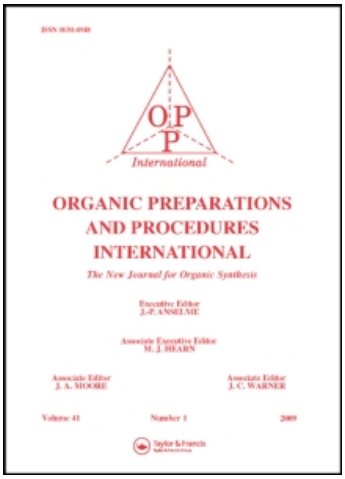

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Elsa Anselmi[a]; Jean-Claude Blazejewski[a]; Claude Wakselman[a]
[a] SIRCOB, ESA CNRS 8086, Universite' de Versailles, Versailles, France

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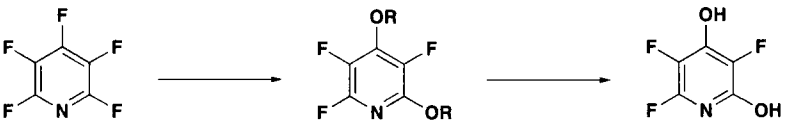
IMPROVED SYNTHESIS OF 3,5,6-TRIFLUOROPYRIDIN-2,4-DIOL

Submitted by Elsa Anselmi, Jean-Claude Blazejewski, Claude Wakselman*
(03/27/00) *SIRCOB, ESA CNRS 8086, Université de Versailles*
45 Avenue des Etats-Unis, 78035 Versailles, France.

As part of our ongoing studies on halogenated acrylic monomers and polymers destined for the elaboration of low optical losses waveguide materials,[1, 2] we needed quantities of 3,5,6-trifluoropyridin-2,4-diol (**3**). This compound may also find use as a template for the preparation of similarly transparent crosslinking agents.[3] Although the preparation of **3** had already been described by the reaction of sodium hydroxide with pentafluoropyridine (**1**), it was only obtained in a modest yield (20%) and on a small scale.[4] We thought that another, more scalable, way to prepare the pyridine derivative **3** could rely on a described experimental protocol where potassium *tert*-butoxide was used as the nucleophile.[5] In this way, trifluoro-2,4-di-*tert*-butoxypyridine **2a** was obtained in an excellent yield as described.[5]



1 **2a** (R = *t*-Bu) **2b** (R = CH_2Ph) **3**

The anticipated facile removal of the *t*-butyl protecting groups in an acidic medium (a reaction not described in the original publication) proved however, to be very sluggish, the fully deprotected pyridindiol **3** being obtained only after a two week reaction. For our purpose this way was thus not satisfactory. Benzyl ethers are known to be easily cleaved by catalytic hydrogenolysis.[6] We thus turned to sodium benzylate as the nucleophile in order to obtain the disubstituted compound **3** *via* the dibenzyl ether **2b** (Scheme, R = CH_2Ph). In our initial trials, we used metallic sodium in an excess of benzyl alcohol to prepare the required nucleophilic reagent. Although the desired compound **2b** was obtained in a satisfactory yield (98%), we experienced some difficulties in removing the excess benzyl alcohol (used as the reaction solvent) during the purification process. Ultimately, the easiest experimental protocol was to carry out the reaction using first sodium hydride with a small excess of benzyl alcohol in freshly distilled THF in order to prepare the nucleophilic reagent, followed by the addition of pentafluoropyridine (**1**). In this way, the trifluoropyridine derivative **2b** was obtained in a excellent yield (97%) on a 23 g scale. Compound **2b** was then smoothly deprotected by catalytic hydrogenation using 10% Pd on charcoal in THF leading very cleanly to the diol **1** (88 % yield on a 8 g scale).

EXPERIMENTAL SECTION

NMR spectra were recorded as $CDCl_3$ solutions, on a Bruker AC-300 spectrometer. The reported coupling constants and chemicals shifts were based on a first order analysis. Internal reference was the residual peak of $CHCl_3$ (d 7.27) for ^1H (300 MHz), central peak of $CDCl_3$ (d 77) for ^{13}C (75 MHz) spectra and internal $CFCl_3$ (0 ppm) for ^{19}F (282 MHz) NMR spectra. IR spectra were obtained as CCl_4 solutions on an Impact 400D Nicolet spectrophotometer. Tetrahydrofuran (SDS, 96%) was freed of 2,6-di-*tert*-butyl-*p*-cresol (used as an oxidation inhibitor) by distillation. Elemental analysis were obtained at ICSN, Gif-sur-Yvette, France.

