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FUNCTIONALLY SUBSTITUTED ORGANOLITHIUM COMPOUNDS. THE LITHIUM DERIVATIVES OF THE DIMETHYLBENZYLAMINES

C. T. VISWANATHAN and CHARLES A. WILKIE
Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233 (U.S.A.)

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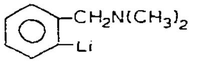
SUMMARY

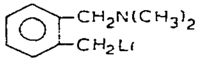
The organolithium derivatives of *N,N*-dimethylbenzylamine (I), *o*-methylbenzyldimethylamine (II), and *o*-trimethylsilylbenzyldimethylamine (VII) have been prepared and isolated. Infrared and NMR spectra indicate that lithiation occurs at the *ortho* position. The molecular weight of all three compounds in DMSO is concentration dependent. The IR, NMR, and UV spectra have all been obtained and interpreted in terms of both intramolecular and intermolecular lithium–nitrogen interactions.

INTRODUCTION

The ortholithiation reaction is well-known to be of considerable synthetic utility. Hauser and his co-workers have prepared a variety of derivatives of *N,N*-dimethylbenzylamine presumably through the intermediacy of a lithium compound. They have suggested that compound I[1], II[2], and III[3] may arise from the interaction of n-butyllithium with the appropriate amine. The thiophene derivative IV, has been suggested by Slocum[4]. The position of lithiation has been established only through derivatization reactions.



(I)



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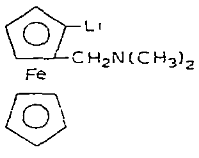

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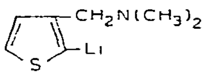
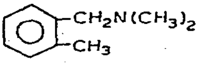


(IV)

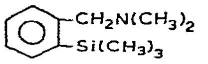
This paper presents our investigations of the ortholithiation reaction. Three organolithium compounds have been isolated and examined in order to determine the position of lithiation as well as to investigate the lithium–nitrogen dative bond that has been drawn in these compounds.

RESULTS AND DISCUSSION

Previous investigators[1–4] have concluded from derivatization results that the lithiation of dimethylbenzylamines occurs at the *ortho* position. In this study the lithium derivative of *N*,*N*-dimethylbenzylamine, I, has been isolated and studied. The integrated NMR spectrum (see Experimental section) is clearly that of a ring-substituted compound; the IR in the region 850–690 cm^{-1} is in agreement with that predicted for four adjacent aromatic protons[5]. The overtone region, 2000–1700 cm^{-1}, shows an *ortho* substitution pattern similar to that reported by Conley[6]. Derivatization of I with methyl iodide and with trimethylchlorosilane yields the *ortho* derivatives V and VI respectively. The *ortho* substitution of these is established both by NMR and IR, both the fundamental and overtone regions are in accord with this substitution.



(V)



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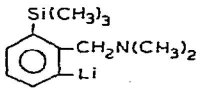

(VII)

V may be lithiated to give only II; NMR and IR and derivatization with trimethylchlorosilane clearly establish that the methyl group is lithiated. VI may be lithiated to give only VII; again the position of lithiation may be established by NMR and IR. Three adjacent aromatic protons are indicated by the C–H out of plane bending mode in the 810–750 region[5]. Again the overtone region is clearly 1,2,3-trisubstituted[6]. Derivatizing VII with trimethylchlorosilane gives a 1,2,3-trisubstituted compound identified by NMR and IR.

Hauser[1] has assumed that the metalation involves an initial coordination of the lithium with the lone pair of electrons on nitrogen. We observe that treatment of *N*,*N*-dimethylbenzylamine with a 7-fold excess of n-BuLi followed by derivatization with deuterium oxide yields only a monodeuterio derivative as shown by NMR and mass spectroscopy. This establishes that only one *ortho* position at a time is available for metalation with n-BuLi; presumably that position is activated by nitrogen coordination.

