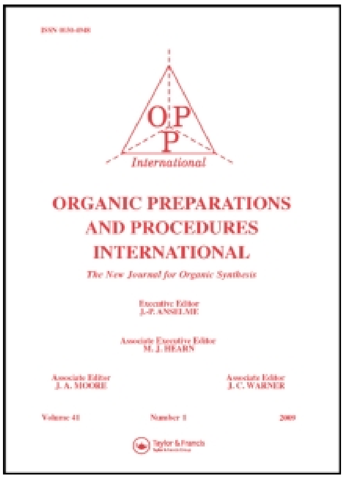

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A Novel Synthesis of Pendimethalin

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Pendimethalin **(6)** is a well-known selective herbicide useful for pre-emergence control of annual broad-leaved weeds and grasses in cotton, soybeans, rice, barley, beans, alliums, vines, ornamentals and orchards of fruit and nut trees.[1] It is also utilized to control suckers of tobacco. Several procedures have been reported for the preparation of pendimethalin[2,3] and it is currently manufactured from o-xylene (**1**), by nitration, catalytic hydrogenation, condensation and dinitration[4] (*Scheme 1*). One problem of this process is that the selectivity of the nitration of o-xylene is poor, giving only about 60% yield of 3,4-dimethylnitrobenzene along with 40% of 2,3-dimethylnitrobenzene.[5] Another difficulty is that the final dinitration step may produce the potentially carcinogenic N-nitroso compound **7**.[4] We report a new approach for the synthesis of pendimethalin **(6)** in a cost-effective, efficient and environmentally friendly manner.

As shown in *Scheme 2*, 3,4-dimethylbromobenzene **(8)** was prepared[6] in 91% yield by bromination of o-xylene (**1**) at -5-0°. Methoxylation of **8** with sodium methoxide in the presence of cuprous bromide gave 3,4-dimethoxyanisole in 96% yield.[7–9] Mono- and dinitration carried out in a stepwise fashion afforded 3,4-dimethyl-2,6-dinitroanisole **(10)** in 90% yield.[10–12] Finally, treatment of **10** with 1-ethylpropylamine led to the title product **6** in 93% yield.[2,3]

This new synthesis of pendimethalin provided a higher yield under milder conditions and especially avoids the generation of the N-nitroso by-product **7** (the content of N-nitroso compound may be controlled to under 10 mg/kg) thus making this route suitable for industrial production of high quality pendimethalin.

Experimental Section

^{1}H NMR Spectra were obtained on a Bruker AC-500 instrument and GC-MS spectra were acquired on an Agilent 6890N GC system equipped with a 5973N mass-selective detector. Melting points were obtained on a Buchi Melting Point B-545 apparatus.

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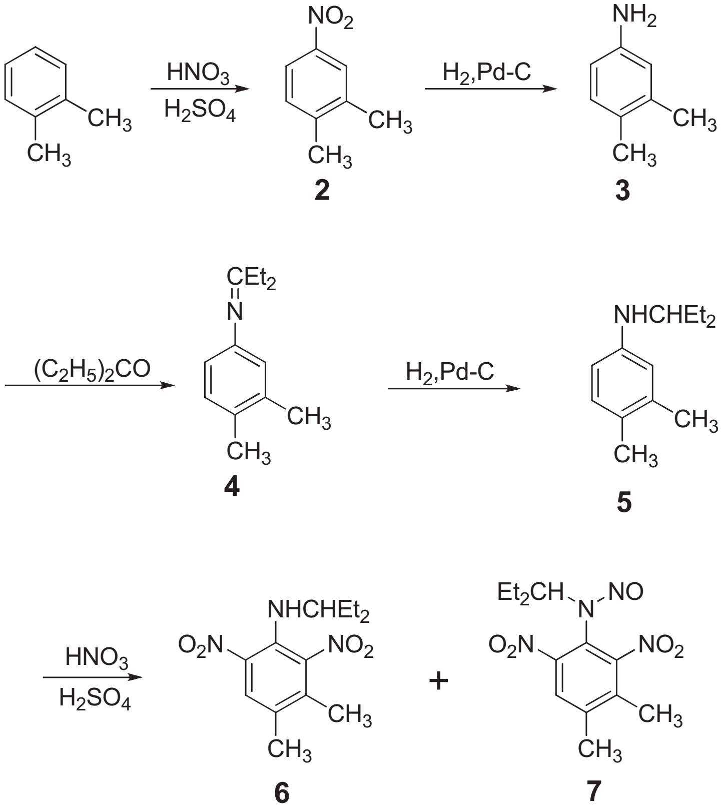
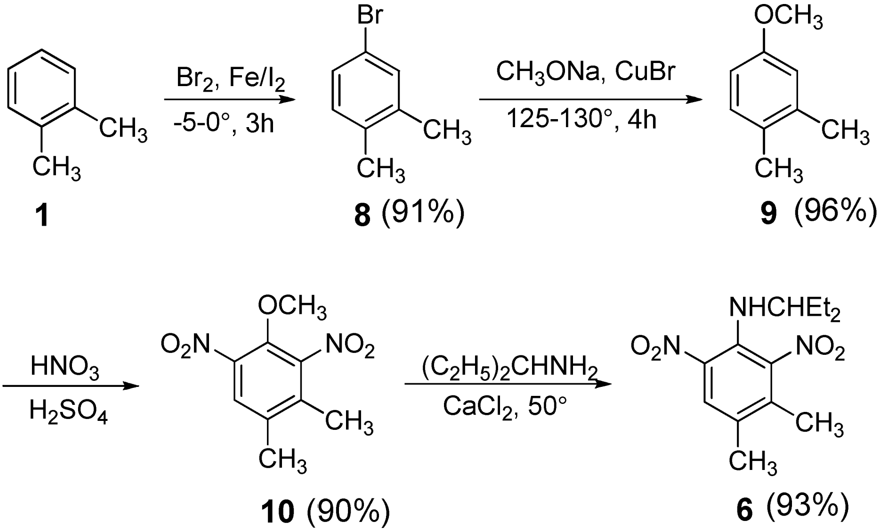


