CARBON DIOXIDE: A REAGENT FOR THE SIMULTANEOUS PROTECTION OF NUCLEOPHILIC CENTERS AND THE ACTIVATION OF ALTERNATIVE LOCATIONS TO ELECTROPHILIC ATTACK. 16.[1] A NOVEL SYNTHETIC METHOD FOR THE SIDE-CHAIN FUNCTIONALIZATION OF N-METHYL-o-TOLUIDINE AND FOR THE PREPARATION OF 2-SUBSTITUTED N-METHYLINDOLES

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Dedicated to the memory of Tetsuji Kametani, excellent scientist and true friend.

Abstract -- N-Methyl-o-toluidine is readily converted into a range of side-chain functionalized derivatives in a one-pot sequence, using carbon dioxide for N-protection. The intermediate lithium carbamate is further lithiated by butyllithium at the side-chain methyl group, and then reacted with an electrophile; the product undergoes acid-catalyzed decarboxylation during work-up. 2-Substituted N-methylindoles are produced when carboxylate esters are used as electrophiles. The yields are good, and no ring-substituted products are detected.

ortho-Substituted anilines are important key starting materials for the synthesis of numerous heterocycles,[2] including important pharmaceuticals such as 1,4-benzodiazepines.[3] A number of alternative methods have been developed for the regiospecific synthesis of ortho-functionalized anilines.[4] Techniques involving heteroatom-facilitated dilithiation of aromatic amines,[5] or the lithiation of N-protected aromatic primary amines,[6] followed by reaction with electrophiles, are recognized as significant routes. However, all possess certain disadvantages, e.g. utilizing an isocyanide,[6a] or difficult-to-remove pivaloyl protection,[6b,c] and/or need drastic reaction conditions for dilithiation. Additionally, three individual operations were needed for protection, functionalization, and deprotection.

In a recent contribution from our own laboratory, a one-pot synthetic sequence, using carbon dioxide as an easily introduced and removed protecting group, has been successfully applied to the conversion of (secondary) N-alkylanilines into o-substituted N-alkylanilines.[7]

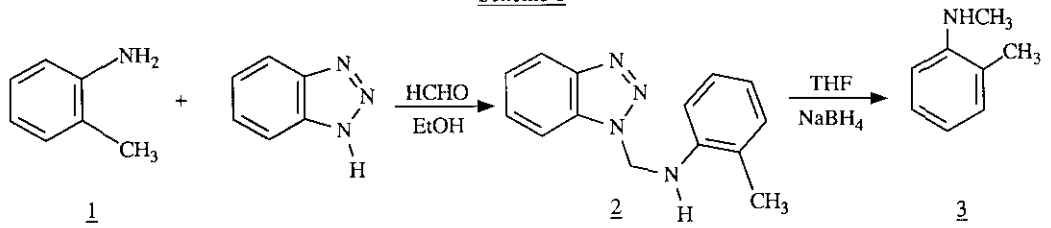
The side-chain elaboration of o-toluidine provides an alternative method to prepare similar compounds. The products from such a sequence contain a methylene group between the functional group and the aromatic ring. This is of particular interest as it provides a new route to the important indole ring system.[8] Indeed, Smith and his co-workers recently reported the preparation of indoles utilizing side-chain functionalization of o-alkylanilines by lithiation and then condensation of carboxylate esters with organodilithium reagents derived from N-trimethylsilyl-o-ethylaniline.[9-10]

We speculated that our novel protecting group, carbon dioxide, which has already been applied to the functionalization of indole,[11] of benzylamine and benzyl alcohol,[12] and of pyridone,[13] could be extended for use in the side-chain substitution of aromatic secondary amines. Indeed, we have reported its utility for the side-chain elaboration of 2-alkylindole.[14] We now show that the lithiation of lithium N-methyl-N-tolylcarbamate, derived from N-methyl-o-toluidine, allows the preparation of side-chain substituted N-methyl-o-toluidines, and provides a new route of 1-methyl-2-substituted indoles. No previous report of the side-chain transformation by metallation of an o-alkylaniline with an N-alkyl moiety, has appeared, and the present method complements the Smith methodology.[9-10]

Results and Discussion

The starting material, N-methyl-o-toluidine, was prepared by the N-methylation of o-toluidine in an application of our benzotriazole methodology[15] as shown in Scheme 1. Reaction of o-toluidine, benzotriazole and formaldehyde in ethanol gave N-(1-benzotriazolylmethyl)-o-toluidine **2**, which was reduced by sodium borohydride to afford N-methyl-o-toluidine **3** in good overall yield.

