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PREPARATION AND USE OF α-BROMOMONO- AND -BROMOBIS-DIFLUOROMETHOXYACETOPHENONES IN THE SYNTHESIS OF POLYMETHYLENEIMIDAZOLES WITH AN ANGULAR NITROGEN ATOM

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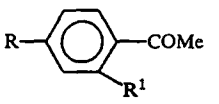
The synthesis of α-bromo-4-difluoromethoxy- and α-bromo-2,4-bis(difluoromethoxy)acetophenones has been carried out. Conditions have been studied for condensing the latter with cyclic tri- and tetramethylenamidinines and with pyridine-containing derivatives. A series of pyrrolo[1,2-a]imidazole and imidazo[2,1-a]pyridine derivatives containing difluoromethoxy groups has been synthesized.

Among condensed imidazole derivatives with an angular nitrogen atom are found substances displaying antiinflammatory, analgesic [1], and cardiotonic activity [2]. In particular, antagonists of angiotensin II [3] and CNC activators [4] have been found in the imidazo[1,2-*a*]pyridine series.

Compounds containing the difluoromethoxy group $OCHF_2$ have been used recently for the synthesis of substances useful in practice such as liquid crystals or biologically active compounds [5]. Thus, the effective hypotensive preparation foridon and analogs of it have been developed from o-difluoromethoxybenzaldehyde [6-7]. The majority of substances containing a difluoromethoxy group have been obtained from the corresponding aromatic aldehydes [8]. However difluoromethoxy substituted aromatic ketones have not been used in practice in the synthesis of potentially biologically active compounds.



I–IV

I R = OH, R^1 = H; II R = R^1 = OH; III R = $OCHF_2$, R^1 = H; IV R = R^1 = $OCHF_2$

The method of [9] for difluoromethylation at the oxygen atom of phenolic hydroxyl groups with difluorocarbene was used. The carbene was generated from Freon 22 (chlorodifluoromethane) by the action of excess sodium hydroxide in a water–dioxan medium at 60-70°C. 4-Difluoromethoxy- (III) and 2,4-bis(difluoromethoxy)acetophenones (IV) were obtained from the appropriate hydroxyketones (I) or (II) in 45-70% yield. Ketone (IV), unknown previously, was a liquid stable on storage and was characterized as its 2,4-dinitrophenylhydrazone. We showed that mono- (III) and bis(difluoromethoxy)-acetophenone (IV) were brominated by dioxan dibromide in good yield with the formation of the corresponding α-bromoketones (V) and (VI). The latter are stable compounds and were used as synthons to make various nitrogen-containing heterocyclic compounds by the Chichibabin method.

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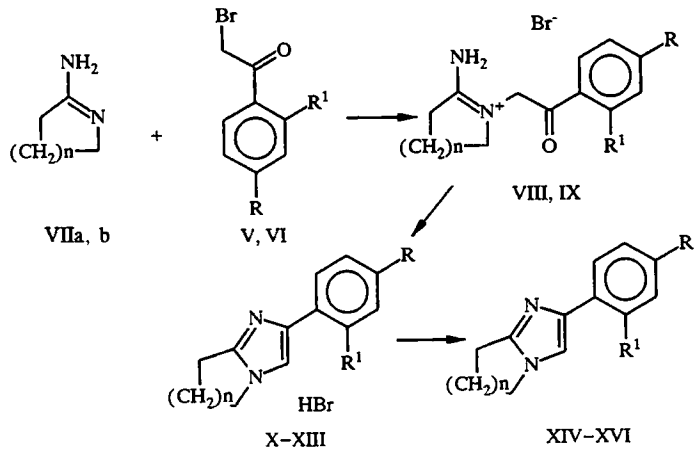


VIIa, b V, VI VIII, IX X-XIII XIV-XVI

V R = $OCHF_2$, R^1 = H; VI R = R^1 = $OCHF_2$; VIIa n = 1; VIIb n = 2; VIII n = 1, R = $OCHF_2$, R^1 = H; IX, X n = 1, R = R^1 = $OCHF_2$; XI n = 2, R = $OCHF_2$, R^1 = H; XII n = 1, R = OH, R^1 = H; XIII n = 2, R = OH, R^1 = H; XIV n = 1, R = $OCHF_2$, R^1 = H; XV n = 2, R = $OCHF_2$, R^1 = H; XVI n = 1, R = R^1 = $OCHF_2$

