Synthesis of 2-Trifluoromethyl-1,3-cyclopentanedione and 2-Trifluoromethyl-1,4-benzoquinone via Chlorous Acid Oxidation of 3-Trifluoromethylphenol

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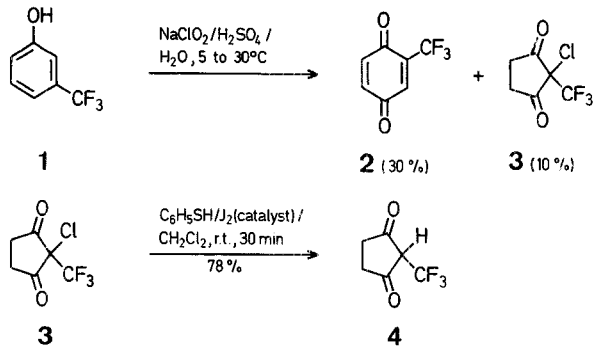
A new synthesis of 2-trifluoromethyl-1,4-benzoquinone and 2-chloro-2-trifluoromethyl-1,3-cyclopentanedione by oxidation of 3-trifluoromethylphenol with sodium chlorite/sulfuric acid (chlorous acid) is described. In addition, the hydrodechlorination of 2-chloro-2-trifluoromethyl-1,3-cyclopentanedione to give 2-trifluoromethyl-1,3-cyclopentanedione by hydroiodic acid (generated in catalytic amounts from iodine and thiophenol) has been achieved.

2-Methyl-1,3-cyclopentanedione has found widespread use in the industrial synthesis of steroid hormones by the Torgov reaction[1]. We have recently shown[2,3] that its trifluoromethylated analogue, 2-trifluoromethyl-1,3-cyclopentanedione **(4)**, could also be used in this reaction leading to angularly trifluoromethyl-substituted steroids with interesting biological properties. We report here our method for the preparation of this fluorinated compound[4], as well as that of 2-trifluoromethyl-1,4-benzoquinone **(2)**, a useful Diels-Alder component[5,6,7].

The oxidation of phenolic compounds with chlorous acid (acidified chlorite)[8] is known to lead to otherwise inaccessible compounds, mainly the chlorinated quinones and muconic acid derivatives resulting from the cleavage of the aromatic ring[9,10]. The behavior of 3-trifluoromethylphenol **(1)** towards this reagent at pH 0.5 is slightly different. The expected 2-trifluoromethyl-1,4-benzoquinone **(2)** is readily isolated in 32% yield, after extraction with *n*-heptane and crystallization, which compares quite well with the yield (33%) of an older procedure[11] using sodium dichromate oxidation of the more elaborated starting material 4-amino-3-trifluoromethylphenol. We also observed the formation of 2-chloro-2-trifluoromethyl-1,3-cyclopentanedione **(3)** in 10% yield, resulting from the ring contraction of the aromatic nucleus.



Although the exact nature of the intermediates involved in the formation of **3** are still under study, the reaction is believed to proceed by a chain mechanism involving a one-electron transfer from the phenol to chlorine dioxide, leading to the initial formation of a phenoxyl radical[12,13].

Since activated chlorine atoms are readily reduced by hydroiodic acid[14], the synthesis of 2-trifluoromethyl-1,3-cyclopentanedione **(4)** from its precursor **3** is straightforward. We find it very convenient to reduce **3** with hydroiodic acid, formed in catalytic amounts from thiophenol and a small amount of iodine in dichloromethane, from which the precipitated dione **4** could be isolated in 78% yield by simple filtration. In the presence of a base this diketone loses its fluorine atoms even more readily than α-perfluoroalkyl ketones[15].

CAUTION! Safety precautions should be taken because of the explosive character of the chlorine dioxide gas[16] evolved during the first experiment. Scaling up of the reaction may be hazardous. Since most byproducts are highly corrosive or lachrymatory, all the experiments should be carried out under an efficient hood.

