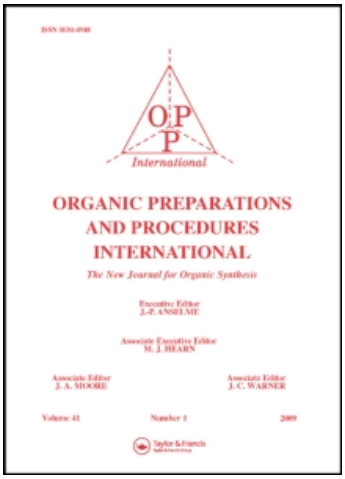

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AN EFFICIENT SYNTHESIS OF 4-HYDROXYBENZOTRIFLUORIDE

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and mass spectra.

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AN EFFICIENT SYNTHESIS OF 4-HYDROXYBENZOTRIFLUORIDE

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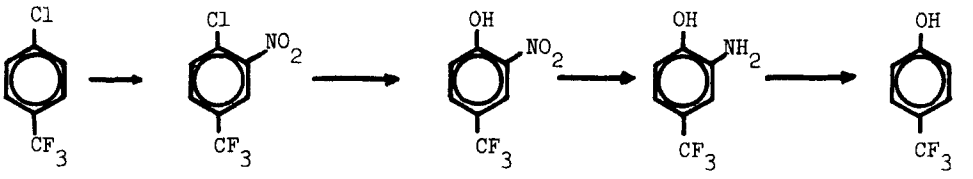
The relatively high cost of 4-hydroxybenzotrifluoride (V) is a limiting factor in its use as a chemical intermediate. Additionally, literature methods[1] for its preparation are cumbersome and not easily adapted to large scale operations. An improved synthesis of V from readily available, inexpensive 4-chlorobenzotrifluoride (I) in four steps is described.



I II III IV V

EXPERIMENTAL[2]

4-Chloro-3-nitrobenzotrifluoride(II), commercially available from several suppliers, can be prepared in 75% yield from I by the method of Benkeser and Buting.[3]

4-Hydroxy-3-nitrobenzotrifluoride(III) was obtained from II in 90% yield using the literature procedure[4] with one modification. Extraction of the reaction mixture with ether before acidification removes unreacted II. Crude III thus produced shows essentially one spot on tlc (SiO_2, Benzene, I_2-lower R_f than II) and can be used directly in the next step. IR (mull) cm^{-1} 1625, 1345, 1175, 1125, 905, 828; NMR ($CDCl_3$) δ 7.31 (d, 1, H_5), 7.86 (dd, 1, H_6), 8.41 (d, 1, H_2), 10.8 (s, 1, OH).

3-Amino-4-hydroxybenzotrifluoride(IV).[5]- A solution of 400 g of III in 3560 ml of ethyl alcohol was hydrogenated in the presence of 25 g of Raney nickel at an initial hydrogen pressure of 50 psi. The reaction was exothermic and the theoretical uptake of hydrogen was achieved in 4 hrs. After removal of the catalyst, the filtrate was concentrated to provide IV as a dark brown solid. This can be used as such for the preparation of V. A pure sample of IV was obtained by recrystallization from benzene-Skelly B; colorless crystals, mp. 120-122°, lit.[5] mp. 121-122°. IR ($CHCl_3$) cm^{-1} 3510, 3270, 1620, 1330, 1178, 1125, 840; NMR ($CDCl_3$/DMSO-d_6) δ 5.58 (bs, 3, OH, NH_2), 6.85 (overlapping complex, 3, arH); Tlc (SiO_2, Benzene, I_2) one spot.

4-Hydroxybenzotrifluoride(V).- To a stirred mixture of 500 g of crude IV, 1100 ml of conc. HCl and 350 ml of H_2O, cooled to between 0° and -10°, was added a solution of 205 g of $NaNO_2$ in 500 ml of H_2O at such a rate as to maintain the temperature at -10 to 0° (addition time 0.75 hr). The mixture was stirred an additional 0.5 hr and 3 liters of 50% hypophosphorous acid, cooled to 0° was added over 0.75 hr. The solution was kept at 0°

overnight and then steam distilled. When approximately 10 liters had distilled, the product was isolated from the distillate by extraction with ether (2-3 liters). Washing the ethereal extracts with H_2O, drying over $MgSO_4$ and concentration afforded 281 g (61%) of V as an oil that solidified on cooling. For most applications this crude V is of suitable purity. Pure material may be obtained by vacuum distillation, bp. 73-75°/8 mm, lit.[1a] bp. 71.5-72°/8 mm. Tlc (SiO_2, benzene, I_2) one spot at greater R_f than IV; IR ($CHCl_3$) cm^{-1} 3240, 1645, 1558, 1330, 1175, 1150; NMR ($CDCl_3$) δ 6.45 (s, 1, OH), 6.90 (d, 2, arH), 7.50 (d, 2, arH).

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