

Lithium diisopropylamide (LDA) reduction of nitroarenes

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Abstract

Lithium diisopropylamide (LDA) was found to reduce a wide variety of nitroarenes to the corresponding azoxyarene and aminoarene at -40 °C.

Keywords: Reduction, azoxyarenes, low-temperature synthesis

Introduction

Although LDA is commonly thought in terms of its basic properties, it has been shown to behave as a single-electron transfer (SET) donor in reactions with geminal diiodides¹, heterocycles,² α -bromo imines,³ and conjugated acetylenes.⁴ LDA is also known to reduce certain haloarenes by donating an α -hydrogen to the aryne intermediate in these reactions.⁵ We⁶ recently reported the first example of LDA functioning as SET agent in its reactions with nitroarenes. In these reactions, 2-,3 and 4-chloronitrobenzene did not react with LDA at - 40 °C to give expected aryne products, but rather were reduced by LDA to 2,2'- 3,'3- and 4,4'-dichloroazoxybenzenes, respectively. No attempts were made to determine if chloroanilines were also formed in these reactions. Prior to this study, no low temperature reduction of nitroarenes to azoxyarenes, some of which are important dyes or exhibit significant biological activity, had been reported. Given the uniqueness and low-temperature reaction conditions of the LDA reduction, we have extended its scope a wide variety of nitroarenes and report the results herein.

Results and Discussion

Thirteen nitroarenes **1a-m** were first treated with varying amounts of LDA at -40 °C for 1 h and found to give mixtures of the corresponding aniline **2a-n** and azoxyarene **3a-m**. The best yields of the azoxyarenes were obtained by using 5 equivalents of LDA per one equivalent of nitroarene. The yields are listed in Table 1. As shown, nitropyrene **1j**, 4-chloronitrobenzene **1d**, 2-methyl-4-nitrobenzoic acid **1j**, and 4-nitrotoluene **1e** gave the corresponding azoxyarenes as

predominant products, *i.e.* **3j** (83%), **3d** (53%), **3i** (37%), and **3e** (38%), respectively. On the other hand, nitrobenzene **1a**, 2-nitrobiphenyl **1h**, 3,4-dimethylnitrobenzene **1k** and 2,4-dimethylnitrobenzene **1n** gave anilines as predominant products, *i.e.* **2a** (51%), **2h** (50%), **2k** (43%), and **2l** (31%), respectively. Separation of the azoxyarenes **3** from anilines **2** was easily accomplished by simple acid-base extraction methodology. Interestingly, yields of **2** and **3** did not vary when the reduction was carried out at -70 °C, although the reactions were much slower, requiring stirring overnight for completion. Attempts to reduce 2- and 4-nitropyridine using LDA failed.

In most cases, products **2** and **3** were known compounds and thus identified by comparison to their physical properties and/or spectral data to those of known compounds. In the case of new compounds, structures were identified on the basis of spectral properties and elemental analysis.

In conclusion, the major finding of this study is that LDA reduces nitrobenzenes to azoxybenzenes and anilines at low temperatures. Prior to our work, LDA had never been implicated as a reducing agent for nitro compounds. This finding is significant in its own right. However, since the reduction occurs at low temperatures to azobenzenes as major products, it might also serve as a valuable alternative to previously reported methods all of which requires room or elevated temperatures and some require several steps. For example, one method requires a two step process at 45 °C which involves the conversion of nitrobenzenes to hydroxylamines followed by reduction with I₂ or FeCl₃.⁷ Catalytic reduction using NaBH₄⁸ or NaBH₄/LiCl in diglyme at 125-162 °C⁹ as well as reductions in basic alcoholic refluxing media, are also commonly used.¹⁰⁻¹² Recently a BiCl₃-Zn promoted reduction has been performed at room temperature.¹³

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp capillary apparatus and are uncorrected with respect to stem correction. IR spectra were recorded on a Nicolet Magna-IRTM 550 FTIR instrument. ¹H and ¹³C NMR spectra were recorded on a 400 MHz Bruker AVANCE DRX-400 Multi-nuclear NMR spectrometer; chemical shifts were referenced to TMS as internal standard and coupling constants *J* are given in Hz.