Trifluoromethyl-1,4-benzoquinone (2):
A solution of sodium chlorite monohydrate (36 g, 332 mmol) in distilled water (100 ml) is poured into a well stirred suspension of 3-trifluoromethylphenol (**1**; 13 g, 80.2 mmol) in 0.6 normal sulfuric acid (300 ml) cooled to 5 °C in an ice-bath. After 15 min the temperature rises to 25–30 °C. Stirring is continued for an additional 15 min. The mixture is then degassed during 30 min under vacuum (water aspirator). The suspended solid is filtered and the aqueous phase extracted with *n*-heptane (6 × 60 ml). The heptane extracts and the solid are pooled and dried with magnesium sulfate. After filtration, the solution is allowed to crystallize at − 30 °C to give **2**; yield: 4.6 g (32%); m.p. 53–54 °C (Ref.[11], m.p. 54–55 °C).

2-Chloro-2-trifluoromethyl-1,3-cyclopentanedione (3):
The aqueous phase of the preceding experiment is saturated with sodium chloride and extracted with ether (5 × 60 ml). After drying with magnesium sulfate and removal of the solvent, a crude product (8 g) is obtained. The products of four such experiments (32 g) are combined and refluxed for 1 h in acetonitrile (400 ml). After removal of the solvent and a short path distillation (bath temperature: 80 °C/2.7 Pa) the distillate is fractionated with a Fischer MMS 202 column to give the cyclopentanedione **3**; yield: 6.2 g (10%); b.p. 95–100 °C/2.4 kPa; which crystallizes on standing; m.p. 45 °C.

$C_6H_4ClF_3O_2$	calc.	C 35.94	H 2.01	Cl 17.68	F 28.42
(200.5)	found	35.85	2.17	17.41	28.30

I.R. (CCl_4): ν = 1760 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 3.13 ppm (s).

^{13}C-N.M.R. ($CDCl_3$/TMS): δ = 35.5 (s, C-4 and C-5); 61.0 (q, C-2, $^2J_{CF}$ = 32 Hz; 121.0 (q, CF_3, J_{CF} = 283 Hz); 198.5 ppm (s, C-1 and C-3).

^{19}F-NMR ($CDCl_3$/$CFCl_3$): δ = − 70.8 ppm (s).

M.S.: *m/e* (rel. intens. %) = 200 (M^+, 70); 55 (100).

2-Trifluoromethyl-1,3-cyclopentanedione (4):
A crystal of iodine (~ 5–10 mg) is added to a stirred solution of 2-chloro-2-trifluoromethyl-1,3-cyclopentanedione (**3**; 1 g, 5 mmol) and thiophenol (1 ml) in dichloromethane (10 ml). After 10 min, the precipitate is filtered and washed with dichloromethane to give the cyclopentanedione **4**; yield: 0.64 g (78%); m.p. ~ 150 °C (dec.).

$C_6H_5F_3O_2$	calc.	C 43.39	H 3.03	F 34.31
(166.1)	found	43.27	3.22	35.03

I.R. (nujol): ν = 2500, 1680, 1590 cm^{-1}.

^{1}H-N.M.R. (tetrahydrofuran-d_8/TMS): δ = 2.57 (m, 4 H); 9.77 ppm (br, 1 H).

^{13}C-N.M.R. (tetrahydrofuran-d_8/TMS): δ = 31.5 (s, C-4 and C-5); 108.0 (q, C-2, $^2J_{CF}$ = 32 Hz); 123.3 (q, CF_3, $^1J_{CF}$ = 270 Hz); 194.0 ppm (s, C-1 and C-3).

^{19}F-N.M.R. (tetrahydrofuran-d_8/$CFCl_3$): δ = − 61.0 ppm (m).

M.S.: *m/e* (rel. intens. %) = 166 (M^+, 60); 56 (100).

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