The infrared spectrum has been examined using lithium isotope effects in order to determine the involvement of the lithium. The spectrum of I using both lithium-6 and lithium-7 has been obtained. Two bands that show a lithium isotope effect are observed. These occur at 355 and 494 cm^{-1} in the lithium-7 case moving to 370 and 500 cm^{-1} respectively for the lithium-6 compound. One of these, probably 355 cm^{-1}, represents the Li–C frequency; in phenyllithium ν(Li–C) occurs near 400 cm^{-1} (ref. 7). The other frequency, 494 cm^{-1}, must then be the lithium–nitrogen stretch. We have suggested a lithium–cyanide interaction at 575 cm^{-1} in $C_6H_5CH(Li)CN$[8]. The presumed lithium–carbon frequency in this molecule comes at 460 cm^{-1}; a large isotope effect, 18 cm^{-1}, is observed for the lithium–carbon mode, for lithium–nitrogen the shift is only 7 cm^{-1}. These shifts are of the same magnitude as observed in I.

Ultraviolet spectra of these compounds have been obtained. Phenyl absorptions are observed in all compounds near 250–260 nm. Additional bands are observed only in the lithium compounds, these occur near 300 nm. The so-called lithium framework absorption has been predicted near 225 nm[9], and between 100 and 400 nm[10]; it has been observed[11] near 220 nm in hexameric n-butyllithium. The bands near 300 nm in compounds I, II, and VII seem too high to come from the lithium framework and must originate elsewhere, a likely origin is the lithium–nitrogen interaction.

The protons on a carbon immediately adjacent to an electropositive atom (the α protons) normally give an NMR signal upfield from the signal in the hydrocarbon. Furthermore, when the metal is coordinated the α protons move to even higher field while the protons of the base move to a lower field. Thus the methyl protons in toluene resonate at $\delta 2.32$ while in benzyllithium the analogous protons are at $\delta 1.62$[12]. The lithium compounds I, II, and VII do not follow this simple behavior, there is little if any difference between a protio compound and the lithio derivative of that compound. Compound II which is similar to benzyllithium shows a signal at $\delta 2.3$ attributable to CH_2Li, this same position is observed for the CH_3 protons in V, the *N*-methyl protons in II come at $\delta 2.15$ while in V they are at $\delta 2.12$. This suggests that I, II, and VII are somehow different from the normal organolithium compounds.

Conductivity measurements establish that the compounds are weak electrolytes in DMSO solution. Cyclic voltammetry can be used to probe the mode of dissociation. The voltammogram of anthraquinone is affected, *i.e.*, the reduction potential is observed to back up in the presence of Li^+ but is unaffected when larger cations are present[8,13,14]. For these compounds the electrochemical technique establishes that lithium ion is not produced in the dissociation. As we have previously discussed[8], the production of Li^+ denies the presence of an electron-deficient compound; the nonproduction of Li^+ allows no conclusion.

Earlier investigators of these compound have always presumed an intramolecular lithium–nitrogen interaction[1,2,3,4]. Molecular weight studies clearly can determine whether this interaction is intramolecular or intermolecular. The molecular weights of compound I, II, and VII have been determined by freezing point depression in dimethylsulfoxide and all show a concentration-dependent molecular weight. At the lowest concentration the association factor is a little less than 2, this increases to greater than 4 at higher concentrations. The concentration dependence of these results indicates that more than one arrangement of the molecules is possible, this can be the result of both intermolecular and intramolecular lithium–nitrogen interactions of similar energies.

The normal organolithium compound is a very good Lewis acid, it is impossible under normal conditions to remove ether from an adduct. Compounds I, II, and VII, on the other hand, show no tendency to retain ether. Ether-free compounds can be obtained at room temperature under vacuum, even DMSO can be removed at room temperature under vacuum. This lack of acidity is presumed to be a consequence of the amine nitrogen interacting with the lithium and thus neutralizing the acidic site.

All the available evidence seems to indicate that there is an inter- or intramolecular lithium–nitrogen interaction in these organolithium compounds and that aggregation occurs through this interaction.

