Convenient Synthesis of 6-Methoxyindole and 6-Methoxytryptophyl Bromide

Paul L. FELDMAN, Henry RAPOPORT*

Department of Chemistry, University of California, Berkeley, CA 94720, U.S.A.

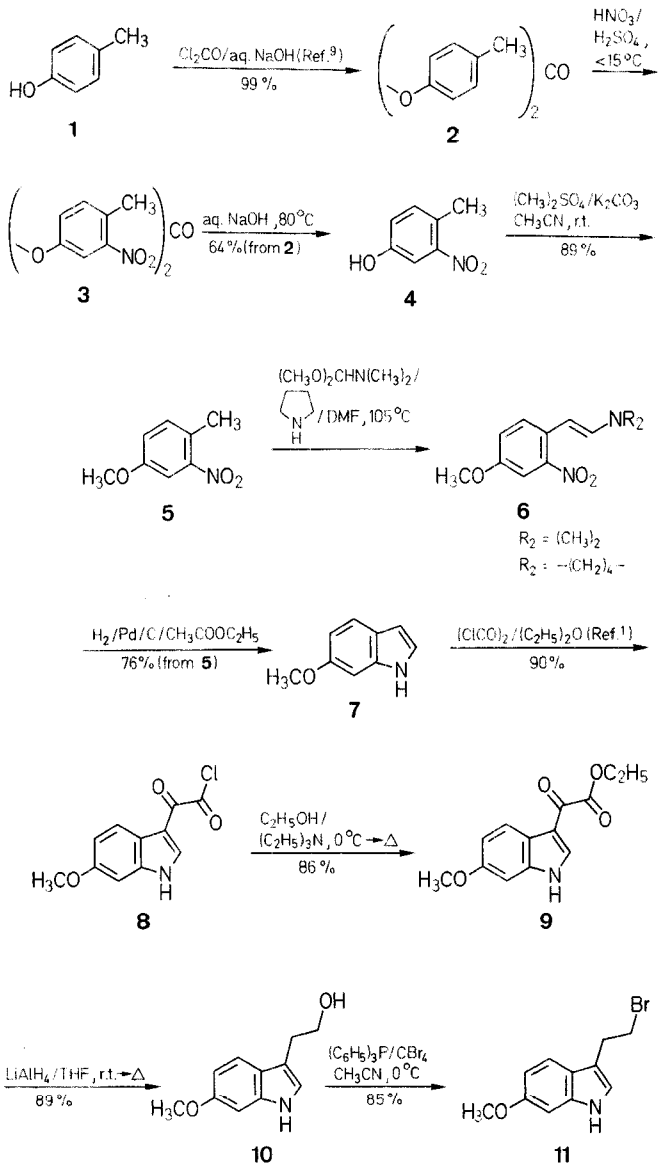
A preparatively convenient synthesis of 6-methoxyindole (**7**) and 6-methoxytryptophylbromide (**11**) is presented starting with *p*-cresol (**1**). Regioselctive nitration of *p*-cresol carbonate (**2**) followed by hydrolysis of the carbonate and methylation gives 4-methoxy-2-nitrotoluene (**5**) which is converted to **7** by the Batcho-Leimgruber indole synthesis. Subsequent oxalylation of **7** followed by esterification, reduction and bromination yields 6-methoxytryptophyl bromide (**11**). The overall yield of **7** and **11** from *p*-cresol is 43% and 25%, respectively.

Two valuable precursors to some important indole and indoline alkaloids are 6-methoxyindole (**7**) and 6-methoxytryptophyl bromide (**11**). A review of the reported synthese of **7** reveals that it has been prepared *via* four different routes. Two of these sequences begin with 4-methoxy-2-nitroaniline and use Meerwein alkylation as the key carbon-carbon bond forming reaction[1,2]. The other two routes begin with 4-methoxy-2-nitrotoluene (**5**) and obtain **7** using the Reissert indole synthesis and more recently the Batcho-Leimgruber method[3,4,5].

