A Novel Non-Acidic Method for the Preparation of 2,2,2-Trifluoro-1-(3-nitrophenyl)ethanone and 1-Nitro-3-trifluoromethylbenzene, Versatile Starting Materials for Trifluoromethyl-Containing Aromatic Compounds

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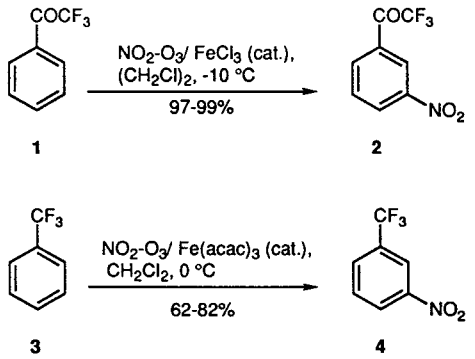
Treatment of 2,2,2-trifluoro-1-phenylethanone **(1)** and α,α,α-trifluorotoluene **(3)** with ozone or ozonized air in chlorinated hydrocarbons in the presence of excess nitrogen dioxide and a catalytic amount of iron(III) salt at −10–0 °C leads to the respective title nitro compounds **2** and **4** in good to excellent yields. The reaction is clean and rapid, little or no hydrolysis of the trifluoromethyl group being observed during the nitration.

Replacement of a methyl group by a trifluoromethyl group in a molecule often brings about a favorable change in its physical and biological properties. Hence this mode of chemical modification has been widely employed in the development of new medicines, agricultural drugs, or advanced materials.

2,2,2-Trifluoro-1-(3-nitrophenyl)ethanone **(2)** and 1-nitro-3-trifluoromethylbenzene **(4)** are convenient starting materials for the synthesis of a wide variety of trifluoromethyl-containing aromatic compounds and so they find many industrial uses. The only practical method in use for large-scale prepration of these compounds has been the nitration of 2,2,2-trifluoro-1-phenylethanone (α,α,α-trifluoroacetophenone) **(1)** and α,α,α-trifluorotoluene **(3)** with either fuming nitric acid alone or nitric acid–sulfuric acid (mixed acid). However, this century-old methodology for aromatic nitration is not ideal. Since the trifluoromethyl group withdraws electrons both inductively and conjugatively (C-F hyperconjugation) to deactivate the aromatic ring, the nitrations of compounds **1** and **3** are conducted under strongly acidic conditions using an excess of the nitrating agent, which inevitably brings about partial hydrolysis of the trifluoromethyl group and consequently the troublesome problem of the disposal of spent acid containing toxic hydrofluoric acid, which corrodes the glass and glass linings of reaction vessels. The trifluoromethyl group attached to an aromatic ring is not stable towards strong acids and easily transformed into the carboxylic acid function and hydrofluoric acid.[1]



Scheme

We have recently found that nitrogen dioxide is activated in the presence of ozone to enter easily into a nonactivated aromatic nucleus as a nitro group at low temperature (referred to the Kyodai-nitration).[2] When this methodology was applied to compound **1**, we were pleased to find that it underwent smooth nuclear nitration in the presence of some acid or metal catalyst at temperatures below 0 °C, giving the corresponding nitro compound **2** almost quantitatively. The reaction was clean and rapid, no polymeric substances being formed. The reaction time was found to be linearly dependent on the amount of ozone introduced. Under the conditions employed, the hydrolysis of the trifluoromethyl group was negligible (< 1%).

Among the catalysts examined, iron(III) compounds such as iron(III) chloride and tris(acetylacetonato)iron(III) gave the most satisfactory results. Methanesulfonic acid and trifluoromethanesulfonic acid were also good catalysts, but strong acid catalysts such as aluminum chloride, titanium(IV) chloride and sulfuric acid proved to be unsatisfactory. Without the catalyst, the nitration was quite slow and incomplete. Dichloromethane and 1,2-dichloroethane were the solvents of choice, but acetonitrile, nitromethane and even hexane may be used without significant influence on the results. It was important to minimize the amount of adventitious water in the reaction mixture. The isomer distribution of the nitration product from ketone **1** was *ortho–meta* > 1:99. In most cases, the *para* isomer could not be detected by GLC. The nitration of ketone **1** has previously been reported to give compound **2** as the sole product.[3] An alternative route to this compound involves the reaction of a trifluoromethylcadmium complex with 3-nitrobenzoyl chloride.[4]

Under similar conditions, α,α,α-trifluorotoluene **(3)** was readily nitrated with nitrogen dioxide in the presence of ozone and an iron(III) catalyst. The reaction was clean and rapid, no tarry matters being formed. Hydrolytic decomposition of the trifluoromethyl group was observed only to an insignificant extent (1–2%). In this case, tris(acetylacetonato)iron(III) was a better catalyst than iron(III) chloride. Compound **3** is rather volatile (bp 102 °C), so it was readily carried away from the reaction system by the escaping gas during the nitration, which appreciably lowered the isolated yield of the product. This problem may be solved in part by raising the concentration of ozone, but we have made no attempts yet because of the limitations of our ozone generator.