Scheme 1



Side-chain functionalization was achieved by the same procedure as that previously described.[1,7,11-12] N-Methyl-o-toluidine was thus readily converted into a range of side-chain substituted derivatives in convenient one-pot synthetic sequences using carbon dioxide for N-protection. The following four operations are involved in the conversion of substrate **3** to the product **9** as shown in Scheme 2.

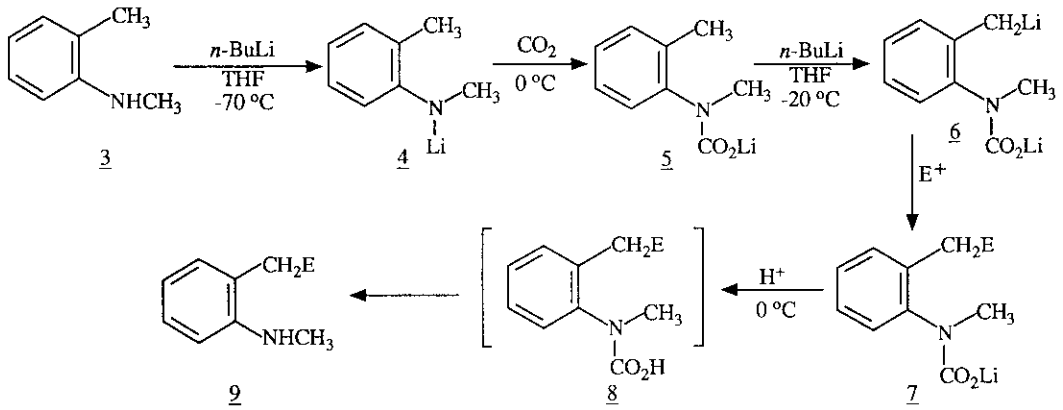
(i) **Protection.** N-Methyl-o-toluidine **3** was converted into its corresponding lithium carbamate **5** by treatment with n-butyllithium in tetrahydrofuran at -70 °C (**3** to **4**), followed by quenching with carbon dioxide (**4** to **5**).

(ii) ***Lithiation.*** *Lithiation of intermediate* **5** *by n-butyllithium or t-butyllithium in tetrahydrofuran at ca. -20 °C* afforded dilithiated species **6**.

(iii) **Carbon-carbon bond formation.** The dilithiated intermediate **6** reacted with an appropriate electrophile at ca. -70 °C. The mixture was then allowed to warm to 25 °C over a few hours.

(iv) **Deprotection and Work-up.** Aqueous 2M hydrochloric acid was slowly added to the mixture at 0 °C to convert **7** to **9** (via **8**), which was then purified and characterized.

Scheme 2



3 4 5 6 7 8 9

The results shown in Table I demonstrate that a wide range of electrophiles may be employed, that the functionalization in all cases proceeded regioselectively to give the expected product of electrophilic attack at the side-chain methyl carbon of the N-methyl-o-toluidine, and that no ring-substituted products were observed. Alkyl halides (either iodides or bromides) react readily to yield the side-chain extended product, o-alkyl-N-methylanilines. Aldehydes and ketones afford the expected secondary and tertiary alcohols. Isocyanates as electrophiles give o-(methylamino)phenylacetamides as products. Deuteration takes place at the side-chain methyl position on using D_2O. The yields ranged from 48 to 95%. All the products obtained, including the novel derivatives, were characterized analytically, and by their ^1H and ^{13}C nmr and ir spectra.

The dilithiated intermediate **6** reacted with carboxylate esters as electrophiles to give the expected 2-substituted 1-methylindoles. Obviously, this transformation takes place via initial carbon-carbon bond formation between the electrophilic carboxylate and the methyl carbon of the organodilithium intermediate **6**. Subsequent intramolecular cyclization during the work-up results in indole ring formation. The examples summarized in Table I thus indicate a new method for the synthesis of 1,2-disubstituted indoles **10**.

