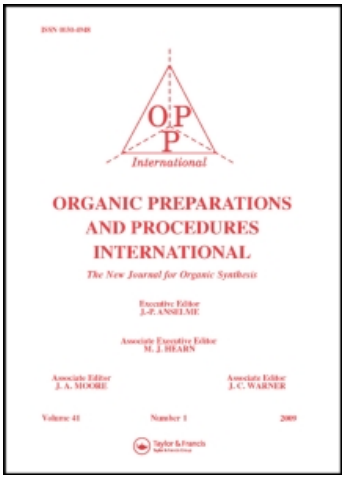

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SONICATION AND ALUMINUM AMALGAM IN THE LEIMGRUBER-BATCHO REACTION. AN IMPROVED PREPARATION OF 6-AMINOINDOLE

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(01/25/95)

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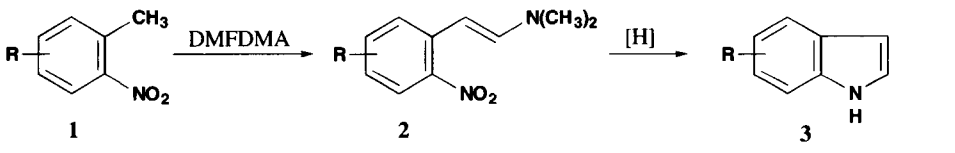
Since its introduction some 20 years ago, the Leimgruber–Batcho indole synthesis has enjoyed great success in the preparation of ring A substituted indoles.[1,2] In general, the reaction involves condensation of the appropriate *o*-nitrotoluene **1** with dimethylformamide dimethyl acetal (DMFDMA) to afford the anticipated β-dimethylamino–2–nitrostyrene **2**. Conversion of the intermediate nitroenamine into the indole **3** requires selective reduction of the nitro group. In the original reaction catalytic hydrogenation was used for this purpose. Good yields of the indole products are usually obtained, with 6–substituted indoles, however, being the exception (6-NH_2, 43%; 6–Cl, 52%; 6–Br, 37%).[3] Alternatively, sodium dithionite,[4] nickel boride,[5] zinc or iron in acetic acid[6] and stannous chloride[7] have been used as reducing agents.



1 **2** **3**

a) R = 6-NH_2 b) R = 6-NHAc
c) R = 6-Br

In the last decade, ultrasound has been used to accelerate a number of synthetically important reactions.[8] The observed effects have been attributed to cavitation: the formation, growth and collapse of bubbles in the reaction mixture. During ultrasound–promoted aluminum amalgam reduction a highly reactive microdispersion is generated by cavitation with simultaneous sonochemical activation.[9] We felt that under sonochemical conditions we could achieve the required reduction of aromatic nitro groups, without affecting the β-aminostyrene, thus providing an inexpensive and efficient route to 6-aminoindole from 2,4-dinitrotoluene. Furthermore, 6-aminoindole could serve as the precursor to other 6-substituted indole derivatives, *via* the Sandmeyer reaction.[10]

To this end we prepared the enamine **2** (R = 4-NO_2) in 99% yield by the condensation of 2,4-dinitrotoluene **1** (R = 4-NO_2) with DMFDMA. We found that by using DMFDMA without solvent we could obtain higher yields than when DMF was used as the solvent. Furthermore, our procedure does not require the preparation of an additional intermediate, the pyrrolidine enamine as required by the original Leimgruber–Batcho procedure. The two aromatic nitro groups were then selectively and rapidly reduced by aluminum amalgam under ultrasound conditions, to afford 6-aminoindole **3a**. In the absence of the ultrasound the reaction with Al(Hg) (or Zn(Hg)) was much

slower and afforded a highly complex mixture. Our procedure may be carried out on the multigram scale but the best results were obtained on a 1-2 gram scale as the larger scale made purification more difficult. The rather reactive 6-aminoindole **3a** can be readily converted to the more stable 6-acetamidoindole **3b**, or subjected to immediate Sandmeyer reaction, for example utilizing CuBr to produce the 6-bromoindole **3c**.