Compound **3** has been nitrated using mixed acid,[5] nitryl fluoride–boron trifluoride–diethyl ether complex,[6] so-

dium nitrate–chlorotrimethylsilane–aluminium chloride,[7] and methyl nitrate.[8] The partial rate factor for the *meta*-nitration was estimated to be 6.7×10^5.[9] The rate of hydrolysis of **3** to benzoic acid was determined in 81–92% sulfuric acid.[9]

Known methods other than direct nitration for the preparation of nitro(trifluoromethyl)benzenes involve the deamination of nitro(trifluoromethyl)anilines,[10,11] fluorinolysis of α,α,α-nitro(tribromomethyl)benzene with antimony(III) fluoride,[11,12] fluorination of nitrobenzoic acid and methyl nitrobenzoate with sulfur(IV) fluoride,[13] trifluoromethylation of halogenonitrobenzenes with in situ generated trifluoromethylcopper(I),[14] oxidation of (trifluoromethyl)aniline with dimethyldioxirane,[15] and base-induced sulfur extrusion from nitrophenyl trifluoromethyl sulfone.[16] However, the use of toxic or expensive reagents, drastic conditions, and unsatisfactory yield due to side reactions diminish the synthetic utility of many of these reported methods.

The results described herein demonstrate the additional advantageous feature of the Kyodai-nitration over the classical nitration based on the use of nitric acid–sulfuric acid.[2]

Compounds **1** and **3** were supplied by Nissan Chemical Industries. Nitrogen dioxide (99% pure) was obtained in a cylinder from Sumitomo Seika Co. and used after transfer distillation. Chlorinated hydrocarbons used as solvent were dried by distillation from calcium hydride. ^{1}H NMR spectra were measured on a Varian Gemini-200 spectrometer for solutions in $CDCl_3$ with TMS as internal standard. IR spectra were recorded on a Shimadzu FT-IR DR 8000/8100 infrared spectrophotometer. Mass spectra (EI) were obtained on a Shimadzu GCMS QP-2000A mass spectrometer at an ionization potential of 70 eV. An apparatus (Nippon Ozone Co., type ON-1-2) was used for the generation of ozone at a rate of 10 mmol h^{-1}, with an oxygen flow of 10 dm^3 h^{-1} and an applied voltage of 80 V.

2,2,2-Trifluoro-1-(3-nitrophenyl)ethanone (2):
A mixture of 2,2,2-trifluoro-1-phenylethanone (0.87 g, 5 mmol), liquid nitrogen dioxide (2.3 g, 25 mmol), iron(III) chloride (50 mg, 6 mol%) and 1,2-dichloroethane (20 g) was stirred vigorously at −10–0°C, while a stream of ozonized oxygen was slowly introduced at a rate of 10 mmol h^{-1} from an inlet tube, the opening of which was placed just below the surface of the liquid mixture. The progress of the reaction was monitored by TLC. After 1 h the reaction was almost complete. The cooling bath was removed and excess of nitrogen dioxide was expelled by blowing air into the solution. The mixture was diluted with sat. aq $NaHCO_3$ and the organic phase was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent left an oily residue, which soon solidified on storage at r.t. The product was found by GLC to contain less than 1% *ortho* isomer, which could be easily removed by recrystallization from hexane–CH_2Cl_2. Yield: 1.06 g (96%). Colorless crystals, mp 54–55°C (lit.[3] 54–55°C).

MS (EI): *m/z* (%) = 150 (100), 104 (42), 76 (45), 50 (27).

IR (KBr): ν = 1732, 1705, 1617, 1538, 1352, 1190, 1055, 712 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.93 (m, 1 H), 8.47 (d, 1 H, J = 7.5), 8.63 (d, 1 H, J = 8.3), 8.89 (1 H, s).

1-Nitro-3-trifluoromethylbenzene (4):
A mixture of α,α,α-trifluorotoluene (7.30 g, 50 mmol), tris(acetylacetonato)iron(III) (10.4 mg, 0.06 mol%) and CH_2Cl_2 (50 mL) was stirred at 0°C in an ice bath, while a stream of ozonized oxygen was introduced through one of the gas inlet tubes, which was submerged just below the surface of the liquid mixture. A stream of nitrogen dioxide was slowly introduced through the other inlet tube. Throughout the reaction, both ozonized oxygen and nitrogen dioxide were fed continuously at a low flow rate. The reaction was almost complete after 5 h. The cooling bath was removed and excess of nitrogen dioxide was expelled. The reaction mixture was diluted with sat. aq $NaHCO_3$ and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic phase was washed with water and dried (Na_2SO_4). Removal of the solvent left an oil, which was found by GLC to be composed of compound **4**, accompanied by the *ortho* isomer (8%). The *para* isomer was formed only in trace amounts. Yield: 7.86 g (82 g). Pale yellow oil (Lit.[6] bp 93–95°C/35 mmHg).

MS (EI): *m/z* (%) = 191 (51, M^+), 145 (100), 95 (43), 75 (24), 71 (28), 69 (54).

IR (neat): ν = 1541, 1360, 1325, 1283, 1177, 1140, 1110, 1069, 741, 700, 689 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.46 (m, 1 H), 8.00 (d, 1 H, J = 7.7), 8.46 (d, 1 H, J = 8.4), 8.52 (1 H, s).

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