Journal of Fluorine Chemistry, *36* (1987) 93–98

Received: September 20, 1986; accepted: February 9, 1987

SYNTHESIS OF POLYFLUORODIBENZ [b,f][1,4]OXAZEPINES BY CYCLIZATION OF POLYFLUORINATED o-HYDROXYBENZYLIDEN-ANILINES

N.I. PETRENKO, M.M. KOZLOVA and T.N. GERASIMOVA

Institute of Organic Chemistry, Siberian Division of the USSR Academy of Sciences, 630090, Novosibirsk (USSR)

SUMMARY

Thermolysis of polyfluorinated o-hydroxybenzylidenanilines leads to cyclization via intramolecular dehydrofluorination. This reaction affords a convenient method for the preparation of hitherto unknown polyfluorodibenz [b,f][1,4]oxazepines.

INTRODUCTION

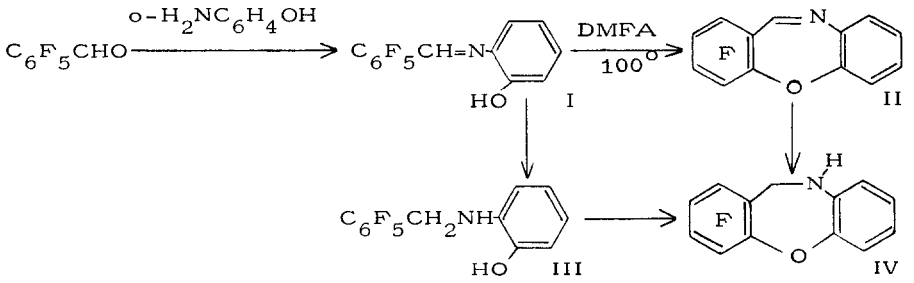
The reaction of intramolecular nucleophilic substitution of ortho-fluorine is known as a specific method for the preparation of poly-fluorinated 5- and 6-membered benzheterocycles [1,2]. However we know only two examples of the formation of 7-membered heterocycles in this way [3,4]. During studies on the chemistry of polyfluoro-aromatic azomethines we have investigated the possibility of such an approach to previously unknown polyfluorodibenz [b,f][1,4]oxazepines whose non-fluorinated analogues show an interesting pharmacological activity [5].

RESULTS AND DISCUSSION

Short heating of o-hydroxy-N(2,3,4,5,6-pentafluorobenzyliden)-aniline (I) (prepared in the usual way from pentafluorobenzaldehyde and o-aminophenol) in dimethylformamide (DMFA) at 100° leads to ejection of fluorine and formation of 1,2,3,4-tetrafluorodibenz [b,f][1,4]-

0022-1139/87/$3.50

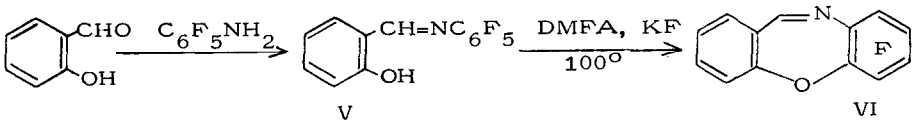
oxazepine (II) quantitatively. Boiling of anil (I) in alcohol or keeping for a long time in DMFA at room temperature gives the same product.



The cyclization of the sodium salt of o-hydroxy-N(2-chloro-5-nitrobenzyliden)aniline to 2-nitrodibenz [b,f][1,4]oxazepine in boiling DMFA has been described [6]. The ease of intramolecular cyclization of compound (I) can be attributed to the considerable mobility of fluorine lying ortho to the carbon of a C=N group, the high acidity of the phenolic OH group, providing a sufficient concentration of anions under the conditions used, and favourable mutual steric disposition of the reaction centers.

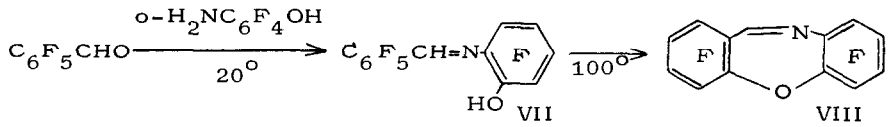
In accord with this explanation, o-hydroxy-N(2,3,4,5,6-pentafluorobenzyl)aniline (III) prepared from compound (I) and $LiAlH_4$, fails to react under the same conditions. Conversion of compound (III) into 1,2,3,4-tetrafluoro-10,11-dihydrodibenz [b,f][1,4]oxazepine (IV) is observed with anhydrous potassium carbonate as a condensing agent.

