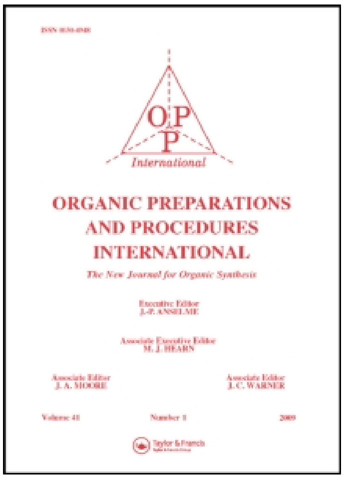

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N-ALKYLATION OF HINDERED SECONDARY AROMATIC AMINES WITH 2-IODOBUTANE

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N-ALKYLATION OF HINDERED SECONDARY AROMATIC AMINES WITH 2-IODOBUTANE

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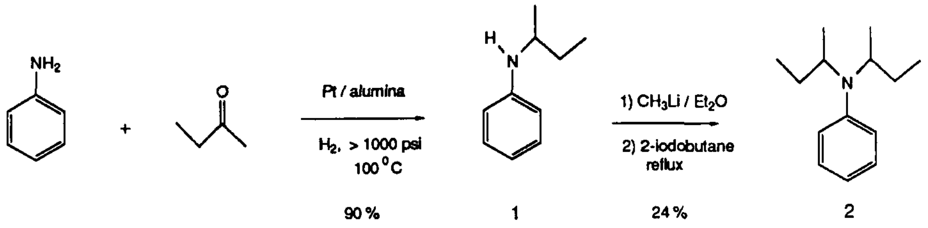
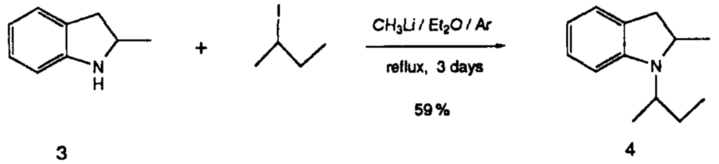
Recently, we needed to prepare aromatic amines disubstituted at the nitrogen atom with secondary alkyl groups. A literature survey disclosed that almost all the known examples of such amines were the least sterically hindered diisopropylamino derivatives. Reaction of sodium amide and bromobenzene with refluxing diisopropylamine gave N,N-diisopropylaniline in 66%[1] or 38% yield via a benzyne mechanism.[2] Catalytic reductive aminoalkylations of a mixture of primary aromatic amines with a ketone and its ketal under hydrogen pressures of 1000 psi at elevated temperatures were reported to give moderate to good yields of N,N-bis(sec-alkyl)amines,[3] e. g., N,N-diisopropylaniline in 56% yield. N,N-bis(sec-Butyl)aniline (2) was also claimed[3] to be prepared but the yield was not given. Unfortunately, our attempts to prepare N,N-bis(sec-butyl)aniline under similar conditions failed. A mixture of one mole of aniline, two moles of 2,2-dimethoxybutane,[4] two moles of butanone and 0.5 g of 1% platinum on alumina was stirred under a pressure of 1400 psi of hydrogen at 92-133 ° for 3 days to give a clean 86% yield of N-sec-butylaniline, but no N,N-bis(sec-butyl)aniline.

However, we were able to adapt a method described in 1960 for the preparation of N,N-diisopropyl-o-toluidine by alkylation of the lithium anion of N-isopropyl-o-toluidine with isopropyl iodide.[5] N-sec-Butylaniline (1) was conveniently prepared by reductive alkylation of aniline with butanone. Alkylation of the lithium salt of 1 with sec-butyl iodide over 4 days in refluxing diethyl ether gave N,N-bis(sec-butyl)aniline (2) in 24% yield after conversion of the residual N-sec-butylaniline to its benzamide (ca. 70% recovery) and fractional distillation under reduced pressure.

The relatively low yield of the tertiary amine reflects the higher steric hindrance of the sec-butyl groups compared with the diisopropyl groups of the literature compounds.





2-Methylindoline (3) was similarly alkylated with 2-iodobutane to give 1-sec-butyl-2-methylindoline (4) in 59% yield. The only previous example of the N-alkylation of 2-methylindoline was methylation to 2,3-dihydro-1,1,2-trimethylindolium iodide.[6]

EXPERIMENTAL SECTION

^1H NMR and ^{13}C NMR spectra were taken on a VXR 300 MHz FT spectrometer in $CDCl_3$ with TMS as internal standard. The model 4768 hydrogenation bomb was from the Parr Instrument Company,IL.

N-(1-Methylpropyl)aniline (1).- Aniline (55.88 g, 0.60 mol), butanone (129.80 g, 1.80 mol) and 1% platinum on alumina (3.0 g) were placed in a hydrogenation bomb. The bomb was charged with hydrogen to a pressure of 1100 psi and the mixture was stirred at 100 ° for 2 days. The catalyst was filtered off, washed with butanone and the excess ketone removed under reduced pressure at 80° to give N-(1-methylpropyl)aniline (1) (93.4 g, 90%) as an orange liquid (containing ca. 2% of aniline).

