Sterically Hindered Lithium Dialkylamides; A Novel Synthesis of Lithium Dialkylamides from *N*-*t*-Alkyl-*N*-benzylideneamines and the Isolation of Highly Hindered *s*-Alkyl-*t*-alkylamines[1]

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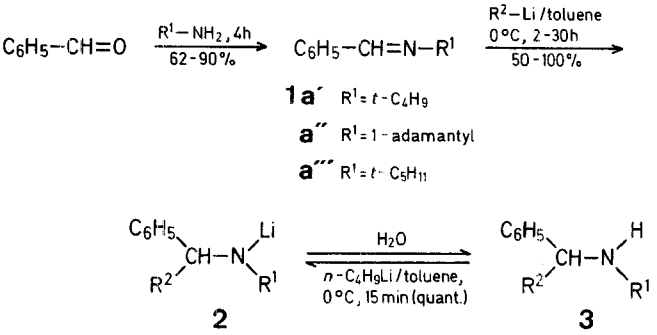
The convenient synthesis of lithium amides from imines **1** and organolithium reagents, and the isolation of the related highly hindered dialkylamines **3** are described.

The sterically hindered lithium dialkylamides are versatile compounds for organic synthesis which combine high basicity with low nucleophilicity[2]. The search for more sterically hindered and less nucleophilic reagents than the standard lithium diisopropylamide has led to the development of lithium di-*t*-alkylamides[3] and lithium *s*-alkyl-*t*-alkylamides[4]. However, the di-*t*-alkylamine substrates, except for 2,2,6,6-tetramethylpiperidine, are not readily available and the *s*-alkyl-*t*-alkylamine substrates such as *t*-butylcyclohexylamine are usually prepared in low yield by the Lewis acid-catalysed condensation of a *t*-alkylamine with a ketone to give an unstable *N*-*t*-alkylketimine which is then reduced either with a metal hydride or by a catalytic method.

A requirement[5] for substantial quantities of a lithium dialkylamide, more sterically demanding than either lithium diisopropylamide or lithium *t*-butylcyclohexylamide, stimulated us to develop a novel synthesis of hindered lithium dialkylamides which did not involve either the deprotonation or the synthesis of the parent amines. Our approach was to consider the use of the *N*-benzylideneamines **1** in the synthesis of *s*-alkyl-*t*-alkylamides.

The *N*-*t*-alkylaldimines **1** in contrast with the *N*-*t*-alkylketimines are not sensitive to moisture and are inexpensively synthesised by the spontaneous reaction of benzaldehyde with *t*-alkylamines (Table 1).

The reaction of the *N*-benzylideneamines **1a′–a‴** with various organolithium reagents gives, after protic decomposition of the intermediate lithium dialkylamides **2a–h**, the hindered dialkylamines **3a–h** (Table 2). The formation of the metal amides **2a–d** is shown to be quantitative by G.L.C. and/or ^{1}H-N.M.R. analysis of the respective mixtures obtained after quenching the reactions with a protic solvent. The highly hindered amides **2a–d** are therefore conveniently formed in this reaction from *N*-benzylideneamines. Their value as non-nucleophilic bases whose highly hindered conjugate acids take little part in proton transfer reactions is evidenced by the formation and subsequent reactions of 8-lithio-4-methyl-5,6,7,8-tetrahydroquinoline[5].



The quantitative yields of the hindered amides **2a–d** produced in the reactions of the organolithium reagents with the *N*-benzylideneamines **1a′,a″** contrast with the lower yields of the amides **2e–h** formed in the analogous reactions from the *N*-benzylideneamines **1a′,a‴**. The non-quantitative yield of the hindered amide **2e** is attributed to the slow rate of reaction at 0 °C between *n*-butyllithium and the highly hindered *N*-benzylidene-*t*-amylamine (**1a″**). The reaction of the imine **1a′** with *s*-butyllithium is neither stereo- nor regioselective: the amine **3f**, as a mixture of diastereoisomers, and the isomeric *N*-(4-*s*-butylbenzylidene)-*t*-butylamine are isolated upon work-up.