The possibility of synthesizing other polyfluorodibenz [b,f][1,4]-oxazepines by the proposed method was investigated. Pentafluoro-N(2-hydroxybenzyliden)aniline (V) with the polyfluorinated aromatic ring carried at the nitrogen of a C=N group was obtained from salicylic aldehyde and pentafluoroaniline. It does not change under the conditions of cyclization used for anil (I) and forms 6,7,8,9-tetrafluorodibenz [b,f][1,4]oxazepine (VI) only in the presence of dried potassium fluoride, frequently used in the synthesis of fluorinated benzheterocycles [7].



V VI

Heating of 2-hydroxynonafluorobenzylidenaniline (VII) (obtained from pentafluorobenzaldehyde and tetrafluoro-o-aminophenol) in organic solvents gives only an intractable tar. However it is completely converted into octafluorodibenzoxazepine (VIII) by thermolysis at 100° without a solvent.



VII VIII

The method of synthesis of polyfluorinated dibenz [b,f][1,4]-oxazepines, proposed in this paper, has made these compounds sufficiently available to allow their properties to be investigated.

EXPERIMENTAL

^{19}F and ^{1}H NMR spectra were recorded on a "Varian A 56/60 A" spectrometer at the frequency of 56.4 and 60 MHz respectively. Internal standards were hexafluorobenzene and hexamethyldisiloxane. Molecular weights were determined mass spectrometrically on GC/MS Finnigan Mat, model 8200.

All the products synthesized in this study are new compounds.

Polyfluoro-o-hydroxybenzylidenanilines

1. An equimolecular mixture of pentafluorobenzaldehyde and o-aminophenol was shaken for 30 min and treated by ethanol. A crystalline material was filtered off, washed with n-hexane and crystallized from ethanol. The yield of o-hydroxy-N(2,3,4,5,6-pentafluorobenzyliden)aniline (I) was 90%, m.p. 185-186° (with decomposition). Found: C, 54.31; H, 2.11; F, 32.83; N, 4.97%; M, 287. $C_{13}H_6F_5NO$ requires C, 54.37; H, 2.11; F, 33.08; N, 4.83%; M 287. IR (KBr), ν, cm^{-1}: 3380 (OH). ^{19}F NMR (THF), δ, p.p.m.: 0.0 ($2F_m$), 11.3 (F_p) and 20.9 ($2F_o$).

2. Salicylic aldehyde (3.6 g) and pentafluoroaniline (5.5 g) were heated at 140° for 10 h. The mixture was cooled, washed with n-hexane to give pentafluoro-N(o-hydroxybenzyliden)aniline (V) (5.2 g, 69%), m.p. 139-140° (from ethanol). Found: C, 54.37; H, 1.92; F, 32.70; N, 4.82%; M 287. ^{19}F NMR (THF), δ, p.p.m.: -0.5 ($2F_m$), 3.2 (F_p) and 10.6 ($2F_o$).

3. A solution containing 1.7 g of pentafluorobenzaldehyde, 1.6 g of tetrafluoro-o-aminophenol and 15 ml ethanol was stirred at 20° for 3 h, poured into water, the precipitate was filtered off and dried. The yield of pentafluoro-N(2-hydroxytetrafluorobenzyliden)aniline (VII) was 73% (2.3 g), m.p. 124-126° (from petroleum ether, b.p. 70-100°). Found: C, 43.50; H, 0.63; F, 47.70; N, 3.57%. $C_{13}H_2F_9NO$ requires C, 43.47; H, 0.56; F, 47.61; N, 3.90%. ^{19}F NMR (THF), δ, p.p.m.: -9.2 (1F), -1.2 (1F), 0.4 (2F), 2.1 (1F), 9.9 (1F), 12.8 (1F) and 21.6 (2F).

o-Hydroxy-N(2,3,4,5,6-pentafluorobenzyl)aniline (III)

2.3 g of anil (I) was added to a vigorously stirred suspension of $LiAlH_4$ (0.64 g) in 80 ml of dry ether at 20°. The mixture was then stirred for 30 min, poured into a mixture of ice and hydrochloric acid and the product was extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated. The yield of (III) was 82% (1.9 g), m.p. 120-122° (from petroleum ether, b.p. 70-100°). Found: C, 54.14; H, 2.82; F, 32.82; N, 4.84%; M 289. $C_{13}H_8F_5NO$ requires C, 53.99; H, 2.79; F, 32.85; N, 4.84%; M 289. IR (CCl_4), ν, cm^{-1}: 3440 (NH), 3610 (OH). ^{1}H NMR (CCl_4), δ, p.p.m.: 4.39 (s, CH_2), 4.54 (br s, NH, OH) and 6.59 (m, Ar). ^{19}F NMR (THF), δ, p.p.m.: -0.4 ($2F_m$), 6.0 (F_p) and 21.3 ($2F_o$).

