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Partially halogenated heterocycles. Synthesis of 5,7-difluoro, 5,6,7-trifluoro- and 7-chloro-6,8-difluoroquinolines

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Abstract

3,5-Difluoro,3,4,5-trifluoro- and 3-chloro-2,4-difluoroanilines react in modified Skraup condensations to produce the corresponding fluorinated quinolines in high yields.

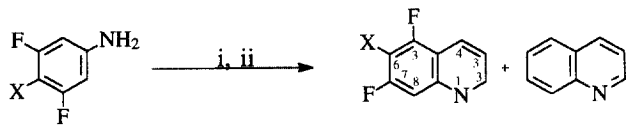
Keywords: Skraup reaction; 5,7-Difluoroquinoline; 5,6,7-Trifluoroquinoline; 7-Chloro-6,8-difluoroquinoline; *m*-Nitrobenzenesulfonic acid

1. Introduction

Some quinoline derivatives substituted with fluorine are well known as efficient antibacterial drugs. As starting materials to synthesize these bioactive molecules, polyfluorinated quinolines can be used [1,2].

We report here the convenient preparation of 5,7-difluoro-, 5,6,7-trifluoro- and 7-chloro-6,8-difluoroquinolines in 73–82% yields by Skraup reactions from the corresponding polyhalogenated anilines.

The Skraup method as modified by Cohn [3] consists in boiling a mixture of the appropriate aniline, glycerol, nitrobenzene, iron(II) sulfate, boric acid in concentrated sulfuric acid followed by steam distillation. 3,5-Difluoro- and 3,4,5-trifluoroanilines in this condensation gave 5,7-difluoro- and 5,6,7-trifluoroquinolines contaminated with 9–10% quinoline. Recrystallization from hexane provided pure compounds in 52–54% yield.



X = H, F (i) glycerol, 96% H_2SO_4, $FeSO_4$, H_3BO_3 (ii) NaOH, steam distillation.

To avoid the quinoline formation, nitrobenzene can be replaced by other oxidizing agents, such as arsenic pentoxide, iodine, iron(III) chloride, sodium *m*-nitrobenzenesulfonate or *m*-nitrobenzenesulfonic acid. The latter seems to be most suitable because its solution in sulfuric acid as used as a medium for Skraup condensation can be readily prepared in situ by heating nitrobenzene with 20% oleum, followed by quenching excess of oleum with concentrated H_2SO_4.

Utilization of the solution thus prepared rather than of nitrobenzene allowed us to obtain targeted products with >99% GLC purity in 80–82% yields for 5,7-difluoro- and 5,6,7-trifluoroquinolines and 73% yield for 7-chloro-6,8-difluoroquinoline immediately after steam distillation. To the best of our knowledge, 5,7-difluoroquinoline has previously been prepared [4] in 78% yield by refluxing the appropriate aniline, sodium m-nitrobenzenesulfonate and glycerol in 70% sulfuric acid. Thus, the difference of our procedure from that in [3] consists in using *m*-nitrobenzenesulfonic acid rather than nitrobenzene and from a procedure in [4] is that *m*-nitrobenzenesulfonic acid is prepared in situ and used in 99% H_2SO_4 instead of using sodium *m*-nitrobenzenesulfonate in 70% H_2SO_4, as well as, to moderate the exothermic reaction arising from proceeding in concentrated sulfuric acid, iron(II) sulfate and boric acid are added to the reaction mixture.

2. Experimental

GLC analysis was performed on a HP 5890 instrument using a HP G1800A GCD system (capillary GC column 0.26 mm/30 m, 0.25 μm film HP-5 phase). Melting points were

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determined in sealed capillaries and are uncorrected. ^1H and ^{19}F NMR spectra were recorded on a Bruker WP-200 SY spectrometer at 200.1 and 188.28 MHz, respectively. Chemical shifts are reported with respect to $(Me_3Si)_2O$ and C_6F_6 as an internal standards. UV spectra were obtained with a Specord M-40 spectrometer. HR-MS were obtained with a Finnigan Mat 8200 spectrometer.

A solution of *m*-nitrobenzenesulfonic acid was prepared as follows: 6.0 g of nitrobenzene was added with stirring to 30.0 g of 20% oleum and the mixture was heated at 120°C for 5 h. After cooling, the reaction mixture was poured into 12,5 g of 96% sulfuric acid. The concentration of *m*-nitrobenzenesulfonic acid in the resulting solution was 20.3% or 1 mmol/g.

