REACTION OF TETRAFLUORODIBENZ[b,f][1,4]OXAZEPIN-11(10H)-ONES WITH NUCLEOPHILES

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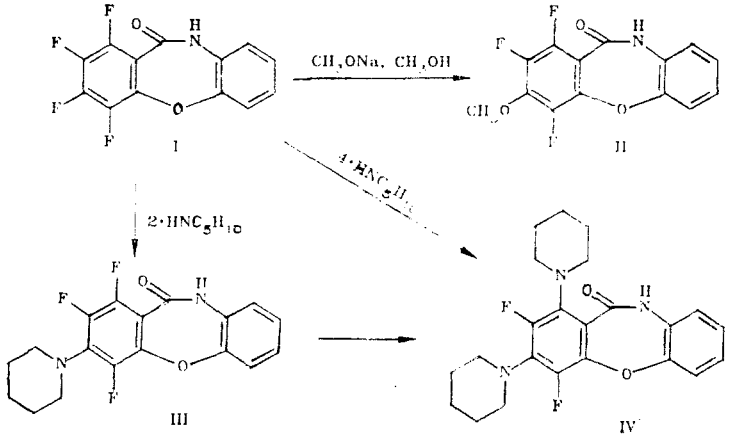
Reaction of 1,2,3,4-tetrafluorodibenz[b,f][1,4]oxazepin-11(10H)-one with nucleophilic reagents (MeONa in refluxing MeOH; piperidine in DMF at 100°C) leads to substitution of the fluorine atom para to the CONH group. 6,7,8,9-Tetrafluorodibenz[b,f][1,4]oxazepin-11(10H)-one is inert to these conditions.

Dibenz[b,f][1,4]-oxazepin-11(10H)-ones show psychotropic properties [1]. Thus 10-[3-(dimethylamino)propyl]-2-nitrodibenz[b,f][1,4]oxazepin-11(10H)-one is used medicinally as an antidepressant [2]. It has been shown that substituents in the seven-membered ring or in the aromatic rings of the dibenzoxazepine system have a significant effect on biological activity [3].

A method for synthesis of 1,2,3,4- and 6,7,8,9-tetrafluorodibenz[b,f][1,4]-oxazepin-11(10H)-ones (I, V) has been reported by us [4]. In the present work we have tried to obtain fluorinated derivatives with substituents in the aromatic ring. The most widely used method for functionalizing polyfluoroaromatics is the nucleophilic substitution of a fluorine atom [5]. As nucleophilic reagents we have used sodium methylate and piperidine.

Refluxing compound I with sodium methylate in methanol for 1 h leads to substitution of a single fluorine atom to form 3-methoxy-1,2,4-trifluorodibenz[b,f][1,4]-oxazepin-11(10H)-one (II) in quantitative yield.

Reaction of I with piperidine was carried out by heating at 100°C in DMF. An approximately twofold amount of piperidine gives 3-piperidino-1,2,4-trifluorodibenz[b,f][1,4]-oxazepin-11(10H)-one (III) and a fourfold amount gives the disubstituted compound IV.



Introduction of the nucleophile *para* to the electron acceptor CONH group agrees with general observations on the orientation of nucleophilic substitution in polyfluoroaromatics [5, 6].

6,7,8,9-Tetrafluorodibenz[b,f][1,4]-oxazepin-11(10H)-one (V), containing the fluorinated ring adjacent to the nitrogen atom of the amide group, does not react when refluxed with sodium methylate in methanol or heating with excess piperidine in DMF at 100°C. Raising the temperature to 120°C leads to a mixture of products and decomposition of the starting V.

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EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for KBr tablets. PMR spectra were recorded on a Varian 56/60 A (60 MHz) instrument with HMDS as internal standard. ^{19}F NMR spectra were taken on a Bruker AC-200 (188 MHz) spectrophotometer using tetrahydrofuran solvent and hexafluorobenzene internal standard. Molecular weights were determined mass spectrometrically (Finnigan MAT 820).

Correct elemental analytical data (C, H, F, N) were obtained for II-IV.

3-Methoxy-1,2,4-trifluorodibenz[b,f][1,4]-oxazepin-11(10H)-one (II, $C_{14}H_8F_3NO_3$). Compound I (1.13 g, 4 mmoles) was added to a solution of sodium methylate prepared from sodium (0.12 g, 5 mmoles) in methanol (30 ml) and refluxed for 1 h. The precipitate was filtered, washed with water, and dried to give II (1.18 g, ~100%) with mp 285-287°C (from chloroform). IR spectrum: 1680 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 4.21 (3H, s, OCH_3); 7.20 (4H, m, H_{arom}), 9.54 ppm (1H, br. s, NH). ^{19}F NMR spectrum (DMSO-d_6): 6.6 (7.0)* (d, J_{12} = 22 Hz, 2-F); 9.3 (9.6) (d, J_{14} = 10 Hz, 4-F); 20.4 (21.0) ppm (dd, 1-F). Intensity ratio 1:1:1. Mass spectrum 295: (M^+).

3-Piperidino-1,2,4-trifluorodibenz[b,f][1,4]-oxazepin-11(10H)-one (III, $C_{18}H_{15}F_3N_2O_2$). A solution of piperidine (0.35 ml, 4 mmoles) in DMF (4 ml) was added dropwise with stirring to a solution of I (0.50 g, 1.8 mmoles) in DMF (35 ml) and heated at 100°C for 3 h. The product was poured into water (50 ml) and neutralized with 10% HCl. The precipitate was filtered off, washed with water, and dried to give III (0.42 g, 70%) with mp 227-229°C (from ethanol). IR spectrum: 1660 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 1.80 (6H, m, $3CH_2$), 3.73 (4H, m, $2CH_2$ piperidine group), 6.93 (4H, m, H_{arom}), 9.33 ppm (1H, br.s, NH). ^{19}F NMR spectrum: 13.1 (14.9) (d, J_{12} = 20 Hz, 2-F), 16.4 (17.5) (d, J_{14} = 10 Hz, 4-F), 21.1 (20.4) ppm (dd, 1-F). Intensity ratio: 1:1:1. Mass spectrum: 348 (M^+).

1,3-Dipiperidino-2,4-difluorodibenz[b,f][1,4]-oxazepin-11(10H)-one (IV, $C_{23}H_{25}F_2N_3O_2$). A. A solution of piperidine (0.88 ml, 8.9 mmoles) in DMF (5 ml) was added dropwise to a solution of I (0.63 g, 2.2 mmoles) in DMF (45 ml) and heated at 100°C for 7 h. The product was neutralized with 10% HCl and the precipitate filtered, washed with water, and dried to give IV (0.50 g, 66%) with mp 260-262°C (from ethanol). IR spectrum: 1660 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.53 (12H, m, $6CH_2$), 3.00 (8H, m, $4CH_2$), 7.10 (4H, m, H_{arom}), 9.53 ppm (1H, br.s, NH). ^{19}F NMR spectrum: 13.4 (15.0) (4-F), 30.1 (27.3) ppm (2-F). Intensity ratio 1:1. Mass spectrum: 413 (M^+).

B. A solution of piperidine (0.057 ml, 0.56 mmole) in DMF (5 ml) was added dropwise to a solution of III (0.05 g, 0.14 mmole) in DMF (10 ml) and heated at 100°C for 7 h. The same workup gave IV (0.04 g, 66%).

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*Here and subsequently the figure in parentheses refers to ^{19}F chemical shifts calculated by an additive scheme [4, 7].