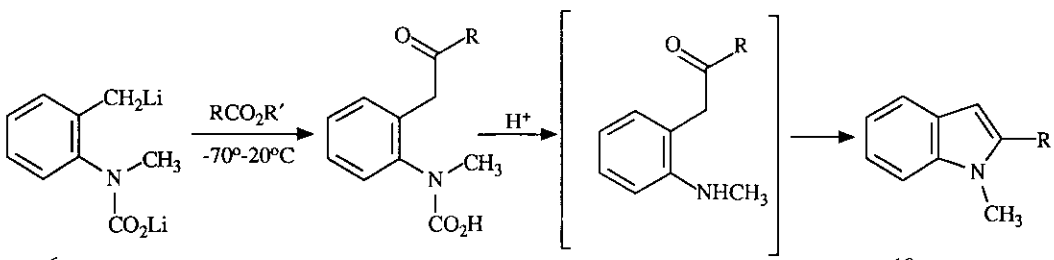
A number of synthetic methods are available for the construction of the indole ring system,[8,17,20-21] including Smith's methodology[9-10] already mentioned, Wender's synthesis of substituted indoles based on the photolysis of 1-alkenylbenzotriazoles,[22] and Gassman's reaction of anilines with t-butyl hypochloride then introduction of a 2-(methylthio)alkan-1-one and subsequent Raney nickel desulfurization.[23] The present novel approach to the indole ring is particularly suited to the preparation of 1-alkyl derivatives. The procedure is one-pot from quite easily available o-alkylanilines, the overall yields are good, and in principle it should be possible to place a wide variety of substituents at the 1-, 2- and 3-positions of the indole nucleus by varying the N-alkyl and o-alkyl group of the

o-alkyl-N-alkylaniline and by selecting the appropriate carboxylate ester. Indeed, 1,3-dimethyl-2-phenylindole (**11**) was prepared from o-ethyl-N-methylaniline via this sequence.

Table I. Preparation of Side-Chain Substituted N-Methyl-o-toluidines **9** and 2-Substituted 1-Methylindoles **10**

run	compd.	electrophile	substituent	butyllithium[a]	yield(%)[b]	mp(°C)	lit. mp
1	**9a**	D_2O	D	n-C_4H_9Li	95[c]	oil	d
2	**9a**	D_2O	D	t-C_4H_9Li	85[c]	oil	d
3	**9b**	CH_3I	CH_3	n-C_4H_9Li	65	oil[e]	95-6/10 mmHg[16]
4	**9c**	n-$C_6H_{13}I$	n-$C_6H_{13}I$	n-C_4H_9Li	48	oil	--
5	**9d**	$PhCH_2Br$	$PhCH_2$	n-C_4H_9Li	56	154-156	--
6	**9d**	$PhCH_2Br$	$PhCH_2$	t-C_4H_9Li	62	154-156	--
7	**9e**	Ph_2CO	$Ph_2C(OH)$	n-C_4H_9Li	89	199-201	--
8	**9e**	Ph_2CO	$Ph_2C(OH)$	t-C_4H_9Li	82	201-203	--
9	**9f**	p-$CH_3C_6H_4CHO$	p-$CH_3C_6H_4CH(OH)$	n-C_4H_9Li	80	oil	--
10	**9g**	$(CH_3)_2CHCHO$	$(CH_3)_2CHCH(OH)$	n-C_4H_9Li	55	oil	--
11	**9h**	t-C_4H_9NCO	t-C_4H_9NHCO	n-C_4H_9Li	63	123-124	--
12	**9h**	t-C_4H_9NCO	t-C_4H_9NHCO	t-C_4H_9Li	71	124-125	--
13	**9i**	PhNCO	PhNHCO	n-C_4H_9Li	67	116-118	--
14	**9i**	PhNCO	PhNHCO	t-C_4H_9Li	74	116-118	--
15	**10a**	$CH_3CO_2C_2H_5$	CH_3[f]	n-C_4H_9Li	65	54-55	54-55[17]
16	**10b**	$PhCO_2C_2H_5$	Ph[f]	n-C_4H_9Li	60	98-100	100-101[18]
17	**10c**	p-$CH_3C_6H_4CO_2C_2H_5$	p-$CH_3C_6H_4$[f]	n-C_4H_9Li	58	94-95	96-98[19]

[a]The butyllithium used in the second lithiation step (from **5** to **6**). [b]Isolated yield. [c]^1H nmr yield. [d]bp of N-methyl-o-toluidine. [e]picrate, mp 134-136°C (lit.[16] 135-136). [f]The substituent at the 2-position of 1-methylindoles.