In order to obtain a large amount of **7** and subsequently **11**, we repeated those sequences that used the readily available 4-methoxy-2-nitroaniline as starting material. Since the reported experimental procedures for the Meerwein alkylation proved to be very cumbersome and the yields were low (0–30%), we examined the alternative of synthesizing **7** via the Batcho-Leimgruber method.

Since synthesis of **7** *via* the Batcho-Leimgruber method requires very costly 4-methoxy-2-nitrotoluene (**5**), we reviewed methods for preparing this key intermediate. One synthesis of **5** involves nitration of the sulfate salt of *p*-toluidine followed by diazotization and heating with aqueous acid to afford 4-methyl-3-nitrophenol (**4**) which is easily converted to **5** by methylation with dimethyl sulphate[6,7,8].

Another route to **5** outlined below proved to be very efficient and, with modifications of reported experimental procedures, could be processed on a large scale. *p*-Cresol (**1**) was dissolved in aqueous sodium hydroxide and treated with phosgene to form **2**[9]. The product precipitates from the



reaction mixture to give nearly a quantitative yield of **2**. Nitration was achieved by slowly adding fuming nitric acid to a 10 °C solution of **2** in 96% sulfuric acid. The crude nitro carbonate was then hydrolyzed with aqueous sodium hydroxide from which, upon acidification with concentrated hydrochloric acid, nitro cresol **4**[3] precipitated. The phenol was methylated using dimethyl sulphate and an excess of potassium carbonate in acetonitrile. Kugelrohr distillation gave **5**[6,7,8].

Two different aminomethylating reagents were used in converting **5** into the corresponding β-dialkylamino-2-nitrostyrene **6**. Since the efficiency of the aminomethylation of nitro toluenes has been reported to decrease with the presence of electron donating substituents on the phenyl ring due to the decreased acidity of the benzylic protons, the reactive aminomethylating reagents tripiperidinomethane and pyrrolidine/dimethylformamide dimethyl acetal were tried[4,10]. Both of these reagents gave similar yields of **7** with convenient reaction times in forming the intermediate β-dialkylamino-2-nitrostyrene **6**. Treatment of **5** with pyrrolidine and dimethylformamide dimethyl acetal in dimethylformamide at 105 °C for 19 hours gave a deep red oil. Reduction of this crude β-dialkylamino-2-nitrostyrene by hydrogenation over 10% palladium on carbon in ethyl acetate for 3 hours yielded 76% of indole **7** after silica gel filtration. The overall yield of 6-methoxyindole **(7)** from *p*-cresol is 43%.

Subsequent transformation of **7** to bromide **11** follows literature precedent with some modification. Treatment of **7** with oxalyl chloride gave the red crystalline α-ketoacid chloride **8**[1]. Reduction of **8** to **10** has been reported using a very large excess of lithium aluminium hydride in tetrahydrofuran[11]. It proved to be more efficient, however, to prepare **10** by treating **8** with ethanol and triethylamine to yield the ethyl ester **9** (86%) and then reduce **9** to **10** with lithium aluminium hydride in refluxing tetrahydrofuran (89%)[12,13]. Finally, treating alcohol **10** with triphenylphosphine/carbon tetrabromide cleanly afforded 6-methoxytryptophyl bromide **(11)** in 85% yield. This mild bromination method is superior to using phosphorous tribromide, which is lower yielding and leads to decomposition of the product if it is not promptly purified[11].

In summary, an efficient and convenient synthesis of indoles **7** and **11** has been accomplished. The synthesis is achieved by modifying various literature procedures and allows preparation of large quantities of **7** and **11** starting from readily available **p**-cresol **(1)**.

