



# A fast and mild method for the nitration of aromatic rings

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**Abstract**—The use of  $N_2O_5$  and a Fe(III) catalyst for the nitration of aromatic rings is described. This methodology is compatible with most functional groups and results in near quantitative yields in 4 min. The reaction conditions are non-oxidising: benzaldehyde and benzyl alcohols are readily nitrated with little or no oxidation (<4%) occurring. The addition of the iron catalyst activates the system to such an extent that nitration of an activated aromatic ring, such as toluene, occurs quantitatively at  $-100^\circ\text{C}$ . This high activity allows compounds with sensitive functional groups such as alkenes to be smoothly nitrated. © 2001 Published by Elsevier Science Ltd.

Conventional methods for the nitration of aromatic rings utilize nitric acid or mixtures of nitric and sulphuric acids. These conditions are incompatible with a range of compounds which are sensitive to oxidising or strongly acidic conditions. Use of nitronium salts, such as those formed from methane sulfonic acid,<sup>1</sup> or from Lewis acids, such as boron trifluoride,<sup>2</sup> are also hampered by liberation of strong acids; in the case of the boron trifluoride/nitronium salt, HF and  $BF_3$  are liberated.<sup>2</sup>

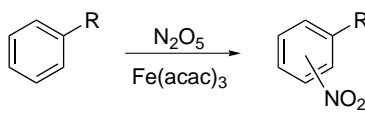
For our studies a mild nitrating agent was required, which could nitrate moderately deactivated aromatic rings in the presence of a variety of functional groups. Recent developments in aromatic nitration methodology using  $NO_2/O_3$  (Kyodai nitration) demonstrated excellent conversions for a variety of aromatic compounds.<sup>3</sup> In the Kyodai nitration the active nitrating agent is thought to be  $N_2O_5$  which is formed in situ from  $NO_2$  and  $O_3$ . The drawbacks to this method include the necessity to generate ozone, which limits the reaction rate, and long induction periods, during which sensitive compounds may undergo degradation.

The direct use of  $N_2O_5$  as a nitrating reagent, instead of generating it in situ, has been previously reported for activated aromatic rings.<sup>4</sup> In our hands  $N_2O_5$ <sup>5</sup> readily nitrated toluene at  $0^\circ\text{C}$  to give a virtually

quantitative yield of *o*- and *p*-nitrotoluene after only 10 min. Attempts to nitrate less activated aromatic rings, such as acetophenone, using this methodology resulted in recovery of unreacted starting material.

The use of an Fe(III) catalyst for the nitration of aromatic rings using  $NO_2$  in the presence of oxygen has been reported.<sup>6</sup> The iron activates the  $NO_2$  although long reaction times, up to 72 h, are required and moderately deactivated substrates are not nitrated. It was thought that Fe(III) might also be capable of catalysing nitration reactions using the more active  $N_2O_5$ .

**Table 1.** Nitration of aromatic rings using  $N_2O_5$  and  $Fe(acac)_3$  for 4 min



R	<i>o</i> : <i>m</i> : <i>p</i>	Isolated yield (%)
CHO	18:60:22	93
COCH <sub>3</sub>	50:44:6	98
CH <sub>2</sub> CN	21:<1:79	96
CH <sub>2</sub> OH	33:<1:67	91
Br	19:32:49	99 <sup>a</sup>
NO <sub>2</sub>	<1:99:<1	94 <sup>b</sup>
CN	68:32:<1	95 <sup>b</sup>

<sup>a</sup> Reaction conducted at  $20^\circ\text{C}$ .

<sup>b</sup> Reaction conducted at  $40^\circ\text{C}$ .

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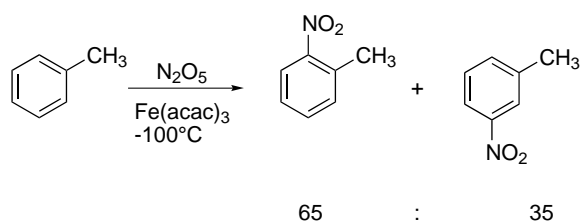
Nitration of acetophenone at 0°C using Fe(acac)<sub>3</sub> and N<sub>2</sub>O<sub>5</sub> in dichloromethane resulted in a near quantitative yield of *o*- and *m*-nitroacetophenone after only 4 min.<sup>7</sup>

This nitrating procedure was found to be applicable to a range of aromatic compounds (Table 1).

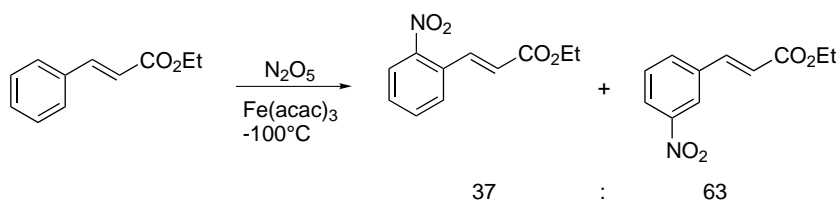
In all cases complete nitration was observed after only 4 min and the products were readily isolated in near quantitative yields.<sup>8</sup> For some deactivated aromatic rings (R=Br, NO<sub>2</sub>, CN) incomplete nitration was observed at 0°C. Conducting these reactions at slightly elevated temperatures (20–40°C) resulted in quantitative yields of nitrated product. These reaction conditions are extremely mild as exemplified by the ready formation of nitrobenzaldehyde, from benzaldehyde, with no evidence of oxidation of the aldehyde functionality. In the case of benzyl alcohol a small amount of benzaldehyde (<4%) is formed.