6 10

Scheme 3 R = CH_3, Ph, p-$CH_3C_6H_4$; R' = C_2H_5

Alternatively, 1,3-dimethyl-2-phenylindole (**11**) was prepared in a one-pot sequence involving three lithiation steps from N-methylaniline. Thus, after the dilithiated intermediate reacted with ethyl iodide in a procedure as

previously described,[7] the mixture was again cooled to -70 °C and an equivalent of n-butyllithium was added. The solution was kept at -20 °C for 1 h and then cooled to -70 °C. Ethyl benzoate (0.01 mol in 5ml of tetrahydrofuran) was added, and the mixture was allowed to return to 25 °C and stirred for 3 h. The work-up and purification were the same as those described above.

In previous papers in this series,[1,7,11-13,24] t-butyllithium was usually used to remove the CH-proton from the lithium carbamate (the second lithiation step). We have now utilized n-butyllithium instead of t-butyllithium as a base in both lithiation processes (from **3** to **4** and from **5** to **6**). The results listed in Table I show no advantage in using t-butyllithium over the more convenient n-butyllithium.

In summary, a general approach to accomplish lithiation and subsequent substitution at the side-chain carbon of N-methyl-o-toluidine has been developed, with carbon dioxide as the reagent used to protect the NH group. In this way, various side-chain substituted N-methyl-o-toluidines were prepared in good yields. The technique also provides a new and versatile method leading to substituted indoles. The particular ease of introduction and of removal of the protecting group offers considerable advantages over those previously applied for these purposes.

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary or an Electrothermal (Shanghai) melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance spectra were recorded on a Varian EM-360L or JEOL JUM-PMX 60 SI spectrometer using tetramethylsilane as the internal standard. ^{13}C nuclear magnetic resonance spectra were obtained on JEOL JNM FX 100 or 90Q instruments. Infrared spectra were taken with a Shimadzu IR-408 spectrophotometer. Elemental analyses were carried out in a Carlo Erda 1106 instrument in Hangzhou University. Tetrahydrofuran was dried by refluxing with benzophenone and sodium and used directly after distillation under dry argon or nitrogen. Carbon dioxide gas was dried by passage through anhydrous calcium sulfate. Processes (i) to (iii) were performed under a dry argon or high purity nitrogen atmosphere.

N-(1-Benzotriazolylmethyl)-2-methylaniline (2). A mixture of benzotriazole (29.8 g, 0.25 mol) and o-methylaniline (26.8 g, 0.25 mol) in ethanol (400 ml) was stirred continuously while formaldehyde (37% aqueous, 0.25 mol) was gradually added at 20 °C. After a few min, a white solid began to separate. The solid was collected, washed with ethanol and dried (85% yield): mp 129-131°C; ^{1}H nmr δ 2.05 (s, 3H), 4.48 (br s, 1H), 5.95 (s, 2H), 6.40-7.90 (m, 8H).

N-Methyl-o-toluidine (3). To the **2** (50 g) in a 500 ml flask was added 350 ml of freshly distilled tetrahydrofuran, and the whole was stirred to give a heterogeneous suspension. Then $NaBH_4$ (8 g) was added over a 15 min period at 20 °C with vigorous stirring. Gas was slowly evolved, and the solid gradually dissolved. The mixture was kept well stirred for 10 h. The solvent was removed under reduced pressure to give an oil which was poured into water and extracted twice with hexane (2 x 200 ml). The extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed to give a pale yellow oil, which was distilled to afford a colorless liquid (20.3 g, 80%): bp 204-206°C (lit.[25] bp 207-208°C); ^{1}H nmr ($CDCl_3$): δ 2.10 (s, CH_3, 3H), 2.82 (s,

NCH_3, 3H), 3.40 (br s, NH, 1H), 6.55-6.85 (m, 2H), 7.00-7.45 (m, 2H).

