

## A Superior Procedure for Generation of Substituted Benzylolithiums from the Corresponding Chlorides

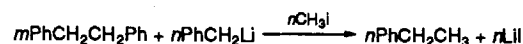
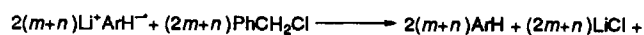
Keith Smith\* and Duanjie Hou

Department of Chemistry, University of Wales Swansea,† Singleton Park, Swansea SA2 8PP, UK

The use of diethyl ether–tetrahydrofuran–light petroleum (b.p. 30–40 °C) (4:3:1) as solvent for the reaction of substituted benzyl chlorides with lithium naphthalenide at low temperature gives useful yields of the corresponding benzylolithium compounds, which react with electrophiles such as iodomethane and water to yield the expected reaction products.

Preparation of benzylolithium directly from benzyl chloride has always proved difficult, since Wurtz coupling, leading to bibenzyl, is a prominent side reaction when benzyl chloride is treated with metallic lithium<sup>1</sup> or phenyllithium.<sup>2</sup> Alternative approaches to benzylolithium, such as the interaction of benzyl Grignard reagents with phenyllithium or metallic lithium,<sup>3</sup> and the cleavage of dibenzylmercury with metallic lithium,<sup>4</sup> are also far from ideal in that they are not one-step syntheses from commercially available reagents and nor are they easily adaptable to substituted derivatives.

Although the reactions of aromatic radical anions with simple alkyl<sup>5,6</sup> and aryl<sup>5</sup> halides in order to prepare the corresponding organolithium compounds have received considerable attention in recent years, the coupling product bibenzyl is obtained rather than benzylolithium when benzyl chloride is treated with lithium naphthalenide in tetrahydrofuran (THF) at –78 °C.<sup>7</sup> Despite these discouraging results,<sup>7,8</sup> and in view of our continuing interest in organolithium chemistry,<sup>9–11</sup> we decided to investigate the reaction of benzyl chloride with lithium aromatic radical anions in order to see if we could produce benzylolithium in high yield under modified reaction conditions. Solutions of lithium naphthalenide (LiN) and lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) in tetrahydrofuran were prepared by the literature procedures.<sup>12</sup> Lithiation was performed by addition of benzyl chloride to a solution of the LiN or LiDBB and the benzylolithium was trapped by addition of an excess of iodomethane (Scheme 1). The amount of ethylbenzene



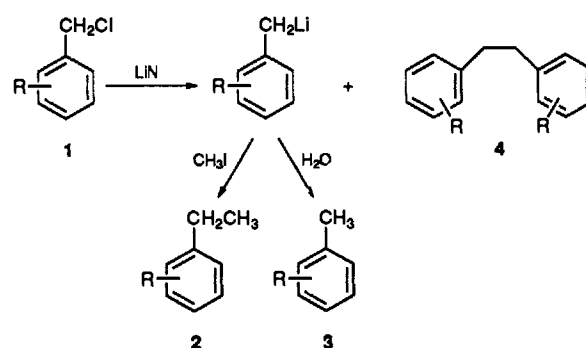
Scheme 1

produced was assumed to reflect the amount of benzylolithium formed during the initial step.

Several factors were found to influence the yield of benzylolithium (Table 1). At –78 or –95 °C the formation of the organolithium reagent proceeds at a satisfactory rate, but at higher temperatures the yield of benzylolithium is lower due to increased formation of bibenzyl. If the solution of benzyl chloride is added too rapidly, such that its concentration can build up in the reaction mixture, the formation of bibenzyl again increases. The most satisfactory addition time was found to be 15 min for 12 cm<sup>3</sup> of 0.1 mol dm<sup>-3</sup> benzyl chloride solution. Excess of lithium naphthalenide gives rise to a higher ratio of benzylolithium to bibenzyl, but little further benefit is obtained beyond a ratio of LiN: benzyl chloride of 2.5:1.

