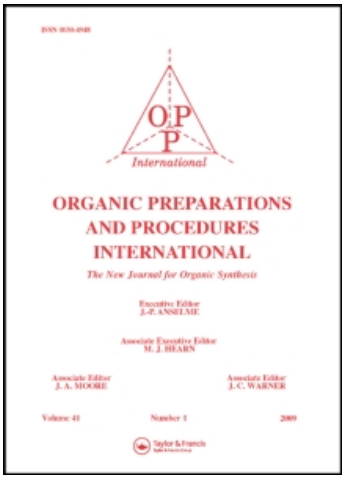

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A CONCISE PREPARATION OF 2,6-DIMETHYL-4-NITROCHLOROBENZENE

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A CONCISE PREPARATION OF 2,6-DIMETHYL-4-NITROCHLOROBENZENE

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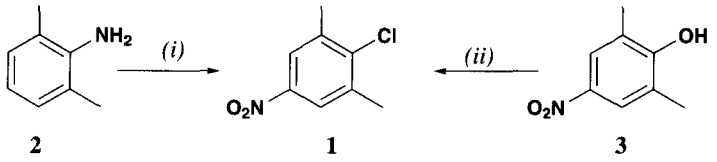
2,6-Dimethyl-4-nitrochlorobenzene (**1**) is an intermediate of potential use for the preparation of a variety of biologically active molecules.[1] Despite the utility of this compound, it remains poorly known in the literature, with details of its preparation confined to three patents and one journal article.[2] Each of these syntheses proceeds in the same manner, starting with 2,6-dimethylaniline (**2**) and carrying out four steps: (1) N-protection; (2) nitration; (3) N-deprotection; and (4) Sandmeyer reaction. In as much as the overall yields for these four step processes averaged only about 15% to

20% and in view of the time required and the waste generated by this process, we sought an alternative method for the preparation of **1** that proceeded from the commercially available[3a] intermediate 2,6-dimethyl-4-nitrophenol (**3**), which has the advantage of having all of the substituents on the aromatic ring in place and in the desired formal oxidation states.[3b] We now describe the synthesis of **1** in one step and 35% to 40% overall yield, taking advantage of commercially available **3** in a process that takes less than 8 hrs to complete.



i): a) TsCl, pyr, 80°; b) fuming HNO_3, H_2O, HOAc, cat. $NaNO_2$, 100°; c) H_2SO_4, H_2O, 20°; d) $NaNO_2$, H_2SO_4, H_2O, 5°, then HOAc, HCl, Cu_2Cl_2, 20° *ii)*: PCl_5, PhOH, 220°

Our synthesis involves conversion of **3** to **1** by reaction with phosphorus pentachloride and phenol at 210-220°,[4] followed by Kugelrohr distillation of the crude **1** from the residual triphenyl phosphate, washing the distillate with alkali and recrystallization to afford analytically pure **1**. A number of other methods reported to be effective for the conversion of 4-nitrophenols to 4-nitrochlorobenzenes were ineffective in this particular case, including treatment of **3** with either phosphorus pentachloride, phosphoryl chloride, phosphorus pentachloride-phosphoryl chloride mixtures, phosphoryl chloride in DMF, dichlorotriphenylphosphorane, thionyl chloride and thionyl chloride in DMF.[5] In each case the starting material **3** was recovered. Attempts to prepare **1** from the tosylate or the known methanesulfonate[6] derived from **3** were also unsuccessful.

The preparation of **1** from **3** required some optimization of reaction conditions. Reaction of **3** with the phosphorus pentachloride-phenol mixture at 150° failed to afford any **1** as determined by GC-MS analysis of the reaction mixture. Heating of the reaction mixture at higher temperatures (in excess of 240°) resulted in frothing and the formation of a dark charred residue. Prolonged heating of the reaction mixture likewise resulted in lower yields.

EXPERIMENTAL SECTION

2,6-Dimethyl-4-nitrophenol (**3**) was obtained from Lancaster Synthesis (Cat. 10372). All other reagents were purchased from Fisher and were used as received. Reactions were carried out under a positive flow of dry nitrogen which was subsequently passed into a hydrogen chloride trap as described by Ault.[7] Evaporations were carried out on a rotary evaporator using aspirator pressure. **CAUTION:** Both phosphorus pentachloride and phenol are *toxic!* All operations involving phosphorus pentachloride and phenol must be conducted in a good fume hood.