EXPERIMENTAL

Materials. n-BuLi was obtained as a solution in hexane from Alfa Inorganics. n-Bu^{6}Li was prepared from ^{6}Li (Oak Ridge National Laboratory) and di-n-butylmercury (Eastman) in diethyl ether. The ether was dried over NaK alloy and distilled before use; DMSO was dried by passing it several times through activated alumina. Reactions producing an air-stable final product were carried out under nitrogen in the hood, reactions producing the lithium compounds as final products were run in a NaK dried, nitrogen filled dry-box. Sample preparation for spectral analysis of air-sensitive materials was carried out in the dry-box. Nuclear magnetic resonance spectra were run on a Varian A-60A, infrared spectra on a Beckman IR-12, ultraviolet spectra on a Cary Model 14.

2-Lithiobenzyldimethylamine (I). A 13.5 g (0.1 mole) sample of *N,N*-dimethylbenzylamine and 44 ml of 2.28 *M* n-BuLi (0.1 mole) in hexane were mixed in 200 ml of anhydrous ether in a flask in the dry-box and stirred magnetically. Within one hour precipitation began, the reaction was allowed to proceed overnight, the solvent decanted and excess ether removed on the vacuum line. A yellow solid was obtained, 14.1 g, 100% yield. Hauser[1] has derivatized I with D_2O, the yield of deuterated amine was nearly quantitative. Spectral data IR, nujol mull (cm^{-1}): 275 w, 335 m, 355 m, 411 m, 435 m, 456 w, 495 w, 620 m, 715 m, 750 s, 821 m, 852 s, 940 m, 972 m, 991 m, 1016 s, 1040 s, 1050 w, 1100 m, 1150 w, 1172 m, 1230 m, 1252 m, 1310 m, 1362 m, 1380 m, 1555 w, 1572 w; NMR (DMSO-d_6): δ3.41 (s, 2, $CH_2N(CH_3)_2$), δ2.18 (s, 6, $CH_2N(CH_3)_2$), δ7.35 (m, 4, C_6H_4); UV max (DMSO): 264 nm (ε500), 306(200); UV max (solid state): 257, 262, 295 nm.

*Anal.** Found: C, 75.69; H, 8.43; N, 10.10; Li, 5.18. $C_9H_{12}NLi$ calcd.: C, 76.54; H, 8.57; N, 9.92; Li, 4.96%.

2-Methylbenzyldimethylamine. V. A 14.1 g sample of I (0.1 mole) was treated with 14.2 g of methyl iodide (0.1 mole). Distillation gave 6 g of V (40% yield) b.p. 68–70° (0.5 mm). Spectral data mass spectrum (70 eV): molecular ion at *m/e* 149; IR (neat): 320 w, 380 s, 420 s, 628 w, 645 w, 660 w, 690 w, 750 s, 772 s, 840 m, 865 w, 940 w, 970 w, 1020 s(br), 1040 s(br), 1100 w, 1150 w, 1180 m, 1260 s, 1315 w, 1360 s, 1460 s, 1490 w, 1555 vw, 1600 w, 1700 w, 1810 w, 1880 w(br), 1910 w(br), 2080 w cm^{-1}; NMR (DMSO-d_6), δ2.12 (s, 6, $N(CH_3)_2$), δ2.30 (s, 3, CH_3), δ3.27 (s, 2, CH_2N), δ7.06 (m, 4, C_6H_4); UV max (i-octane) 254 (ε300), 260(500), 268(400) nm.

*Anal.*** Found: C, 80.58; H, 10.39; N, 8.72. $C_{10}H_{15}N$ calcd.: C, 80.48; H, 10.14; N, 9.38%.