Materials. These were obtained from commercial sources. The LDA used was obtained as a 2.0M solution in hexanes.

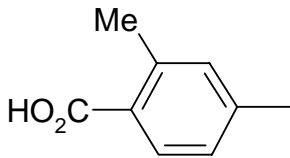
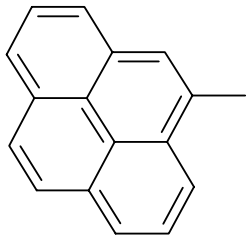
General procedure for LDA reduction of nitroarenes **1a-m**

A 12.5 ml portion of 2.0 M solution of LDA (25 mmol) was added to a flame-dried flask flushed with nitrogen and containing 10 ml of THF and the resulting mixture was cooled to -40 °C. The appropriate nitroarene (5 mmol) was then added, and the resulting solution was first stirred for 5 min then allowed to warm to rt where it was quenched with sat. aq. NH₄Cl (30 mL). The

resulting crude mixture was dissolved in methylene chloride and extracted with 3 x 10 mL of dil HCl. The methylene chloride extracts was dried, and evaporated to give impure **3** which was purified by flash column chromatography (silica gel) using a mixture of hexane/ethyl acetate (9:1). Pertinent physical and spectral properties of the azoxybenzenes **4-6** are given below.

Table 1

$$\text{ArNO}_2 + \text{LDA} \longrightarrow \text{ArNH}_2 + \text{Ar}-\text{N}^+=\text{N}-\text{Ar}$$

1		2		3	
Nitroarene	Ar	Aminoarene	Yield, %	Azoxyarene	Yield, %
1a	Ph-	2a	51	3a	32
1b	2-Cl-C ₆ H ₄	2b	21	3b	23
1c	3-Cl-C ₆ H ₄	2c	18	3c	29
1d	4-Cl-C ₆ H ₄	2d	12	3d	53
1e	4-Me-C ₆ H ₄	2e	23	3e	38
1f	4-MeO-C ₆ H ₄	2f	29	3f	35
1g	4-Ph-C ₆ H ₄	2g	42	3g	45
1h	2-Ph-C ₆ H ₄	2h	50	3h	4
1i		2i	13	3i	37
1j		2j	5	3j	83
1k	2,3-diMe-C ₆ H ₃	2k	43	3k	28
1l	2,4-diMe-C ₆ H ₃	2l	31	3l	24
1m	1-naphthyl	2m	10	3m	7

Azoxybenzene (3a). mp 35-36 °C (lit.¹⁴ 36 °C).

Bis-2-chloroazoxybenzene (3b). Red solid, mp 114-115 °C (lit.⁶ 58-59 °C. IR (KBr) ν 1619 (N=N), 776 and 730 cm^{-1} (*o*-substitution); ¹H NMR (d_6 -acetone) δ 6.99-7.01 (1 H, m), 7.21-7.22 (1 H, m), 7.44-7.46 (1 H, m), 7.58-7.62 (3 H, m), 8.22 (1 H, d, J = 8.2 Hz). ¹³C NMR (d_6 -acetone) δ 116.3, 118.4, 124.5, 125.9, 126.1, 126.8, 127.6, 128.9, 130.7, 125.6, 136.3, 141.6. (Found: C, 54.1; H, 3.2; 10.5. $\text{C}_{12}\text{H}_8\text{N}_2\text{OCl}_2$ requires C, 54.0; H, 3.0; N, 10.5).

Bis-3-chloroazoxybenzene (3c). Light yellow solid, mp 105-106 °C (lit.⁶ 96-97 °C).

Bis-4-chloroazoxybenzene (3d). Light yellow solid, mp 158-159 °C (lit.⁶ 158 °C).