Polyfluorodibenz[b,f][1,4]oxazepines

1. A mixture of 0.29 g of anil (I) and dried DMFA (10 ml) was heated at 100° for 15 min and poured into water. The precipitate was filtered off and dried to give 1,2,3,4-tetrafluorodibenz[b,f][1,4]-oxazepine (II), the yield was 0.27 g (99%), m.p. 126-127° (from ethanol). Found: C, 58.66; H, 1.91; F, 28.45; N, 5.24%; M 267. $C_{13}H_5F_4NO$ requires C, 58.44; H, 1.89; F, 28.45; N, 5.24%; M 267.

^{1}H NMR ($(CD_3)_2CO$), δ, p.p.m.: 7.28 (br s, Ar) and 8.64 (s, =CH). ^{19}F NMR (THF), δ, p.p.m.: 1.1, 5.8, 12.4 and 18.6.

2. To 0.20 g of anil (V), dissolved in 10 ml dry DMFA, was added 0.20 g dried potassium fluoride and the mixture was stirred for 20 min at 100°, then poured into water and the precipitate was filtered off. The yield of 6,7,8,9-tetrafluorodibenz[b,f][1,4] oxazepine (VI) was 0.16 g (80%), m.p. 140-141° (from ethanol). Found: C, 58.33; H, 1.95; F, 28.34; N, 5.17%; M 267. ^{19}F NMR (THF), δ, p.p.m.: -0.4, 3.2, 4.1 and 15.5.

3. 0.50 g of anil (VII) was warmed for 1 h at 100°, the product was dissolved in benzene and chromatographed on a column of SiO_2 (L 40/100) to give 0.44 g (93%) of 1,2,3,4,6,7,8,9-octafluorodibenz-[b,f][1,4]oxazepine (VIII), m.p. 100-101° (from ethanol). Found: C, 44.83; H, 0.20; F, 46.09; N 4.14%; M 339. $C_{13}HF_8NO$ requires C, 44.82; H, 0.30; F, 46.04; N, 4.13%; M 339. ^{19}F NMR (THF), δ, p.p.m.: 2.1, 3.5, 5.3, 6.4, 8.0, 15.1, 16.7 and 20.6.

1,2,3,4-Tetrafluoro-10,11-dihydrodibenz[b,f][1,4] oxazepine (IV)

(a) 0.27 g of compound (II) were added to a suspension of $LiAlH_4$ (0.04 g) in dry ether (20 ml) at 20°. The mixture was stirred for 1 h, poured into mixture of ice and hydrochloric acid and the product extracted with ether. The ethereal solution was then washed with water; after drying ($MgSO_4$), distillation of the ether layer yielded 0.23g (85%) oxazepine (IV), m.p. 67-68° (after sublimation at 90°/2 mm Hg). Found: C, 58.33; H, 2.50; F, 28.21; N, 5.11%; M 269. $C_{13}H_7F_4NO$ requires C, 58.00; H, 2.62; F, 28.23; N, 5.20%; M 269. IR (CCl_4), ν, cm^{-1}: 3340 (NH). ^{1}H NMR (CCl_4), δ, p.p.m.: 3.70 (s, NH), 4.44 (s, CH_2) and 6.70 (ABCD, Ar). ^{19}F NMR (THF), δ, p.p.m.: -0.5, 4.4, 5.3 and 15.8.

(b) 0.20 g of compound (III) and 0.20 g of anhydrous potassium carbonate in dry DMFA were heated at 150° for 2 h. The mixture was poured into water with hydrochloric acid and extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated to yield 0.18 g of compound, shown by NMR spectroscopy to be identical with (IV).

REFERENCES

1 G.G. Yakobson, T.D. Petrova and L.S. Kobrina, Fluor. Chem. Revs, 7 (1974) 115.
2 M. Hudlicky, Israel. J. of Chem., 17 (1978) 80.
3 T.D. Petrova, V.P. Mamaev, G.G. Yakobson and N.N. Vorozhtsov, Khim. Geterotsikl. Soedin., (1968) 771.
4 A.C. Alty, R.E. Banks, B.R. Fishwick, R.G. Pritchard and A.R. Thompson, J. Chem. Soc. Chem. Commun., (1984) 832.
5 C.O. Okafor, Heterocycles, 7 (1977) 391.
6 K. Nagarajan, A. Venkateswarlu, C.L. Kulkarni and R.K. Shah, Indian J. of Chem., 12 (1974) 227.
7 G.G. Yakobson and N.E. Akhmetova, Synthesis, (1983) 169.