2-Trimethylsilylbenzyldimethylamine. VI. A 14.1 g sample of I (0.1 mole) was treated with 10.8 g (0.1 mole) of trimethylchlorosilane. Distillation yields 12.4 g of VI, 60% yield, b.p. 85–90° (0.5 mm). Spectral data mass spectrum (70 eV): molecular ion at *m/e* 207; IR (neat): 345 w, 380 w, 445 m, 480 w, 500 vw, 630 m, 700 m, 730 m, 750 s, 850 vs, 950 w, 980 m, 1040 s, 1050 s, 1080 m, 1100 w, 1130 vs, 1150 m, 1180 m, 1260 vs, 1310 m, 1370 m, 1445 m, 1468 s, 1500 w, 1570 w, 1595 m cm^{-1}; NMR (DMSO): δ0.3 (s, 9, $Si(CH_3)_3$, δ2.1 (s, 6, $N(CH_3)_2$), δ3.42 (s, 2, CH_2N), δ7.2 (m, 4, C_6H_4); UV max (i-octane), 262 (200), 265 (200), 273 (200) nm.

*Anal.*** Found: C, 70.10; H, 10.63; N, 7.26. $C_{12}H_{21}NSi$ calcd.: C, 69.52; H, 10.21; N, 6.75%.

Attempted polylithiation of N,N-dimethylbenzylamine. A 5.4 g (0.04 mole) sample of *N,N*-dimethylbenzylamine in ether was treated in the hood with 123 ml of

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* Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

** Chemalytics, Inc., Tempe, Arizona 85281.

2.28 *M* n-BuLi (0.28 mole) in hexane. The reaction was allowed to reflux with stirring overnight. The solution, which still contained n-butyllithium was treated with an excess of deuterium oxide. Work-up by distillation gave the deuterated material. Mass spectroscopy shows the base peak at *m/e* 136, monodeuterated compound, and a peak at *m/e* 137 indicating a few percent at most of dideuterated compound.

2-*N,N-dimethylaminomethyl-3-trimethylsilylphenyllithium* (*VII*). A 4.14 g (0.02 mole) sample of VI was dissolved in dry ether in a flask in the dry box and treated with 8.4 ml of 2.28 *M* n-BuLi (0.02 mole) in hexane. The solution was stirred magnetically overnight. The solution turned bright red upon mixing and the product was ether soluble. The ether was removed on the vacuum line at room temperature leaving a quantitative yield of brownish-red solid. The compound was analyzed by allowing it to react with water followed by an acidimetric titration of the base produced. Found: Li, 3.43; calcd.: Li, 3.29. Spectral data IR (nujol mull): 270 w, 370 m, 430 m, 520 s(br), 620 w, 690 w, 700 w, 730 vw, 760 s, 840 s, 850 s, 880 m, 960 w, 980 w, 990 w, 1010 m, 1040 w, 1060 s, 1125 s, 1150 vw, 1170 w, 1250 s, 1262 w, 1300 m(br), 1350 s, 1380 s, 1535 w, 1550 w, 1570 w cm^{-1}; NMR (DMSO-d_6) δ0.28 (s, 9, $Si(CH_3)_3$), δ2.1 (s, 6, $N(CH_3)_2$), δ3.43 (s, 2, CH_2N), δ7.19 (m, 3, C_6H_3); UV max (DMSO), 265 (ε1000), 295 (100), 325 (700) nm, UV max (solid): 264, 272, 293 nm.

2,6-*Bis(trimethylsilyl)benzyldimethylamine*. A 4.3 g sample of VII (0.02 mole) was treated with 2.7 g (0.025 mole) of trimethylchlorosilane. The compound was isolated by distillation. b.p. 95–100° (0.5 mm) yield 4.5g, 85%. Spectral data mass spectrum (70 eV): molecular ion at *m/e* 279; IR (neat): 255 w, 325 m, 350 m, 428 w, 465 w, 610 s, 675 s, 735 vw, 745 s, 775 w, 840 s(br), 970 m, 1020 m, 1030 m, 1070 w, 1080 w, 1110 w, 1130 m, 1160 m, 1195 w, 1240 s(br), 1285 w, 1350 s, 1380 s, 1400 s, 1430 w, 1455 s, 1550 m, 1680 w, 1700 w, 1880 w, 1930 w cm^{-1}; NMR(DMSO), δ0.3 (s, 18, $Si(CH_3)_3$), δ2.06 (s, 6, $N(CH_3)_2$), δ3.68 (s, 2, CH_2N), δ7.2–7.6 (m, 3, C_6H_3); UV max (i-octane), 256 (ε800), 265 (700), 273 (600) nm.