When an ethereal hydrocarbon solvent mixture is used for the reaction of the imine **1a′** with *n*-butyllithium the yield of the amine **3a** is markedly reduced, even in the presence of excess organometallic reagent. The formation of the amide **2g** from the reaction of the imine **1a′** with methyllithium in ether is likewise incomplete in the presence of excess methyllithium. This result is in accordance with previous work[6]

Table 1. *N*-*t*-Alkyl-*N*-benzylideneamines **1** prepared

Product No.	Yield [%][a]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. data	I.R. (Neat)[c] ν [cm^{-1}]	^{1}H-N.M.R. (Solvent/TMS$_{int}$)[d] δ [ppm]
1a′	90	92–94°/15	92°/8[6]	2960, 1636, 1575, 1445, 747, 685	($CDCl_3$): 1.32 (s, 9H, t-C_4H_9); 7.40 (m, 3H$_{arom}$); 7.75 (m, 2H$_{arom}$); 8.38 (s, 1H, =CH)
1a″[e]	62	59–60°	58.5–60°[7]	2900, 1640, 1579, 1089, 750, 690[f]	(DMSO-d_6): 1.60–1.80 (m, 15H$_{adamantyl}$); 7.45 (m, 3H$_{arom}$); 7.75 (m, 2H$_{arom}$); 8.32 (s, 1H, =CH)
1a‴	80	113–114°/15	$C_{12}H_{17}N$ (175.3)[g]	2970, 1642, 1582, 1450, 754, 693	($CDCl_3$): 0.82 (t, 3H, J = 7 Hz, CH_2—CH_3); 1.25 (s, 6H, CH_3—C—CH_3); 1.65 (q, 2H, J = 7 Hz, CH_3—CH_2); 7.39 (m, 3H$_{arom}$); 7.75 (m, 2H$_{arom}$); 8.24 (s, 1H, =CH)

[a] The yields refer to isolated pure products with satisfactory I.R. and ^{1}H-N.M.R. spectral data.
[b] The microanalyses were in satisfactory agreement with the calculated values (C, H, N ± 0.4).
[c] The I.R. spectra were recorded on a Perkin-Elmer 983G or 521 spectrophotometer.
[d] The N.M.R. spectra were recorded on a Bruker WP200 SY or on a Varian EM360 spectrometer.
[e] This compound was prepared using a Dean-Stark apparatus and boiling toluene as the solvent.
[f] In Nujol.
[g] The perchlorate salt isolated from ether had m.p. 138–141 °C.

Table 2. Lithium Amides **2** prepared and Their Conversion to Hindered Amines **3**