General Procedure of Lithiation. A solution of N-methyl-o-toluidine (1.20 g, 0.01 mol) in tetrahydrofuran (30 ml) in a Schlenk type reactor under an argon atmosphere was cooled to -70 °C and n-butyllithium (4.0 ml of 2.5 M n-hexane solution) was slowly added dropwise. The resulting solution was kept at -70 °C for a few minutes, and the temperature was then allowed to rise to ca. 0 °C. Carbon dioxide gas was passed through the solution for about 5 min. The solvent was removed under reduced pressure to give the lithium N-methyl-N-tolylcarbamate. The atmosphere was replaced with argon and tetrahyrofuran (30 ml) was added. The solution was again cooled to ca. -70 °C, and n-butyllithium (4.4 ml of 2.5 M n-hexane solution) or t-butyllithium (6.5 ml of 1.7 M n-pentane solution) was added slowly. The cooling bath was changed to ice-salt, and the solution was kept at -20 °C for 45 min. The whole was then cooled to -70 °C, and the electrophile (0.01 mol) in 5 ml of tetrahydrofuran was added. The reaction mixture was allowed to return to 25°C and stirred at that temperature for a few h. The solvent was removed and aqueous hydrochloric acid (2M, 10 ml) was added at 0°C. The aqueous solution was neutralized with solid sodium bicarbonate and extracted with chloroform (2 X 20 ml). The extract was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave the crude product. Purification was carried out by recrystallization for solid products and by column chromatography (silicia gel, chloroform) for oily ones.

2-Ethyl-N-methylaniline (9b). ^{1}H Nmr ($CDCl_3$): δ 1.00 (t, J = 7 Hz, 3H) 2.60 (q, J = 7 Hz, 2H), 2.90 (s, 3H, NCH_3), 3.50 (br s, 1H, NH), 6.50-6.85 (m, 2H), 6.95-7.30 (m, 2H).

2-n-Heptyl-N-methylaniline (9c). ^{1}H Nmr ($CDCl_3$): δ 0.88 (t, J = 7 Hz, 3H, CH3), 1.33 (m, 10H), 2.40 (t, J = 7 Hz, 2H, CH_2), 2.90 (s, 3H, NCH_3), 5.80 (br s, 1H, NH), 6.55-6.80 (m, 2H), 7.00-7.40 (m, 2H); ^{13}C nmr: δ 13.9 (CH_3), 22.5, 26.7, 28.4, 29.0, 29.6, 30.8, 31.7, 109.7, 116.9, 126.4, 126.8, 128.6, 146.4; ir(neat): 3400 (NH), 2900, 1580, 1500, 1120, 750, 700 cm^{-1}. Anal. Calcd for $C_{14}H_{23}N$: C, 81.95; H, 11.22; N, 6.83. Found: C, 82.19; H, 11.02; N, 6.51.

1-Phenyl-2-(2-methylaminophenyl)ethane (9d). ^{1}H Nmr ($CDCl_3$): δ 2.85 (s, 3H, NCH_3), 3.05 (A_2B_2 system, 4H, CH_2CH_2), 7.03-7.70 (m, 9H, ArH); ^{13}C nmr: δ 32.1 (CH_3), 36.7, 37.2, 122.7, 126.1, 127.8, 128.3, 128.6, 128.8, 131.1, 134.5, 135.8, 140.5; ir(KBr): 3420 (NH), 2920, 1580, 1500, 1460, 1130, 755, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{17}N$: C, 85.31; H, 8.06; H, 6.64. Found: C, 85.03; H, 8.37; N, 6.47.

1,1-Diphenyl-2-(2-methylaminophenyl)ethanol (9e). ^{1}H Nmr ($CDCl_3$): δ 3.00 (s, 3H, NCH_3), 3.65 (s, 2H, CH_2), 5.85 (br, 2H, OH and NH), 6.65-7.55 (m, 14H, ArH); ^{13}C nmr: δ 33.8, 40.6, 77.3 (COH), 119.7, 125.1, 125.3, 126.2, 126.5, 128.7, 132.1, 136.7, 144.6; ir(KBr): 3450 (sh. NH), 3340 (OH), 2950, 1585, 1495, 1450, 1120, 1055, 760, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.17; H, 6.93; N, 4.62. Found: C, 82.89; H, 6.72; N, 4.81.

1-(4-Methylphenyl)-2-(2-methylaminophenyl)ethanol (9f). ^{1}H Nmr ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 2.80 (s, 3H, NCH_3), 2.90 (m, 2H, CH_2), 3.20 (br, 2H, OH, and NH), 4.90 (t, J = 7 Hz, 1H, CH), 6.65-7.45 (m, 8H, ArH); ^{13}C nmr: δ 21.0 (CH_3), 30.7 (NCH_3), 41.8 (CH_2), 75.1 (CHOH), 110.6, 117.4, 123.7, 125.5, 127.9, 129.0, 130.8, 137.1,

141.3, 148.0; ir (neat): 3500 (sh. NH), 3350 (OH), 3020, 2920, 1620, 1600, 1510, 1465, 1310, 1050, 815, 750 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.65; H, 7.88; N, 5.81. Found: C, 80.06; H, 8.09; N, 5.49.