N,N-Bis(1-methylpropyl)aniline (2).- To a stirred solution of 1.4 M methyllithium in ether (433 mL, 0.606 mol) in dry ether (500 mL) under argon was added dropwise N-sec-butylaniline (1) (83 g, 0.55 mol) over 5 hrs. The mixture was refluxed for 5 hrs., and 2-iodobutane (200 g, 1.09 mol) was added dropwise over 20 min. After reluxing under argon for 4 days, the reaction was quenched with methanol (150 mL) and water (300 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (400 mL). The combined organic layers were washed with water (500 mL) and dried (K_2CO_3). The solution was filtered and solvent removed under reduced pressure at 85° to yield an orange liquid (107.1 g). To a solution of the crude product in benzene (300 mL) was added anhydrous potassium carbonate (69 g, 0.5 mol) and benzoyl chloride (80 mL, 0.7 mol) and the obtained mixture was stirred under nitrogen for 20 hrs. Water (300 mL) was added and stirring continued for 1 hr further. The product was washed with 20% sodium hydroxide (50 mL) followed by 10% sodium hydroxide (200 mL) and dried (Na_2CO_3). After removal of the solvent the resulting deep brown liquid (163.4 g) was fractionally distilled to give 13.4 g, bp. 40-78 °/0.03 mm, of N,N-bis(1-methylpropyl)aniline (2) (88% pure by NMR), 16.6 g, bp. 78-80 °/0.03 mm, of 2 (95% pure by NMR), 15.6 g of N-sec-butyl-N-benzoylaniline (>90% pure by NMR), bp. 81-142°/0.03 mm, and finally 94.8 g of N-sec-butyl-N-benzoylaniline, bp. 143-144°/0.3 mm. Redistillation of the second fraction gave an analytical sample of the tertiary amine as a colorless liquid, bp. 106-107 °/1.7 mm; ^{1}H NMR (mixture of diastereomers): δ 7.15 (m, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.65-6.73 (m, 1H), 3.42 (m, 2H), 1.50-1.75 (m, 4H), 1.24 (d, J = 6.8 Hz, 6H), 0.91 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (mixture of diastereomers): δ 148.8, 148.7, 128.4, 117.6, 117.4, 116.9, 116.8, 54.5, 54.4, 29.1, 28.6, 19.1, 18.5, 12.0, 11.9.

Anal. Calcd. for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82
Found: C, 81.78; H, 11.24; N, 6.82

1-(1-Methylpropyl)-2-methylindoline (4).- To a stirred solution of 1.4 M methyllithium in ether (180 mL, 252 mmol) further diluted with ether (120 mL), was added dropwise 2-methylindoline (3) (31.25 mL, 240 mmol) under argon. After reflux of the mixture for 3 hrs, 2-iodobutane (47.22 ml, 410 mmol) was added and the mixture was refluxed for 3 days further under argon. The excess methyllithium was destroyed by methanol (20 mL) and water (30 mL) and the organic layer was separated. The aqueous layer was extracted with ether (50 mL) and the combined organic layers were dried (K_2CO_3) and filtered. Acetic anhydride (40 mL) was added and the mixture was concentrated first on a water bath at 80-90° and then the excess acetic anhydride was removed under reduced pressure at 80-90 °. The concentrate was dissolved in ether (100 mL) and washed with 20% potassium carbonate (4 X 20 mL) and 40% potassium carbonate (20 mL). After drying over anhydrous potassium carbonate and removal of the solvent at 70-90 ° a brownish yellow liquid

(41.4 g) was obtained which contained about 80% 1-(1-methylpropyl)-2-methylindoline (4) (estimated by NMR). Fractional distillation gave pure 4 (26.6 g, 59%) as a colorless liquid, bp. 63-64 °/0.03 mm. ^{1}H NMR (mixture of diastereomers): δ 6.95-7.20 (m, 2H, Ar), 6.51-6.59 (m, 1H, Ar), 6.38-6.46 (m, 1H, Ar), 3.70-3.90 (m, 1H, ring CH), 3.33 (sextet, J = 7.1 Hz, 0.5H, side chain CH), 3.15-3.25 (m, superimposed, 0.5H, side chain CH), 3.11-3.20 (m, 1H, ring CH_2), 2.50-2.60 (dd, 1H, ring CH_2), 1.70-1.85 (m, 1H, side chain CH_2), 1.48-1.62 (m, 1H, side chain CH_2), 1.25 (d, J = 6.1 Hz, 3H, 2-CH_3), 1.19 (t, J = 4.77 Hz, 3H, CH_3(CH), side chain), 0.95 (m 3H, CH_3(CH_2), side chain); ^{13}C NMR (mixture of diastereomers): δ 151.1, 150.6, 128.9, 128.7, 127.1, 126.9, 124.1, 116.1, 116.0, 107.4, 106.9, 56.9, 56.3, 54.0, 53.5, 37.7, 37.5, 28.0, 27.5, 22.6, 22.0, 16.9, 16.4, 11.90, 11.88.

Anal Calcd. for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40

Found: C, 82.39; H, 10.08; N, 7.37

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