Products **2** and **3**	R^1	R^2	Reaction time [h]	Yield[c] of **2** [%]	Yield[a] of **3** [%]	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[b] or Lit. data	I.R. (Neat)[c] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[d] δ [ppm]
a	*t*-C_4H_9	*n*-C_4H_9	2	100	90	100–104°/4	–[e]	3330, 2960, 1452, 1365, 1229, 700	0.80–1.70 (m, 9H, *n*-C_4H_9); 0.98 (s, 9H, *t*-C_4H_9); 1.15 (br. s, 1H, NH); 3.68 (br. t, 1H, J = 6.5 Hz, CH); 7.10–7.30 (m, 5H, C_6H_5)
b	*t*-C_4H_9	*t*-C_4H_9[h]	4	100	93	52–54°/0.3	–[i]	3360, 2950, 1360, 1225, 727, 700	0.82 (s, 9H, *t*-C_4H_9); 0.90 (s, 9H, *t*-C_4H_9); 1.16 (br. s, 1H, NH); 3.36 (br. s, 1H, CH); 7.10–7.30 (m, 5H, C_6H_5)
c	1-Ad	*n*-C_4H_9	4[j]	100	76	170–172°/0.75	$C_{21}H_{31}N$ (297.5)	3350, 2910, 1450, 1357, 1147, 700	0.84 (t, 3H, J = 7 Hz, CH_3); 1.0–2.0 [m, 22H, Ad + —$(CH_2)_3$— + NH]; 3.70 (t, 1H, J = 7 Hz, CH); 7.10–7.40 (m, 5H, C_6H_5)
d	*t*-C_4H_9	C_6H_5[k]	22[j]	100	90	54–56.5°	53.5–54°[g]	3310, 2960, 1222, 1020, 708, 699[f]	1.03 (s, 9H, *t*-C_4H_9); 1.17 (br. s, 1H, NH); 4.91 (br. s, 1H, CH); 6.90–7.40 (m, 10H, $2C_6H_5$)
e	*t*-C_5H_{11}	*n*-C_4H_9	2 18	83 95[l]	60 –	86–94°/1	$C_{16}H_{27}N$ (233.4)	3340, 2960, 1450, 1378, 1197, 700	0.75–1.70 (m, 15H, *n*-C_4H_9, C_2H_5, NH); 0.79 (s, 3H, CH_3); 0.92 (s, 3H, CH_3); 3.70 (t, 1H, J = 7 Hz, CH); 7.10–7.40 (m, 5H, C_6H_5)
f	*t*-C_4H_9	*s*-C_4H_9[m]	3	–	61[n]	120°/10	$C_{15}H_{25}N$ (219.4)	3360, 2960, 1451, 1362, 1230, 702	0.70 (d, 3H, J = 7 Hz, CH—C$\underline{H}_3$ isomer A); 0.84 (d, 3H, J = 7 Hz, CH—C$\underline{H}_3$ isomer B); 0.87 (t, 3H, J = 7 Hz, CH_2—C$\underline{H}_3$ isomer B); 0.89 (t, 3H, J = 7 Hz, CH_2—C$\underline{H}_3$ isomer A); 0.95 (s, 18H, 2*t*-C_4H_9, isomer A + B); 1.00 (m, 2H, $2CH_3$—C$\underline{H}$, isomer A + B); 1.09 (br. s, 2H, 2NH, isomer A + B); 1.25–1.65 (m, 4H, $2CH_2$, isomer A + B); 3.57 (d, 1H, J = 6 Hz, CH, isomer A); 3.61 (d, 1H, J = 6 Hz, CH, isomer B); 7.10–7.25 (m, 10H, $2C_6H_5$, isomer A + B);
g	*t*-C_4H_9	CH_3[o]	4 30	50 88	– 51	42–44°/0.75	88–90°/11[6]	3350, 2960, 1360, 1224, 758, 697	0.95 (s, 9H, *t*-C_4H_9); 1.10 (br. s, 1H, NH); 1.25 (d, 3H, J = 7 Hz, CH—C$\underline{H}_3$); 3.85 (q, 1H, J = 7 Hz, CH_3—C$\underline{H}$); 7.00–7.30 (m, 5H, C_6H_5)
h	*t*-C_4H_9	C_6H_6N[p]	5.5	80[q]	33[r]	45–50°	$C_{17}H_{22}N_2$ (254.4)[s]	3320, 2900, 1592, 768, 700, 560[f]	0.82 (s, 9H, *t*-C_4H_9); 1.70 (br. s, 1H, NH); 2.90, 3.00, 4.19 (ABX System, J_{AB} = 13 Hz, J_{AX} = 9 Hz, J_{BX} = 6 Hz; CH_AH_B—CH_X); 6.99–7.58 (m, 8H, C_6H_5 + $3CH_{pyridyl}$); 8.56 (m, 1H, $CH_{pyridyl\text{-}6\text{-}H}$)

For footnotes a–d, and f, see: Table 1.

[e] The yields were estimated by G.L.C. or ^{1}H-N.M.R. data.

[g] The hydrochloride salt isolated from ethanol had m.p. 164–166°C (Lit. [9], 161°C).

[h] The alkylation was performed with 1.4 molar solution of *t*-butyllithium in pentane.

[i] The hydrochloride salt isolated from ether-propan-2-ol had m.p. 254–259°C (Lit. [9], 240°C).

[j] The reaction mixture was warmed to room temperature after 2 h.

[k] The alkylation was performed with 2.3 molar solution of phenyllithium in cyclohexane/ether (70 : 30).

[l] The yield was not optimized.

[m] The alkylation was performed with 1.2 molar solution of *s*-butyllithium in cyclohexane.

[n] The product consisted of a 55 : 45 mixture of diastereoisomers. The isomeric *N*-(4-*s*-butylbenzylidene)-*t*-butylamine was also isolated in 12% yield.
^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.28 (s, 9H, *t*-C_4H_9); 0.70–1.70 (m, 8H, C_2H_5, CH—CH_3); 2.58 (m, 1H, CH); 7.25 (d, J = 8 Hz, $2H_{arom}$); 7.65 (d, J = 8 Hz, $2H_{arom}$); 8.25 ppm (s, 1H, CH).
I.R. (Nujol): ν = 2920, 1641, 1579 cm^{-1}.

