Preliminary Note

The interaction of 2,6-dimethyl-3,5-dicarboxy-4-phenylpyridine with SF_4 in HF solution

L.M. Yagupolskii*, K.I. Petko, A.N. Retchitsky and I.I. Maletina

Institute of Organic Chemistry, Ukrainian Academy of Sciences, 253660 Kiev 94 (Ukraine)

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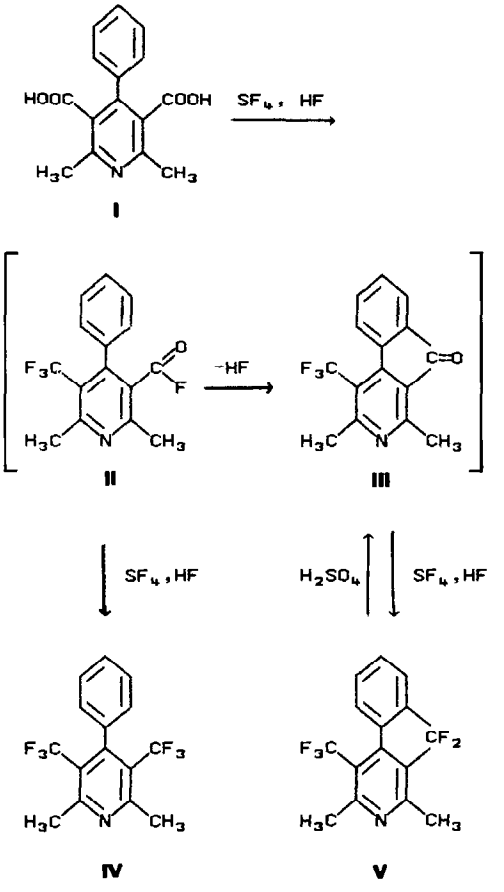
Abstract

Reaction of 2,6-dimethyl-3,5-dicarboxy-4-phenylpyridine with sulphur tetrafluoride in HF solution leads to 1,3-dimethyl-4-trifluoromethyl-9,9′-difluoro-2-azafluorene as the main product accompanied by a minor yield of 2,6-dimethyl-3,5-bis(trifluoromethyl)-4-phenylpyridine.



4-Aryl-1,4-dihydropyridine-3,5-dicarboxylic diesters are of great interest due to their high biological activity. Some of them have become almost indispensable for the treatment of cardiovascular diseases. The 1,4-dihydropyridines are the most effective amongst the calcium antagonists or calcium channel blockers. It has been shown [1], that biotransformations of these drugs lead to pyridine derivatives.

In the present study, we have approached the question of the possibility of replacing the carboxylic groups in compounds of type **I** by the much more lipophilic trifluoromethyl substituents. The best agent in this respect is SF_4 in HF solution. However, we have found that in this reaction besides the expected 2,6-dimethyl-3,5-bis(trifluoromethyl)-4-phenylpyridine (**IV**), 1,3-dimethyl-4-trifluoromethyl-9,9′-difluoro-2-azafluorene (**V**) was formed as the main product. Compound **V** is probably formed from the intermediate fluoroanhydride **II** via an intramolecular Friedel–Crafts-type cyclization to form ketone **III**. Similar cyclization of compound **I** to the corresponding ketone takes place when the former is heated with concentrated sulphuric acid [2]. Ketone **III** was probably converted into compound **V** on treatment with SF_4 in HF solution. The alternative route to **V** via a difluorocarbo cation may also be considered [3]. The CF_2 group in **V** can be easily converted back to the carbonyl group by heating with concentrated sulphuric acid.

Experimental

Sulphur tetrafluoride was prepared according to ref. 4. NMR spectra were obtained using a Bruker WP-200 NMR spectrometer at 200 MHz for ^1H and 188.28 MHz for ^{19}F using $Me_3SiOSiMe_3$ and $CFCl_3$ as internal

*Author to whom correspondence should be addressed.

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standards. IR spectra were recorded with a UR-20 spectrometer as KBr disks.

Reaction of 2,6-dimethyl-3,5-dicarboxy-4-phenylpyridine (I) with SF_4 in HF solution

Acid **I** (10.8 g) [2] was treated with a mixture of SF_4 (30 g) and anhydrous HF (35 g) in a stainless-steel pressure vessel for 10 h at 110 °C. Volatile products were removed and the reaction mixture was poured on to ice and then treated with 5 N KOH to pH 10. The products were extracted with ether (3×100 ml) and dried over anhydrous $MgSO_4$. The obtained mixture of **IV** and **V** was separated by column chromatography (SiO_2 L40/100, CH_2Cl_2/pentane 10:1).

3,5-Bis(trifluoromethyl)-4-phenylpyridine (**IV**) was distilled *in vacuo*, b.p. 72 °C/0.05 mmHg, yield 23%. ^{1}H NMR δ: 2.71 (s, 6H, CH_3); 7.5–7.8 (m, 5H, H arom.) ppm. ^{19}F NMR δ: −52.0 (s, 6F, CF_3) ppm. Analysis: Found: C, 56.55; H, 3.74; F, 35.37%. $C_{15}H_{11}F_6N$ requires: C, 56.42; H, 3.44; F, 35.73%.

1,3-Dimethyl-4-trifluoromethyl-9,9'-difluoro-2-azafluorene (**V**) was recrystallized from hexane, m.p. 148–149 °C, yield 41%. ^{1}H NMR δ: 2.74 (s, 6H, CH_3); 7.54–7.66, 7.98 (m, m, 4H, H arom.) ppm. ^{19}F NMR δ: −55.44 (s, 3F, CF_3); −115.0 (s, 2F, CF_2) ppm. Analysis: Found: C, 60.29; H, 3.36; F, 31.77%. $C_{15}H_{10}F_5N$ requires: C, 60.20; H, 3.34; F, 31.77%.

Hydrolysis of 1,3-dimethyl-4-trifluoromethyl-9,9'-difluoro-2-azafluorene (V)

Compound **V** (0.3 g) was treated with conc. H_2SO_4 (4 ml) at 40–60 °C for 40 min. The reaction mixture was poured into water (50 ml), neutralized with ammonia and extracted with ether (3×20 ml). The extract was washed with water and dried over anhydrous $MgSO_4$. The ether was removed and the product recrystallized from pentane, m.p. 140 °C, yield 70%. ^{19}F NMR δ: −54.8 (s, 3F, CF_3) ppm. IR (ν, cm^{-1}): 1725 (C=O). Analysis: Found: C, 64.96; H, 3.44; F, 20.63%. $C_{15}H_{10}F_3NO$ requires: C, 64.96; H, 3.61; F, 20.57%.

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