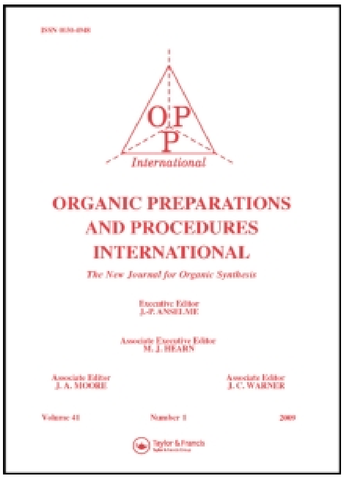

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A PRACTICAL SYNTHETIC METHOD FOR N-METHYL-*o*-TOLUIDINE

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A PRACTICAL SYNTHETIC METHOD FOR N-METHYL-o-TOLUIDINE

Submitted by
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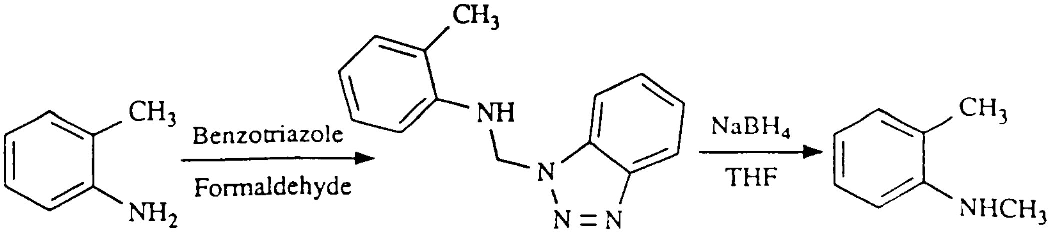
Literature methods for the preparation of N-alkylanilines include: imination-reduction,[1] carbonylation-alkylation-hydrolysis,[2] direct alkylation,[3] succinimide-aminal reduction,[4] and 2-alkylation of an N-alkylaniline.[5] The procedure herein described is more convenient for synthesis than any of the foregoing because of the ease of purification of the product. The traditional methods require additional manipulations to remove starting material and side-products such as polyalkylated amines.[3] We now report a modification of our general synthetic method[6] for the N-alkylation of anilines suitable for use in large scale preparations. It has not previously been applied to o-toluidine. Here its practicability for the synthesis of N-methyl-o-toluidine on the 0.47 mol scale is demonstrated.



The procedure requires no unusual reagents, solvents or apparatus. Residual o-toluidine is easily removed at the stage of the solid aminal. No dialkylation product was detected by TLC or by proton NMR. The desired product is easily purified by distillation. Our method has the advantage that the procedure gives the desired pure product in 87% yield. This procedure is general for the mono N-alkylation of anilines.[6]

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian Model EM 360 L with Me_4Si as an internal standard.

Synthesis of N-Methyl-o-toluidine.- A mixture of benzotriazole (55.8 g, 0.47 mol) and o-toluidine (50.0 ml, 0.47 mol) in a 1L flask was heated on a steam bath to give a homogeneous solution and ethanol (300 ml) was then added. The whole was stirred continuously while formaldehyde (37% solution in water, 35.1 ml, 0.47 mol) was gradually added at 20° over a period of 5 min.; this reaction was exothermic. After a few minutes, a colourless solid began to separate. After 30 minutes, the whole was cooled at 0° for 10 min. The solid was collected, washed with pre-cooled (0°) ethanol (200 ml), and then hexane (500 ml) to remove 2-methylaniline and water, and dried in a dessicator under reduced pressure. To the solid in a 1 L flask was added 500 ml of freshly distilled tetrahydrofuran (dried over calcuim hydride), and the whole stirred to give a heterogeneous suspension. Then solid sodium borohydride (10.0 g) was added during 15 minutes at 20° with vigorous stirring. Gas was slowly evolved, and the solid gradually dissolved. The mixture was kept well stirred at 20° for 10 hours. After rotary evaporation, the residue was poured into water (500 ml) and ice (ca 100 g). The whole was extracted twice with hexane (300 ml x 2) and the extract was washed with water (200 ml), and dried over anhydrous magnesium sulfate (20 g). The crude product was distilled under dry nitrogen to give 44.9 g (87%) of a colourless liquid bp. 203.5-205.0°, lit.[7] bp. 207-208°. Proton NMR showed less than 2% of o-toluidine on the basis of the area ratio of the 2-methyl and N-methyl proton peaks. TLC (silica-gel, benzene:hexane = 1:9) also indicated a pure product.

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4-(2-ARYLALKENYL)-3-CYANO-2H-1-BENZOPYRAN-2-ONES

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As a continuation of our investigation of the condensation of CH-acids containing a methyl group in γ-position with respect to the electron-acceptor group,[1,2] we studied the condensation of 3-cyano-4-methylcoumarin (1) with aromatic aldehydes. Our initial experiments have shown that