Unless otherwise noted materials were obtained from commerical suppliers and were used without further purification. Acetonitrile, triethylamine, and ethanol were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium and benzophenone. Melting points are uncorrected. IR spectra were determined with a Perkin-Elmer 1320 infared recording spectrometer. ^{1}H-NMR spectra were determined on the UCB-250 spectrometer using TMS as internal reference. Column chromatography was performed with 70–30 (gravity) or 230–400 (flash) mesh silica gel.

***p*-Cresol carbonate (2)** is prepared as reported[9] using one mole of *p*-cresol **(1)**; yield: 120 g (99%); m.p. 110–112 °C (Lit.[9], m.p. 113 °C).

IR ($CHCl_3$) ν = 2940, 1775, 1510, 1230 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.35 (s, 3H); 7.19 ppm (m, 4H).

4-Methyl-3-nitrophenol (4):
To concentrated sulphuric acid (96%, 100 ml) is added **2** (20 g, 82.5 mmol). The solution is cooled to 10 °C and fuming nitric acid (7.6 ml, 0.175 mol) is added at a rate such that the temperature does not exceed 15 °C. The deep red viscous reaction mixture is stirred for 2 additional h at 15–20 °C and then the entire mixture is poured onto crushed ice while stirring. The yellow solid is removed by filtration, washed with cold water and immediately taken into the next reaction by heating to 80 °C in aqueous 1 molar sodium hydroxide (220 ml) for 3 h. After the aqueous solution is cooled to 15 °C and acidified to pH 2 with concentrated hydrochloric acid, the crude phenol that precipitates is vacuum filtered, washed with cold water, then pressed to remove excess water. Further drying under high vacuum affords **4** as a light brownish yellow solid; yield: 15.1 g (64%); m.p. 75–76 °C (Lit.[9], m.p. 76–77 °C).

IR ($CHCl_3$): ν = 3600, 3600–3250, 1535, 1160 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 7.02 (dd, 1H, J = 2.68, 8.37 Hz); 7.24 (d, 1H, J = 8.38 Hz); 7.49 ppm (d, 1H, J = 2.66 Hz).

4-Methoxy-2-nitrotoluene (5):
To phenol **4** (15 g, 97.9 mmol) and potassium carbonate (20.3 g, 0.147 mol) in acetonitrile (200 ml) is added dimethyl sulphate (11.6 ml, 0.122 mol) and the mixture is stirred at room temperature for 2 h. The acetonitrile is evaporated *in vacuo* and the residue is dissolved in saturated aqueous glycine (50 ml). This solution is heated to 50 °C for 1 h to destroy excess dimethyl sulphate, cooled, and extracted with ether (2 × 50 ml). The combined organic layer is washed with aqueous 1 molar sodium hydroxide solution (25 ml), dried with sodium sulfate and concentrated to a dark oil. This residue is Kugelrohr distilled under reduced pressure to give **5** as a light yellow oil; yield: 14.6 g (89%); b.p. 55–60 °C (bath temp)/2 torr (Lit.[8], 120–122 °C/6 torr).

IR (Neat): ν = 2990, 2960, 2865, 1635, 1535 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.52 (s, 3H); 3.85 (s, 3H); 7.05 (dd, 1H, J = 2.75, 8.5 Hz); 7.22 (d, 1H, J = 8.49 Hz); 7.49 ppm (d, 1H, J = 2.7 Hz).

6-Methoxyindole (7): To **5** (17.9 g, 0.107 mol) in dry dimethylformamide (200 ml) is added dimethylformamide dimethyl acetal (42 ml, 0.316 mol) and pyrrolidine (10 ml, 0.12 mmol). The mixture is heated at 105 °C for 19 h under nitrogen, then cooled, diluted with water and extracted with ether (8 × 50 ml). The ether layer is extracted with water (3 × 25 ml), dried with sodium sulfate, and concentrated to give a deep red oil which is dissolved in ethyl acetate (150 ml), and to the solution is added 10% palladium on carbon (1.8 g). Hydrogenation at 50 p.s.i. with shaking for 3 h and then filtration through celite gives a light brown filtrate. This filtrate is evaporated to a purple oil which is chromatographed on silica gel (eluent: dichloromethane) to give **7**; yield: 12.0 g (76%); m.p. 86–86 °C (Lit.[ ], m.p. 91–92 °C).