[o] The alkylation was performed with 1.6 molar solution of methyllithium in ether.

[p] 2-Picolyl.

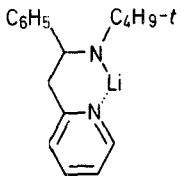
[q] The sample was worked-up by an inverse addition to methanol. The yield of **2h** was 14% when the sample was worked-up by the addition of water to the reaction mixture as in the typical procedure.

[r] Isolated yield of pure compound after chromatography.

[s] The compound was hygroscopic.

which shows that compound **3g** is obtained in 25% yield from a similar reaction employing 2.5 molar equivalents of methyllithium in boiling ether after 10.5 h. It appears therefore that in non-polar solvents the organometallic reagents will undergo nucleophilic addition across the imine double bond to give the amides **2a–g** in preference to basic attack leading to *ortho*-metallation of the phenyl ring.

The formation of the chelated amide **2h** from the imine **1a'** and 2-picolyllithium is reversible and the quantitiy of product **3h** isolated depends upon the work-up procedure. Thus inverse addition of the lithium amide **2h** to the quenching agent results in a vastly improved yield of the amide **3h**.



2h

The amides **2e–h** are not formed in a quantitative manner by the addition of organolithium reagents to *N*-*t*-alkyl-*N*-benzylideneamines **1a',a'''** and thus this method of preparation of the amides **2e–h** is inappropriate. However, the generation of the amides **2a–h** may also be achieved in a more standard fashion from the amines **3a–h** by proton abstraction with *n*-butyllithium and this is the method of choice for the compounds **2e–h**. The amines **3a–h** are simply separated from reaction mixtures in very high yields by extraction into low boiling hydrocarbon solvents and may be recycled after distillation. These amines are therefore cost effective in large scale synthesis. The lithium amides **2a–h** have superiority[5] over the much less hindered lithium diisopropylamide because the amines **3a–h** undergo less proton transfer side-reactions and are less nucelophilic than diisopropylamine or the more common hindered amines in standard use.

N-Benzylidene-t-butylamine 1a'; Typical Procedure:
A mixture of benzaldehyde (106 g, 1.0 mol) and *t*-butylamine (80.3 g, 1.1 mol) is stirred for 4 h with water cooling. Hexane (1 l) is added and the upper layer separated and evaporated. Distillation gives the title compound; yield: 146 g (90%); b.p. 92–94°C/15 torr (Table 1).

Lithium *N*-*t*-butyl-*N*-(1-phenylpentyl)amide 2a: Typical Procedure from Imine 1a':
A solution of the imine **1a'** (16.1 g, 0.1 mol) in toluene (30 ml) is added dropwise to a solution of 1.55 molar solution of *n*-butyllithium in hexane (64.5 ml, 0.1 mol) and toluene (20 ml) at 0°C under an inert atmosphere. After 2 h, an aliquot is quenched with water or methanol and G.L.C. analysis or ^{1}H-N.M.R. spectrometry indicates the quantitative formation of the compound **2a**.

***N*-*t*-Butyl-*N*-(1-phenylpentyl)amine 3a; Typical Procedure:**
An aqueous quench of the reaction mixture from the above procedure followed by separation of the layers and drying of the organic phase gives, after distillation, the dialkylamine **3a**; yield: 19.7 g (90%); b.p. 100–104°C/4 torr (Table 2).

Lithium *N*-*t*-butyl-*N*-(1-phenylpentyl)amide 2a; Typical Procedure from Amine 3a:
A stirred solution of 1.55 molar solution of n-butyllithium in hexane (323 ml, 0.5 mol) at 0°C under an inert atmosphere treated dropwise with the amine **3a** (109.5 g, 0.5 mol) in toluene (400 ml) gives after a further 15 min a quantitative yield of the compound **2a** in solution.

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[1] This work was reported in part at the International Symposium on the Chemistry of Carbanions, Durham, U.K, July, 1984.
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