2,6-Dimethyl-4-nitrochlorobenzene (1).- A 500 mL single-neck round bottom flask was fitted with a Claisen adapter. The straight tube of the adapter was fitted with a mechanical stirrer and the side arm was fitted with a T-tube connected to a supply of dry nitrogen and a hydrogen chloride trap. The flask

was charged with 28.2 g (0.3 mol) of phenol and the stirrer was started. Phosphorus pentachloride (20.8 g, 0.1 mol) was added in three portions through the side arm of the Claisen adapter. A brisk evolution of hydrogen chloride ensued; when this subsided the mixture was heated in a 105° oil bath for 1 hr. The flask was then removed from the oil bath and allowed to cool, at which point 16.7 g (0.1 mol) of **3** was added *via* the Claisen adapter side-arm. When the evolution of hydrogen chloride slowed, the mixture was heated in a 140° oil bath for 1 hr, after which the bath temperature was raised to 215° The mixture was kept at 215° for 45 min and then allowed to cool. After cooling, the reaction flask was removed and the crude **3** was distilled using a Kugelrohr apparatus at a pressure of 1 torr and an oven temperature of up to 140°.[8] A total of 10.75 g of distillate was obtained. This was partitioned between 200 mL of water and 200 mL of ether, the phases were separated and the ether was washed alternately with 1 M potassium hydroxide and water. The washing was repeated five more times, then the ether was washed with brine, dried ($MgSO_4$) and evaporated to afford 9.12 g (49%) of a white crystalline residue.[9] This was recrystallized from hexanes (35 mL) with cooling in ice to give 6.86 g (37%) of **1** as white needles, mp 102-104° (lit[2] mp 102-104). ^1H NMR ($CDCl_3$): δ = 7.95 (s, 2 H); 2.46 (s, 6 H). MS (EI): *m/z* = 185 (M^+).

Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N 7.55. Found: C, 51.66; H, 4.32; N 7.44

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3. a) 2,6-Dimethyl-4-nitrophenol is available from Aldrich (Cat. 13,271-3), Fluka (Cat. 40890), Lancaster Synthesis (Cat. 10372) and Avocado Research (Cat. 15472). Lancaster Synthesis and Avocado Research are considerably less expensive (about 3-fold) than Aldrich and Fluka. b) While the 2,6-dimethyl-4-nitrophenol starting material used in this preparation is initially more expensive (about $2.50 per gram) than the alternate starting material 2,6-dimethylaniline ($0.07 per gram), the latter starting material incurs substantial downstream expenses when used to prepare 2,6-dimethyl-4-nitrochlorobenzene because of the additional reagents and time required to effect the conversion to the product and, more importantly, because of the substantial volumes of acid wastes generated by the nitration, deprotection and Sandmeyer reactions. Chromatographic purification of intermediates is occasionally required in processes using 2,6-dimethylaniline as a starting material, contributing to additional overall expense.

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8. An Aldrich "coffee pot" Kugelrohr, cat. Z10,046-3, was used. The receiving bulb was cooled in an ice bath.

9. The product at this point exhibited satisfactory ^{1}H NMR and GC-MS spectra, and had a mp. 100-102°.

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A FACILE SYNTHESIS OF 9-HYDROXYBENZO[a]PYRENE

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One important way to elucidate the mechanisms of metabolic activation of polyaromatic hydrocarbons is to study the DNA adducts formed thereof.[1] Synthetic DNA adducts are also molecular biomarkers for measuring human exposures to chemical carcinogens.[2] It is well documented that the *bay-region* diol epoxides of BAP** are the principal active forms of this carcinogen[3] and the key step in its tumor initiation is thought to be the covalent binding of these epoxides to DNA.[4] Although the corresponding K-region epoxides were shown not to be responsible for the binding to DNA found in cellular systems,[5] evidence indicated that 9-hydroxy-BAP-4,5-oxide might also be an active metabolite of BAP which could bind to nucleic acids *in vivo*.[6-8] In order to assess the human health risk posed by BAP, it is necessary and timely to synthesize the DNA adduct of 9-hydroxy-BAP-4,5-oxide as a biomarker. The key intermediate is 9-hydroxy BAP (**6**) which was synthesized by Harvey,[6] Yagi[9] and Sims[10] from 9,10-dihydrobenzo(a)pyren-7(8H)-one. However, these syntheses require either several steps under harsh conditions[9,10] or the use of expensive and hazardous osmium tetroxide.[6]

We now report here a facile synthetic route to 9-hydroxy-BAP from a relatively more economical starting material, 7-hydroxy-7,8,9,10-tetrahydro-BAP (**1**) which was converted to 7-*p*-chlorobenzoyloxy-7,8,9,10-tetrahydro-BAP (**2**) quantitatively by treatment with *p*-chlorobenzoyl chloride, pyridine and catalytic amount of DMAP in chloroform at room temperature. 7-*p*-Chlorobenzoyloxy-7,8-dihydro-BAP (**3**) can be obtained selectively when **2** is treated with DDQ in hot benzene. The process can be easily monitored by TLC on silica gel.