2.1. Typical experimental procedure. Preparation of 5,7-difluoroquinoline

A dry, two-necked, 50 ml round-bottomed flask, equipped with stir-bar and condenser, was charged with 0.47 g of iron(II) sulfate, 1,80 g (13.9 mmol) of 3,5-difluoroaniline, and a solution of 0.86 g boric acid in 5.00 g of glycerol. To this mixture 8.30 g (8.3 mmol) of the solution of *m*-nitrobenzenesulfonic acid was added with stirring and cooling. The mixture was heated to boiling point and refluxed for 7 h, cooled to room temperature, and made alkaline with 35% sodium hydroxide. Steam-distillation gave 1.85 g (80%) of 5,7-difluoroquinoline (GLC purity > 99%), m.p. 78–79°C (lit. [4] 77–78°C). U.V. (MeOH): $\lambda_{max} = 228, 275, 305, 320$ nm. ^1H NMR (CCl_4/acetone-d_6) δ: 7.00 (td, $J = 9$ Hz, $J = 2.5$ Hz $1H^6$); 7.33 (dd, $J = 8.5$ Hz, $J = 4$ Hz, $1H^3$); 7.51 (d, $J = 10$ Hz, $1H^8$);[2] 8.28 (d, $J = 8.5$ Hz, $1H^4$);[3] 8.85 (dd, $J = 4$ Hz, $J = 1$ Hz, $1H^2$) ppm. ^{19}F NMR (CCl_4/acetone-d_6) δ: 42.10 (t, $J = 10$ Hz, $1F^7$); 54.34 (d, $J = 9$ Hz, $1F^5$) ppm.

[2] Couplings assigned in the signals of H^6 and H^2 to H^8 and H^4 respectively here are obscured by line broadening.

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2.2. Preparation of 5,6,7-trifluoroquinoline

The procedure described for 5,7-difluoroquinoline was used. From 2.00 g (13.6 mmol) of 3,4,5-trifluoroaniline 2.04 g (82%) of 5,6,7-trifluoroquinoline (GLC purity > 99%), m.p. 81–82°C was prepared. U.V. (MeOH): $\lambda_{max} = 225, 275, 300, 314$ nm. ^1H NMR (CCl_4/acetone-d_6) δ: 7.40 (dd, $J = 8.5$ Hz, $J = 4$ Hz, $1H^3$); 7.62 (ddd, $J = 11$ Hz, $J = 7$ Hz, $J = 2$ Hz, $1H^8$); 8.30 (dd, $J = 8.5$ Hz, $J = 1$ Hz, $1H^4$); 8.83 (dd, J = 4 Hz, J = 1 Hz, $1H^2$) ppm. ^{19}F NMR (CCl_4/acetone-d_6) δ: 2.23 (td, $J = 18$ Hz, $J = 7$Hz, $1F^6$); 16.21 (dd, $J = 18$ Hz, $J = 8$ Hz, $1F^5$)[4]; 31.69 (ddd, $J = 18$ Hz, $J = 11$ Hz, $J = 8$ Hz, $1F^7$) ppm. HR-MS: Calc. For $C_9H_4F_3N$ 183.02958. Obs., 183.02960.

2.3. Preparation of 7-chloro-6,8-difluoroquinoline

The procedure described for 5,7-difluoroquinoline was used. From 2.20 g (13.5 mmol) of 3-chloro-2,4-difluoroaniline 1.96 g (72%) of 7-chloro-6,8-difluoroquinoline (GLC purity > 99%), m.p. 139–140°C was prepared. U.V. (95% EtOH): $\lambda_{max} = 204, 230, 275, 304, 317$ nm. ^1H NMR (acetone-d_6) δ: 7.46 (dd, $J = 9$ Hz, $J = 2$ Hz $1H^5$); 7.52 (dd, $J = 8$ Hz, $J = 4$ Hz $1H^3$); 8.20 (d, $J = 8$ Hz, $1H^4$); 8.85 (d, $J = 4$ Hz, $1H^2$) ppm. ^{19}F NMR (C_6F_6, acetone-d_6) δ: 42.47 (s, $1F^8$); 47.49 (d, $J = 9$ Hz, $1F^6$) ppm. HR-MS: Calc. For $C_9H_4ClF_2N$ 199.00003. Obs., 198.99991.

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[4] Coupling assigned in the signal of H^8 to F^5 here is obscured by line broadening.