IR ($CHCl_3$): ν = 3510, 3140, 2865, 1640 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 3.85 (s, 3H); 6.49 (m, 1H); 6.81 (dd, 1H, J = 2.28, 8.62 Hz); 6.91 (br d, 1H, J = 2.2 Hz); 7.11 (dd, 1H, J = 2.37, 3.19 Hz); 7.2 (d, 1H, J = 8.6 Hz); 8.1 ppm (br s, 1H).

3-(2-Hydroxyethyl)-6-methoxy Indole (10):
3-(2-Ethoxycarbonyl-1-oxoethyl)-6-methoxy Indole **(9)**: To **8**[1] (7.9 g, 33.3 mmol) in absolute ethanol (60 ml) at 0 °C is slowly added triethylamine (5.1 ml, 36.6 mmol). A nitrogen stream is used to remove the hydrogen chloride gas liberated. After all the triethylamine is added the solution is heated to reflux for 3 h, cooled to 0 °C, and the yellow solid that precipitates is collected by vacuum filtration. The solid is washed with cold ethanol and then dried under high vacuum to afford **9**; yield: 7.1 g (86%); m.p. 208 °C.

Conversion of **9** *to* **10**: Ester **9** is added directly to a suspension of lithium aluminum hydride (3.28 g, 86.4 mmol) in tetrahydrofuran (150 ml) at room temperature. After the addition, the reaction is refluxed for 4 h, quenched by adding water (3 ml), aqueous 1 molar sodium hydroxide solution (3 ml), and finally water (9 ml). The suspension is vacuum filtered and the filtercake is digested twice with hot ethanol (50 ml). The combined filtrate is diluted with water (200 ml) and extracted with ether (5 × 75) and the combined organic phase is dried with sodium sulfate and concentrated to give **10**; yield: 4.9 g (89%); m.p. 95 °C (Lit.[10], m.p. 96–97 °C).

IR ($CHCl_3$): ν = 3670, 3560, 3510, 3030, 2975, 2865, 1640 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 3.0 (t, 2 H, J = 6.3 Hz); 3.85 (s, 3 H); 3.9 (m, 2 H); 6.8 (dd, 1 H, J = 2.2, 8.6 Hz); 6.87 (d, 1 H, J = 2.0 Hz); 6.98 (d, 1 H, J = 1.4 Hz); 7.48 (d, 1 H, J = 8.55 Hz); 7.9 ppm (br s, 1 H).

6-Methoxytryptophyl Bromide (11): To alcohol **10** (1 g, 5.23 mmol) and carbon tetrabromide (2.42 g, 7.32 mmol) in acetonitrile (40 ml) at 0 °C is added triphenylphosphine (1.8 g, 6.8 mmol) over a 10 min concentrated and chromatographed on silica gel using hexanes/ethyl acetate (6:4) as eluent to give **11**; yield: 1.13 g (85%); m.p. 109–110 °C.

$C_{11}H_{12}BrNO$	calc.	C 52.00	H 4.76	N 5.51
(254.1)	found	52.21	4.82	5.60

IR ($CHCl_3$): ν = 3490, 2850, 2770, 1640, 1170 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 3.27 (t, 2 H, J = 7.54 Hz); 3.6 (t, 2 H, J = 7.54 Hz); 3.83 (s, 3 H); 6.79 (dd, 1 H, J = 2.1, 8.58 Hz); 6.84 (br s, 1 H); 6.95 (d, 1 H, J = 2 Hz); 7.43 (d, 1 H, J = 8.58 Hz); 7.9 ppm (br s, 1 H).

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