The solvent used for the lithium–halogen exchange is very important. When tetrahydrofuran alone was used, the yield of benzylolithium was only 33% at –78 °C. Diethyl ether–tetrahydrofuran–light petroleum (b.p. 30–40 °C) (4:4:1) resulted in 71% and diethyl ether–tetrahydrofuran (3:1) afforded 54% at –78 °C. The solvent mixture found to be most suitable was diethyl ether–tetrahydrofuran–light petroleum (b.p. 30–40 °C) (4:3:1). This is similar to Trapp's solvent, which is known to be useful in lithiation reactions,<sup>11</sup> but as far as we are aware this is the first example of advantageous use of such a solvent for a lithium–halogen exchange reaction or for a reaction involving a lithium arene radical anion. At –95 °C in this solvent the yield was 86%. In reactions with simple alkyl halides LiDBB has been found to be superior to LiN for generation of alkylolithiums,<sup>12</sup> but in the present case there was little difference between the two. Therefore, the more stable and more convenient LiN was selected.

In view of the above findings, a general procedure was adopted for the synthesis of substituted benzylolithiums (Scheme 2). To a LiN solution (3.0 mmol) in diethyl ether–tetrahydro-



fur–light petroleum (b.p. 30–40 °C) (4:3:1) at –95 °C was slowly added a substituted benzyl chloride (1.2 mmol) in the same solvent over a period of 15 min. After a further 12 min excess of iodomethane or water was added and the mixture was worked up. The results are shown in Table 2. As shown in Table 2, yields of organolithium compounds obtained from the lithium–halogen exchange of substituted benzyl chlorides are reasonable, demonstrating that this is a useful new synthetic method for the organic chemist. In order to show that there were no isolation problems resulting from the particular method used, two reactions were scaled up and the products were isolated (see Table 2). For these cases the period of addition of the benzyl chloride was extended somewhat in order to maintain the low temperature.

† Formerly known as The University College of Swansea.

**Table 1** Lithium-halogen exchange of benzyl chloride with lithium aromatic radical anions under various conditions

Entry	Solvent	Temp. (°C)	Period of addition (min)	Radical anion used (LiArH)	Ratio LiArH to PhCH <sub>2</sub> Cl	Yield <sup>a</sup> PhCH <sub>2</sub> CH <sub>3</sub> (%)	Yield <sup>a</sup> bibenzyl (%)
1	THF	-78	10	LiN	3	23	77
2	THF	-78	15	LiN	3	33	67
3	Et <sub>2</sub> O-THF (3:1)	-78	15	LiN	3	54	34
4	Et <sub>2</sub> O-THF-LP (4:4:1)	-78	15	LiN	3	71	26
5	Et <sub>2</sub> O-THF-LP (4:4:1)	-95	15	LiN	3	78	18
6	Et <sub>2</sub> O-THF-LP (4:4:1)	-95	1	LiN	3	56	41
7	Et <sub>2</sub> O-THF-LP (4:3:1)	-95	15	LiN	3	86	11
8	Et <sub>2</sub> O-THF-LP (4:3:1)	-95	15	LiN	2.5	85	12
9	Et <sub>2</sub> O-THF-LP (4:3:1)	-95	15	LiN	2.2	82	17
10	THF	-78	15	LiDBB	3	57	37
11	Et <sub>2</sub> O-THF-LP (4:3:1)	-95	15	LiDBB	3	81	14

<sup>a</sup> Determined by GC using an internal standard.

**Table 2** Lithium-halogen exchange of substituted benzyl chlorides with lithium naphthalenide under standard conditions<sup>a</sup>

R	Yield (%) <sup>b</sup>		
	2 <sup>c</sup>	3 <sup>d</sup>	4
H	85 (81) <sup>e</sup>		12
4-F		67	32
4-MeO	50 <sup>f</sup>		3
2-Me	47		35
		58	35
2,5-Me <sub>2</sub>		50	41
3-Me	80 (78) <sup>e</sup>		13
		85	13
4-Me		64	36

<sup>a</sup> See text. <sup>b</sup> Determined by GC using an internal standard. <sup>c</sup> Iodomethane as electrophile. <sup>d</sup> Water as electrophile. <sup>e</sup> The figures in parentheses are yields of isolated products from reactions carried out on a somewhat larger scale (4 mmol of the benzyl halide). <sup>f</sup> The low yield in this case is probably due to polymerization of the starting material on contact with the metal of the syringe needle and could probably be improved by use of non-metallic transfer equipment.