Scheme 1



Scheme 2

3,4-Dimethylbromobenzene (8)

In a 250 ml four-necked flask with a mechanical stirrer, an addition funnel, a condenser and a thermometer was placed *o*-xylene **(1)** (106 g, 114 ml, 1.0 mol), clean iron filings (1.2 g) and iodine (0.1 g). The mixture was stirred and cooled in an ice-salt mixture. Bromine (160 g, 1.0 mol) was added dropwise at -5-0° over a period of 3 h. After all the bromine had been added, the reaction mixture was allowed to stand overnight with stirring. It was poured into water and washed successively with a 100 ml portion of water, a 100 ml portion of 20% sodium hydroxide solution and a 100 ml portion of water. The organic layer was separated from the water and dried over magnesium sulfate. The crude product was purified by fractional distillation under vacuum to give 167.4 g (91% yield) of 3,4-dimethylbromobenzene **(8)** as a colorless liquid, bp. 104–105°C/76 mm Hg, *lit.*[6] 214–215°C/760 mm Hg. MS (m/e): 186, 184, 105, 89, 77.

3,4-Dimethylanisole (9)

In a polytetrafluoroethylene-lined autoclave reactor with a stirrer was charged with compound **8** (184 g, 1.0 mol), sodium methoxide (59.4 g 1.1 mol), methanol (250 ml), and cuprous bromide (1.8 g) as a catalyst. The mixture was stirred and then heated to 125–130°C. After 4 h, the reaction mixture was cooled to room temperature. Then the mixture was filtered by gravity to remove solids. The filtrate was washed with 100 ml of water and the organic layer was separated and dried over magnesium sulfate to give the product [192.0 g, 96% yield, 98% purity (GC)], as a colorless liquid, bp. 198–201°C, *lit.*[13] 202°. MS (m/e): 136, 121, 105, 91, 77.

3,4-Dimethyl-2,6-dinitroanisole (10)

To a solution of compound **9** (136 g, 1.0 mol) in 1,2-dichloroethane (200 ml) at 20–25°C, was added dropwise 95% fuming nitric acid (73 g, 1.1 mol) at the same temperature over 2 h. After stirring for 3 h at the same temperature, the mixture was allowed to separate into two phases. The organic phase contained approximately 1,2-dichloroethane (200 ml) and the *mono*-nitro derivative of compound **9** (172 g). Then it was heated to 55–60°C and 95% fuming nitric acid (132.6 g, 2.0 mol) in concentrated sulfuric acid (265 g) was added dropwise at the same temperature over 2 h. After stirring for an additional 3 h at the same temperature, the mixture was allowed to separate into two phases. The organic phase was washed successively with water, a 20% sodium hydroxide solution and water. The organic layer was separated from the water and dried over magnesium sulfate. The solvent was removed under reduced pressure. The solid residue was crystallized from ethyl alcohol to give a pale yellow solid [214.7g, 90% yield, 95% purity (GC)], mp. 67–69°C, *lit.*[3] 67–68°C. MS (m/e): 226, 121, 105, 91, 77.

N-(1-Ethylpropyl)-3,4-dimethyl-2,6-dinitroaniline (6)

A mixture of compound **10** (226 g, 1.0 mol), 1-ethylpropylamine (130.5 g, 1.5 mol) and calcium chloride (5.1 g) as a catalyst was stirred at 50°C. The progress of the reaction was monitored with GC/MS. After completion of the reaction, excess of 1-ethylpropylamine was recovered from the reaction mixture by distillation. The residue was dissolved in dichloromethane and the solution was successively washed with 5% hydrochloric acid, 5% sodium hydroxide, and then with water until neutral and then dried. The solvent was removed by distillation leaving a pale yellow oil which solidified [267 g, 93% yield, 98% purity (GC)], mp. 55–57°, lit.[14] 54–58°. MS (m/e): 281, 252, 236, 220, 208, 191, 174, 162, 145. ^{1}H NMR (DMSO):δ 8.42 (1H, s), 6.62 (1H, d, $J = 5.0$ Hz), 3.34–3.26 (1H, m), 2.42 (3H, s), 2.30 (3H, s), 1.55–1.46 (4H, m), 0.82–0.79 (6H, t).

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