The regioselectivity of the nitration reaction is similar to that observed for reactions conducted under standard nitrating conditions, HNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub>, except for nitration of compounds containing a carbonyl group, e.g. benzaldehyde and acetophenone, which produce increased amounts of the *o*-isomer. Reactions conducted under non-acidic conditions using N<sub>2</sub>O<sub>5</sub> have also been reported to exhibit this enhanced *o*-nitration.<sup>3</sup> It has been postulated that in the absence of acidic protons the carbonyl group is not protonated leading to *o*-nitration whilst the protonated carbonyl group is *meta* directing.

Whilst deactivated aromatic rings are readily mononitrated under these conditions, nitration of toluene, a mildly activated aromatic ring, leads to the formation



Scheme 1.



Scheme 2.

of 2,4- and 2,6-dinitrotoluene. The mono-nitrated product can be obtained by conducting the nitration reaction at –100°C (dry ice/ether bath) (Scheme 1). In the absence of the iron the reaction occurs at 0°C, this dramatic difference in reaction temperature clearly illustrates the activating effect of the iron catalyst.

The ability to conduct the nitration reaction at such low temperatures allows the nitration of compounds containing functional groups which are themselves susceptible to nitration. Nitration of ethyl cinnamate at 0°C resulted in attack at the double bond leading to a complex mixture of products. However, conducting the nitration reaction at –100°C (dry ice/ether bath) for 4 min gave a quantitative yield of nitrated product, indicating the high reactivity of this methodology (Scheme 2).

The structure of the active nitrating complex is not clear nor is the mechanism of the reaction. Unlike other nitrating systems involving Lewis acids,<sup>9</sup> such as BF<sub>3</sub>, this reaction is clearly catalytic. Addition of N<sub>2</sub>O<sub>5</sub> to a solution of Fe(acac)<sub>3</sub> results in the formation of a pale pink solid. Attempts to isolate and characterise this complex have to date been unsuccessful as the complex decomposes readily in moist air although it can be filtered and washed with dichloromethane under nitrogen. This washed complex does not nitrate aromatic rings stoichiometrically in the absence of N<sub>2</sub>O<sub>5</sub> but the reaction proceeds normally upon the addition of further amounts of N<sub>2</sub>O<sub>5</sub>. It is also critical to add the N<sub>2</sub>O<sub>5</sub> to the Fe(III) to form the complex prior to the addition of the aromatic substrate. If the complex is not preformed the nitration reaction is significantly slower, and similar results are obtained to those in reactions conducted in the absence of the Fe(III). Addition of substrate to the nitrating complex causes an immediate colour change to an intense red/brown colour, and the complex dissolves. The nitration reaction is self-indicating as the mixture reverts to a lighter colour and the solid catalyst is reformed once nitration is complete.

The use of N<sub>2</sub>O<sub>5</sub> and Fe(acac)<sub>3</sub> is a simple, fast and mild procedure for the nitration of aromatic rings. The reaction is tolerant of a range of functional groups and gives virtually quantitative yields in less than 4 min.

## References

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4. Furukawa, K.; Yoshizawa, F.; Akutsu, Y.; Arai, M.; Tamura, M. *Kayaku Gakkaishi* **1999**, *60*, 143.
5. Freshly distilled fuming nitric (100%) was added slowly to a distillation flask containing  $P_4O_{10}$ . Slow distillation affords  $N_2O_5$  with liberation of nitrogen oxides. The collected  $N_2O_5$  is placed in a freezer until a solid is formed, the product is then warmed slowly to  $10^\circ C$  at which time any liquid nitrogen oxides are discarded, to leave a white/yellow solid. It is important that the  $N_2O_5$  used is free of nitrogen oxide(s) CAUTION:  $N_2O_5$  is highly corrosive and liberates toxic nitrogen oxides. Small amounts can be quickly neutralised with copious amounts of water.
6. Suzuki, H.; Yonezawa, S.; Nonoyama, N.; Mori, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2385.
7. Addition of  $N_2O_5$  (15 mmol) to a stirred solution of 10 ml  $CH_2Cl_2$  and  $Fe(acac)_3$  (0.1 mmol) at  $0^\circ C$  results in the formation of the nitrating complex as a light pink solid. Substrate (5 mmol) is added to the reaction, which is stirred for 4 min at  $0^\circ C$ , and then quenched with 2 M HCl (20 ml) (water or  $Na_2CO_3$  solution can also be utilized for acid sensitive substrates). The reaction was extracted with  $CH_2Cl_2$  and washed with aqueous  $Na_2CO_3$  and brine. Removal of solvent afforded the pure nitrated compounds in near quantitative yields.
8. All compounds were fully characterized using  $^1H$  and  $^{13}C$  NMR.
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