EXPERIMENTAL SECTION

Sonication was carried out by submerging the reaction vessel in a Bransonic 1200 sonicator (Branson Ultrasonic Corp., Danbury, CT) filled with water. ^{13}C NMR and ^{1}H NMR spectra were obtained on a Varian Gemini 200 spectrometer and IR spectra were run on a Nicolet 5DXB FTIR spectrometer. Mass spectra were obtained under electron impact conditions at 70 eV on a VG11-250S instrument.

β-(N,N-Dimethylamino)-2,4-dinitrostyrene (2).- A solution of 2,4-dinitrotoluene (15.0 g, 0.082 mol) in dimethylformamide dimethyl acetal (100 mL) was refluxed for 2 hrs.[11] After cooling to 25°, the dinitrostyrene (19.5 g, 99%) was collected. The dark purple needles, mp. 166-167°, lit.[2] mp. 173-174°, can be stored in a dark bottle at 0° for prolonged periods. IR (KBr): 1631, 1581, 1293, 1262, 1125, 818 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.59 (d, J = 1.7 Hz, 1H, *H-3*), 8.02 (d, J = 12.8 Hz, 1H, *H-β*), 8.01 (dd, J = 9.4, 1.7 Hz, 1H, *H-5*), 7.84 (d, J = 9.4 Hz, 1H, *H-6*), 5.90 (d, J = 12.8 Hz, 1H, *H-α*), 3.07 (s, 6H, $N(CH_3)_2$) ppm.

6–Aminoindole (3a).- To a solution of the above nitrostyrene (2.00 g, 8.43 mmol) in THF (80 mL) was added freshly prepared aluminum amalgam[12] (2.23 g, 0.085 g-atom). The resulting dark red reaction mixture was placed in the sonicator and distilled water (2 mL) was added, resulting in the vigorous evolution of gas during the first 15 min. The reaction mixture was further sonicated for 5 hrs,[13] after which the inorganic materials were removed by filtration through a pad of Celite on a sintered glass funnel and washed with acetonitrile. Concentration of the filtrate afforded the crude 6-aminoindole as a brown solid. Chromatography by elution with 9:1 CH_2Cl_2:ethanol (R_f = 0.45), followed by recrystallization from benzene/hexanes, afforded the pure 6-aminoindole (0.73 g, 64%) as a light brown solid, mp. 67–69°, lit.[14] mp. 66-67°. IR (KBr): 3393, 3356, 3300, 1625, 1337, 1256, 1087, 843, 793, 762, 725 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.05 (br s, 1H, indole-*NH*), 7.48 (dd, J = 8.3, 0.7 Hz, 1H, *H-4*), 6.95 (collapsed dd, J = 3.3, 2.5 Hz, 1H, *H-7*), 6.61 (dd, J = 8.3, 1.9 Hz, 1H, *H-5*), 6.49 (m, 1H, *H-2*), 6.34 (m, 1H, *H-3*), 3.51 (s, 2H, NH_2, *exch.*) ppm. ^{13}C NMR ($CDCl_3$): δ 141.9 (*C-6*), 137.3 (*C-7a*), 122.7 (*C-2*), 121.4 (*C-3a*), 121.3 (*C-4*), 111.0 (*C-5*), 102.2 (*C-3*), 97.3 (*C-7*) ppm. EIMS: m/z(%), 132(100), 131(40), 121(16), 108(19), 105(31), 104(40), 77(16), 66(14), 51(10).

6–Acetamidoindole (3b).- To a solution of crude 6-aminoindole (0.31 g, 2.35 mmol) in dry benzene (20 mL) was added freshly distilled acetic anhydride (0.50 mL, 5.28 mmol). The reaction mixture was stirred at 25° under N_2. After approximately 30 min the acetamide began to slowly precipitate as a slightly pink solid. After being stirred for 4 hrs at 25°, the reaction mixture was maintained at 0° for 20 hrs. The acetamide was collected and washed with cold benzene, and recrystallized from CH_2Cl_2:hexanes to afford the pure 6-acetamidoindole (0.24 g, 59%) as a pale pink solid, mp. 171-