Anal.[*] Found: C, 64.28; H, 10.73; N, 4.86. $C_{15}H_{29}NSi_2$ calcd.: C, 64.43; H, 10.46; N, 5.01%.

2-*N,N-dimethylaminomethylbenzyllithium II*. A 3.0 g (0.02 mole) sample of V was dissolved in ether in a flask in the dry box and treated with 8.8 ml of 2.28 *M* n-BuLi (0.02 mole) in 20 ml ether. The solution was magnetically stirred overnight, the product was ether soluble. The solvent was removed on the vacuum line at room temperature to give a yellowish solid. Analysis was by acidimetric titration of the hydrolyzed product. Found: Li, 4.37; calcd.: Li, 4.52. Yield 77%. Spectral data IR (nujol mull), 280 vw, 410 vw, 660 w, 680 w, 750 m, 890 s, 1000 w, 1065 s, 1130 s(br), 1180 vw, 1270 w, 1320 vw, 1330 w, 1385 s, 1595 w cm^{-1}; NMR(DMSO-d_6), δ2.15 (s, 6, $N(CH_3)_2$), δ2.3 (s, 2, CH_2Li), δ3.27 (s, 2, CH_2N), δ7.35 (m, 4, C_6H_4); UV max (DMSO), 264 (ε500), 306 (200) nm; UV max (solid); 242, 268, 300 nm.

2-*Trimethylsilylmethylbenzyldimethylamine*. A 3.1 g sample (0.02 mole) of II was treated with 2.16 g (0.02 mole) of trimethylchlorosilane. Work-up by distillation gave 2.7 g, 55% yield, b.p. 75–80° (0.75 mm), NMR (DMSO), δ0.3 (s, 9, $Si(CH_3)_3$), δ2.3 (s, 2, CH_2Si), δ2.15 (s, 6, $N(CH_3)_2$), δ3.4 (s, 2, CH_2N), δ7.2 (m, 4, C_6H_4).

Molecular weights. The measurement was made by freezing point depression in DMSO in the normal way[8]. Solutions were prepared by weight and checked by

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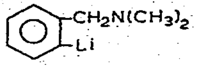
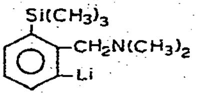
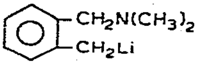
[*] Chemalytics, Inc., Tempe, Arizona 85281.

TABLE 1

MOLECULAR WEIGHTS

Compound	*Concentration*[a] *(M)*	*Observed mol. wt.*	*Association*
	0.0248	263	1.87
	0.0301	305	2.16
	0.0411	275	1.95
	0.0582	658	4.67
	0.0819	628	4.45
	0.0766	375	1.76
	0.0851	457	2.14
	0.109	468	2.20
	0.117	665	3.12
	0.142	893	4.18
	0.0450	287	1.84
	0.0789	357	2.29
	0.0940	466	2.98
	0.125	432	2.76

[a] Concentrations figured as monomer.

titration. Each value is the average of three determinations at that concentration. The results are collected in Table 1. The results are believed to be accurate to at least 10%.

Conductivity. The conductivity of the three lithium compounds, I, II, and VII, have been determined in DMSO. Solutions were prepared by weight and checked by titration[8]. All are weak electrolytes, the following equilibrium constants may be abstracted: I, $2 \cdot 10^{-4}$; II, $4 \cdot 10^{-3}$; VII, $6 \cdot 10^{-3}$.

Electrochemistry. The cyclic voltammogram of 0.001 *M* anthraquinone was obtained in DMSO and DMF solution. To this was added an equal amount of I and the voltammogram reobtained, no change was observed in either solvent. Identical results were obtained with lithium compounds II and VII. Lithium chloride in either solvent backs up the reduction potential[8].

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