4-Methyl-1-(2-methylaminophenyl)-2-butanol (9g). ^1H Nmr ($CDCl_3$); δ 0.95 (d, J=7 Hz, 6H), 1.80 (m, 1H, CH), 2.60 (d, J = 7 Hz, 2H, CH_2), 2.80 (s, 3H, NCH_3), 3.35-3.70 (m, 3H, CHOH and NH), 6.50-7.35 (m, 4H); ^{13}C nmr: δ 17.0, 18.5 (CH_3), 30.4, 33.5, 36.1, 77.3 (CHOH), 110.7, 117.5, 124.7, 127.3, 129.8, 148.0; ir(neat): 3500 (sh. NH), 3350 (OH), 2950, 1600, 1590, 1510, 1470, 1310, 1170, 1000, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.61; H, 9.84; N, 7.25, Found: C, 74.75; H, 9.96; N, 7.02.

2-Methylaminophenyl acetic acid t-butyl amide (9h). ^1H Nmr ($CDCl_3$): δ 1.20 (s, 9H, But), 2.90 (s, 3H, NCH_3), 3.40 (s, 2H, CH_2), 4.70 (br s, 1H, NH), 5.50 (br, 1H, CONH), 6.55-7.45 (m, 4H, ArH); ^{13}C nmr: δ 28.5, 30.5, 42.4, 51.2, 110.4, 116.9, 120.4, 128.7, 130.4, 148.1, 170.9 (CONH); ir(KBr): 3350, 3300, 2960, 1635, 1590, 1550, 1520, 1450, 1220, 1175, 760 cm^{-1}. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.91; H, 9.09; N, 12.73. Found: C, 70.74; H, 9.24; N, 12.44.

2-Methylaminophenyl acetic acid anilide (9i). ^1H Nmr ($CDCl_3$); δ 2.25 (br s, 1H, NH), 3.00 (s, 3H, NCH_3), 3.50 (s, 2H, CH_2), 6.80-7.75 (m, 9H, ArH), 9.15 (br s, 1H, CONH); ^{13}C nmr: δ 26.1, 35.7, 108.0, 120.6, 122.3, 124.4, 127.8, 129.0, 129.8, 130.4, 136.6, 137.2, 153.4 (CONH); ir(KBr): 3420 (NH), 3270 (CONH), 1660, 1600, 1550, 1500, 1440, 1180, 750, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 75.00; H, 6.67; N, 11.67. Found: C, 74.68; H, 6.89; N, 11.41.

1,2-Dimethylindole (10a). ^1H Nmr ($CDCl_3$): δ 2.55 (s, 3H, CH_3), 3.75 (s, 3H, N-CH_3), 6.65 [s, 1H, C(3)H], 7.15-7.80 (m, 4H).

1-Methyl-2-phenylindole (10b). ^1H Nmr ($CDCl_3$): δ 3.70 (s, 3H, NCH_3), 6.55 [s, 1H, C(3)H], 7.20-7.75 (m, 9H).

1-Methyl-2-(4-methylphenyl)indole (10c). ^1H Nmr ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 3.72 (s, 3H, N-CH_3), 6.60 [s, 1H, C(3)H'], 7.16-7.80 (m, 8H, ArH); ^{13}C nmr: δ 21.2, 31.0, 101.3, 109.5, 119.7, 120.3, 121.4, 128.0, 129.0, 129.1, 129.9, 137.6, 138.2, 141.6; Anal. Calcd for $C_{16}H_{15}N$: C, 86.88; H, 6.79; N, 6.33. Found: C, 86.82; H, 6.85; N, 6.25.

1,3-Dimethyl-2-phenylindole (11). This compound was prepared in 54% via the same lithiation procedure with o-ethyl-N-methylaniline; mp 66-67.5 °C, (pet. ether) (lit.[26] 69 °C); ^1H nmr($CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.60 (s, 3H, N-CH_3), 7.15-7.80 (m, 9H, ArH); ir (KBr): 3010, 2950, 1600, 1505 cm^{-1}.

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