3,5,6-Trifluoropyridin-2,4-diol Dibenzyl Ether (2b).- Benzyl alcohol (22.4 g, 207 mmol) was added dropwise to a suspension of sodium hydride (4.97 g, 207 mmol) previously washed with pentane, in 250 mL of freshly distilled tetrahydrofuran. The mixture was stirred for 15 min at room temperature, then 7.6 mL of pentafluoropyridine **1** (11.7 g, 69 mmol) was added *via* a syringe. The resulting pale yellow solution was diluted with diethyl ether, washed with water, and extracted three times with diethyl ether. The combined ethereal layers were dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo*. The resulting oil was purified by a short path distillation at 0.04 mm Hg (bath warmed at 100°) to give 23.16 g (67 mmol, 97%) of the *dibenzyl ether* **2b** as a solid, mp. 48-49°; ^1H NMR d 7.58-7.75 (10 H, aromatic H), 5.64 and 5.59 (4 H, benzylic H); ^{19}F NMR d -165.7 (1F, d, J = 22.9 Hz, F5), -158.4 (1F, d, J = 25.4 Hz, F3), -93.9 (1F, t, J = 24.2 Hz, F6); ^{13}C NMR d 145.5 (1C, ddd, $^2J_{CF}$ = 14.7, $^3J_{CF}$ = 11.9, $^4J_{CF}$ = 2.6 Hz, C2), 145.0 (1C, td, $^2J_{CF}$ = 9.9, $^3J_{CF}$ = 5.7 Hz, C4), 144.4 (1C, ddd, $^1J_{CF}$ = 234.5, $^2J_{CF}$ = 13.9, $^3J_{CF}$ = 3.1 Hz, C5), 136.4 (1C, dd, $^1J_{CF}$ = 254, $^3J_{CF}$ = 6.8 Hz, C3), 135.7 (1C, s, Ar*C*), 135.2 (1C, s, Ar*C*), 132.3 (1C, dd, $^1J_{CF}$ = 252.3, $^2J_{CF}$ = 30.5 Hz, C6), 128.6 (1C, s, Ar*C*H), 128.4 and 128.3 (2C, s, Ar*C*H), 128.0 (1C, s, Ar*C*), 127.9 and 127.7 (2C, s, Ar*C* and Ar*C*H), 75.1 (1C, t, J_{CF} = 4.5 Hz, *C*H_2), 68.5 (1C, s, *C*H_2); IR (cm^{-1}) 1646 ($n_{C=C}$), 2968 (n_{CH}), 3096 ($n_{=CH}$); m/z (EI) 345 (M^+, 2%), 254 (M^+ - $PhCH_2$, 1%), 91 ($PhCH_2^+$, 100%).

Anal. Calcd for $C_{19}H_{14}F_3NO_2$: C, 66.09; H, 4.09; F, 16.50; N, 4.06. Found: C, 65.79; H, 4.08; F, 16.84; N, 3.91

3,5,6-Trifluoropyridin-2,4-diol (3).- Dibenzyl ether **2b** (19.7 g, 57 mmol) was hydrogenated over a catalytic quantity of 10% palladium on charcoal (90 mg, 0.08 mmol) in THF under a dihydrogen atmosphere (*ca.* 1 bar). The solution was stirred overnight at room temperature. After filtration through a pad of Celite and washing with THF, the solvent was removed under vacuum. The white solid so obtained was purified by sublimation (oil bath at 95° / 0.06 mm Hg) to yield 8.26 g (50 mmol, 88%) of pure *trifluoropyridin-2,4-diol* **3** as a solid, mp. 182°, *lit.*[4] 188° ; ^{19}F NMR d -171.8 (1F, d, J = 24.2 Hz, F5), -164.4 (1F, d, J = 25.5 Hz, F3), -95.2 (1F, t, J *ca.* 24 Hz, F6); ^{13}C NMR d 144.6 (2C, m, C2 and C4), 143.7 (1C, ddd, $^1J_{CF}$ = 229.2, $^3J_{CF}$ = 12.4, $^4J_{CF}$ = 2.8 Hz, C3), 133.0 (1C, dd, $^1J_{CF}$ = 245.1, $^2J_{CF}$ = 6.4 Hz, C5) 129.2 (1C, dd, $^1J_{CF}$ = 245.3, $^2J_{CF}$ = 31.7 Hz, C6); IR (cm^{-1}) 3358 (n_{OH}), 3230 (n_{OH}); m/z (EI) 165 (M^+, 100%).

Anal. Calcd for $C_5H_2F_3NO_2$: C, 36.38; H, 1.22; F, 34.53; N, 8.49. Found: C, 36.37; H, 1.21; F, 34.61; N, 8.38

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REFERENCES

1. J.-C. Blazejewski, J. W. Hofstraat, C. Lequesne, C. Wakselman and U. E.Wiersum,. *J. Fluorine Chem.*, **91**, 175 (1998).

2. J.-C. Blazejewski, J. W. Hofstraat, C. Lequesne, C. Wakselman and U. E. Wiersum, *ibid.*, **97**, 191 (1999).

3. J. Scheirs, "Modern Fluoropolymers", Wiley, New York, **1997**.

4. R. E. Banks, J. E. Burgess, W. M. Cheng. and R. N. Haszeldine, *J. Chem. Soc.*, 575 (**1965**).

5. C. L. Cheong and B. J. Wakefield, *J. Chem. Soc. Perkin. Trans 1,* 3301 (**1988**).

6. H. Sajiki, H. Kuno and K. Hirota, *Tetrahedron Lett.*, **39**, 7127 (1998) and references therein.

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