173°, lit.[14] mp. 170-171°. IR (KBr): 3295, 3203, 1634, 1615, 1513, 1419, 1283, 1013, 896, 865, 809, 766, 717 cm^{-1}. ^1H NMR (DMSO-d_6): δ 10.98 (br s, 1H, indole-*NH*), 9.83 (br s, 1H, *NH*$COCH_3$), 8.00 (m, 1H, *H-7*), 7.39 (d, J = 8.0 Hz, 1H, *H-4*), 7.25 (m, 1H, *H-2*), 7.03 (dd, J = 8.0, 2.3 Hz, 1H, *H-5*), 6.35 (m, 1H, *H-3*), 2.07 (s, 3H, NHCO*CH_3*) ppm. ^{13}C NMR (DMSO-d_6): δ 167.8 (*C=O*), 136.0 (*C-7a*), 133.6 (*C-6*), 124.8 (*C-2*), 122.7 (*C-3a*), 119.7 (*C-4*), 112.2 (*C-5*), 102.1 (*C-7*), 101.2 (*C-3*), 24.1 (*CH_3*) ppm.

6-Bromoindole (3c).- In a modification of a reported procedure[10] to a solution of chromatographically pure 6-aminoindole (0.50 g, 3.79 mmol) in 1M HCl (30 mL), stirred rapidly at -10°, was slowly added (30 min) a cold solution of sodium nitrite (0.29 g, 4.20 mmol) in water (5 mL), so as to maintain the reaction temperature at approximately 0°. After 5 min, the diazonium salt was slowly added to a solution of copper(I) bromide[15] (0.55 g, 3.84 mmol) in water (5 mL), the temperature being maintained below 0°, and the reaction mixture was stirred at -10° for 3 hrs. After 3 hrs, the cold solution was extracted with CH_2Cl_2 (5 x 20 mL) and the organic extracts were dried (Na_2SO_4) and concentrated to yield a dark orange paste. The crude product was chromatographed by elution with 3:1 hexanes:EtOAc (R_f = 0.42) affording a light orange solid (0.63 g, 85%). Recrystallization from CH_2Cl_2/hexanes yielded a pinkish solid, mp. 91-94°, lit.[3] mp. 92-95°. IR (KBr): 3400, 1606, 1337, 1231, 1093, 893, 862, 806, 762, 731, 612 cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.12 (br s, 1H, indole *NH*), 7.55 (m, 1H, *H-2*), 7.52 (d, J = 9.1 Hz, 1H, *H-4*), 7.24 (dd, J = 8.5, 1.7 Hz, 1H, *H-5*), 7.18 (collapsed dd, J = 3.2, 2.5 Hz, 1H, *H-7*) 6.55 (m, 1H, *H-3*) ppm. ^{13}C NMR (DMSO-d_6): δ 136.8 (*C-7a*), 126.7 (*C-3a*), 126.4 (*C-2*), 121.8, 121.7 (*C-4*, *C-5*), 114.0 (*C-7*), 113.7 (*C-6*), 101.4 (*C-3*) ppm.

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11. In some cases crystallization began to occur during the reflux. In this case, more DMFDMA may be added to the reaction mixture to ensure complete reaction.

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13. Reaction times varied from 5-12 hrs depending on how well the aluminum was amalgamated. The reaction may be followed by TLC (elution with 9:1 CH_2Cl_2:ethanol) by the appearance of the product (R_f = 0.43-0.45) and disappearance of the starting material (R_f = 0.85, blue spot).

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A NOVEL SYNTHESIS OF TRIARYLBISMUTH DISULFONATES

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Pentavalent triarylbismuth compounds (Ar_3BiX_2, X-Cl, O_2CR, O_3SR, etc.) are a class of important organic bismuth reagents. They are especially useful in organic synthesis as mild and selective arylating agents.[1,2] Although there are several ways to prepare triarylbismuth diacetates,[3,4] to our knowledge triarylbismuth disulfonates have been prepared only by one method, *i. e.* the reaction of triarylbismuth carbonates with sulfonic acids.[2,5]

Usually. triarylbismuth carbonates have been synthesized by use of triarylbismuth dihalides as intermediates that are obtained from triarylbismuthine. Considering that triarylbismuth diacetates can be prepared directly from triarylbismuthines,[4b] we used triarylbismuth diacetates to react with sulfonic acids in order to develop a facile method for the synthesis of some new triarylbismuth disulfonates[3]. Since sulfonic acids are stronger than acetic acid, we believed that acid group transposition could occur easily. In fact the reaction of triarylbismuth diacetates with various sulfonic acids