## Experimental

**Representative Procedure.**—A pre-formed solution of lithium naphthalenide in tetrahydrofuran (0.74 mol dm<sup>-3</sup>; 13.5 cm<sup>3</sup>, 10.0 mmol) was transferred with a syringe into an oven-dried 150 cm<sup>3</sup> flask equipped with a pre-cooling spiral tube inlet system and a glass stirring bar. Diethyl ether (18 cm<sup>3</sup>) and light petroleum (b.p. 30–40 °C; 4.5 cm<sup>3</sup>) were added and the flask was immersed to the top of the inlet spiral in a dish filled with acetone, which was then cooled by addition of liquid nitrogen until the acetone just froze (measured temperature -95 °C). A solution of benzyl chloride (0.510 g, 4.0 mmol) in diethyl ether (15 cm<sup>3</sup>), tetrahydrofuran (11 cm<sup>3</sup>), and light petroleum (b.p. 30–40 °C; 3.8 cm<sup>3</sup>) was added with a double-ended needle via the cooling spiral to the stirred lithium naphthalenide over a period of 30 min. The resultant mixture was stirred for a further 15 min at -95 °C after which iodomethane (3.5 cm<sup>3</sup>, 56 mmol) was added dropwise to it with a syringe. The mixture was stirred

at -95 °C for 20 min, after which the cooling bath was removed and the mixture was warmed to room temperature. The resultant mixture was filtered and GC analysis of the filtrate showed the presence of ethylbenzene (85% yield) and bibenzyl (11% yield). The solvent was removed by distillation through a Vigreux column and the residue was then twice distilled by short-path, bulb-to-bulb distillation at 150–175 °C to yield ethylbenzene (0.345 g, 81%) as a pure, colourless liquid.

## Acknowledgements

D. H. thanks the British Government for an ORS award and the University of Wales, Swansea, for financial support.

## References

- 1 K. Ziegler and H. Colonius, *Liebigs Ann. Chem.*, 1930, **479**, 135; H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.*, 1955, **77**, 3134.
- 2 G. Wittig and H. Witt, *Chem. Ber.*, 1941, **74**, 1474.
- 3 K. Ziegler and F. Dersch, *Chem. Ber.*, 1931, **64**, 448.
- 4 S. Bywater and D. J. Worsfold, *J. Organomet. Chem.*, 1971, **33**, 273.
- 5 N. L. Holy, *Chem. Rev.*, 1974, **74**, 243.
- 6 D. J. Rawson and A. I. Meyers, *Tetrahedron Lett.*, 1991, **32**, 2095.
- 7 H. E. Zieger, I. Angres and L. Maresca, *J. Am. Chem. Soc.*, 1973, **95**, 8201.
- 8 S. Bank and J. F. Bank, *Tetrahedron Lett.*, 1971, 4581.
- 9 K. Smith and G. J. Pritchard, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 282; K. Smith, C. M. Lindsay and G. J. Pritchard, *J. Am. Chem. Soc.*, 1989, **111**, 665; K. Smith, C. M. Lindsay, I. K. Morris, I. Matthews and G. J. Pritchard, *Sulfur Lett.*, 1994, **17**, 197.
- 10 K. Smith, A. Pelter and A. Norbury, *Tetrahedron Lett.*, 1991, **32**, 6243.
- 11 A. S. Fletcher, K. Smith and K. Swaminathan, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1881; G. Köbrich, H. R. Merkle and H. Trapp, *Tetrahedron Lett.*, 1965, 969; G. Köbrich, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 41 (see p. 46); B. Bánhidai and U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 836.
- 12 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924; *Tetrahedron Lett.*, 1976, 1849.

Paper 4/07156E

Received 23rd November 1994

Accepted 23rd November 1994