyde. Then 57 mg (1 mol %) of $Pd(PPh_3)_4$ was added to the solution while maintaining a positive pressure of Ar, followed by the addition of 4.6 mmol of a 2 M hexanes solution of Et_2Zn. The reaction mixture was stirred at 25 °C for 5 h and was quenched with HCl_{aq} and extracted with ether. The aqueous layer was saturated with solid NaCl, and the organic phase was dried over Na_2SO_4. GLC analysis of aliquots from this organic phase showed that toluene was formed exclusively in 82% yield.

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(19) α-Bromo-*p*-toluic acid ethyl ester was prepared from the commercially available α-bromo-*p*-toluic acid via the corresponding acid chloride.