Bis-4-methylazoxybenzene (3e) mp 63-65 °C (lit.¹⁴ 66-68 °C)

Bis-4-methoxyazoxybenzene (3f) mp 115-116 °C (lit.¹⁵ 116-118 °C)

Bis-4-phenylazoxybenzene (3g). Yellow solid, mp 212-214 °C. IR (KBr) ν : 3056, 3033, 1598, 1481, 1461, 1443, 843, 762 cm^{-1} . ¹H NMR (CDCl_3) δ 7.41 (m, 2 H), 7.51 (m, 4 H), 7.68 (t, J = 8.8 Hz, 1 H), 7.75 (d,d, J_1 = 8.8 Hz, J_2 = 7.6 Hz, 4 H), 8.35 (d, J = 8.8 Hz, 2 H), 8.43 (d, J = 8.8 Hz, 2 H). ¹³C NMR (CDCl_3) δ 122.9, 126.3, 127.2, 127.4, 127.5, 127.9, 128.3, 129.0, 129.1, 139.6, 140.2, 142.4, 143.3, 144.6, 147.5. Calcd for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}$: C, 82.3; H, 5.2; N, 8.0. Found: C, 82.1; H, 5.2; N, 7.9.

4-Carboxy-3-chloroazoxybenzene (3i). Brown solid, mp 290 °C (decom). IR (CDCl_3) ν 3410 (br), 2975, 1707, 1600, 1465, 1249, 1045, 831, 757. ¹H NMR (DMSO-d_6) δ 7.72 (d, J = 8.60, 1 H), 7.79 (d, J = 8.8 Hz, 1 H), 8.21 (d, J = 8.8 Hz, 1 H), 8.34 (d, J = 8.6 Hz, 1 H), 8.52 (s, 1 H), 8.57 (s, 1 H), Anal. Calcd for C. Calcd. For $\text{C}_{14}\text{H}_7\text{N}_2\text{O}_5\text{Cl}_2$: C, 47.5; H, 2.0; N, 7.9. Found: C, 47.6; H, 1.9; N, 7.8.-

Azoxy-1-pyrene (3j). Yellow solid, mp 240-242 °C. IR (KBr) ν : 3037, 1594, 1499, 1154, 1022, 838, 783 cm^{-1} . ¹H NMR (CDCl_3) δ 8.09 (7.6, Hz 1 H), 8.18 (m, 5 H), 8.27-8.37 (m, 8 H), 8.67 (d, J = 8.8 Hz, 1 H), 8.78 (d, J = 8.8 Hz, 1 H), 8.91 (d, J = 8.8 Hz, 1 H), 9.78 (d, J = 8.8 Hz, 1 H). Anal. Calcd for C. Calcd for $\text{C}_{32}\text{H}_{18}\text{N}_2\text{O}$: C, 86.1; H, 4.1; N, 6.3. Found: C, 86.2; H, 4.2; N, 6.4.

Bis-(3,4-dimethyl)azoxybenzene (3k). Yellow solid, mp 141.-142 °C. IR (CDCl_3) ν 3018, 2969, 2918, 1609, 1491, 1465, 1317, 867, 821. ¹H NMR (CDCl_3) δ 2.34 (s, 3 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 2.38 (s, 3 H), 7.24 (d, J = 8.4 Hz, 2 H), 8.03 (m, 3 H), 8.09 (s, 1 H). ¹³C NMR (CDCl_3) δ 19.6, 19.8, 19.9, 20.0, 119.6, 122.9, 123.0, 126.8, 129.7, 129.8, 129.7, 129.8, 136 (3l):.8, 137.2, 138.7, 140.5, 142.2, 146.4. Calcd for C. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$: C, 75.6; H, 7.1; N, 11.0. Found: C, 75.7; H, 7.2; N, 10.9.

(2,4-Dimethyl)azoxybenzene (3l). Colorless crystals mp 56-57.5 °C. ¹H NMR (CDCl_3) δ 2.35 (s, 6 H), 2.38 (s, 3 H), 2.48 (s, 3 H), 7.08 (d, J = 8.4 Hz, 2 H), 7.12 (s, 2 H), 7.56 (d, J = 8.8 Hz, 1 H), 8.12 (d, J = 8.4 Hz, 1 H). ¹³C NMR (CDCl_3) δ 18.9, 19.0, 21.5, 21.7, 122.0, 124.0, 127.0, 127.4, 131.4, 131.8, 132.7, 135.1, 129.2, 140.5, 140.9, 147.9. Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$: C, 75.6; H, 7.1; N, 11.0. Found: C, 75.7; H, 7.2; N, 10.9.

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