Conditions have been studied for condensing the α-bromoketones (V) and (VI) with cyclic tri- and tetramethylenamidines (VIIa, b) [10] in solvents of various polarity over a wide temperature range. It was shown that it was optimal to carry out the condensation in ether or chloroform at 20-25°C. An increase in the reaction temperature leads to significant resinification. The quaternary salts (VIII) and (IX) obtained by the condensation were colorless crystalline substances, stable on storage. On boiling in water, with addition of 1-2 drops 48% hydrobromic acid they were cyclized into aryltri- and aryltetramethylenimidazoles (X) and (XI) with retention of the difluoromethoxy group. With a large excess (up to 5 ml 48% HBr) cyclization was accompanied by destruction of the difluoromethoxy group with the formation of the corresponding hydroxy derivatives (XII) and (XIII). The structure of the products obtained was confirmed by data of PMR spectra. The quaternary salts (VIII) and (IX) were characterized by signals for the methylene groups of the pyrroline nucleus at 2.4-4.0 ppm and two-proton singlets for the methylene group of the phenacyl group at 5.25 ppm. Cyclization of salt (IX) into 2-[2,4-bis(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole hydrobromide (X) was accompanied by disappearance of the methylene group signal at 5.25 ppm and the appearance of a one-proton singlet at 7.63 ppm. This was assigned to the proton at position 3 of the imidazole ring formed in the condensed system. Hydrolysis of the difluoromethoxy groups in compounds (XI) and (XIV) to hydroxy group [compounds (XII) and (XIII)] was accompanied by a change in the chemical shifts of the aromatic protons observed in the PMR spectra. When the $OCHF_2$ group was in the para position of the aromatic ring, a four-proton doublet of doublets was recorded at 7.32 and 7.68 ppm, while the appearance of hydroxyl groups entailed a displacement of the proton resonance signals to 7.12 and 7.59 respectively.

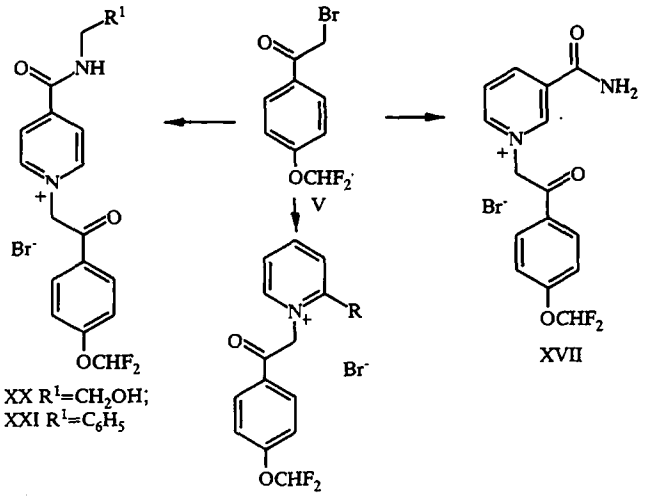
Difluoromethoxy groups in the benzene ring of the 2-aryl heterocycles (X) and (XI) proved to be more stable to the action of alkali. Bases (XIV)-(XVI) were obtained by treating aqueous solutions of salts (X)-(XIII) with 10% sodium hydroxide solution.

α-Bromo-4-(difluoromethoxy)acetophenone (V) was also used as a reagent for the N-alkylation of a series of pyridine derivatives. The reaction of α-bromoketone (V) with an equimolar quantity of 2-bromopyridine, α-picoline, and isonicotinic acid N-(β-hydroxyethyl)amide or N-benzylamide gave the corresponding quaternary salts (XVII)-(XXI).

Characteristic signals for the $OCHF_2$ group at 6.67-6.86 ppm were seen in the PMR spectra of salts (XVII)-(XXI) in addition to signals for the pyridine ring protons with appropriate substituents.

EXPERIMENTAL

The PMR spectra were taken on a Bruker 200 (200 MHz) spectrometer for solutions in trifluoroacetic acid (internal standard was TMS).



2,4-Bis(difluoromethoxy)acetophenone (IV). 2,4-Dihydroxyacetophenone (114 g: 0.75 mole), dioxan (700 ml), 46% NaOH solution (450 ml), and water (300 ml) were loaded into a 2 liter three-necked reactor fitted with a stirrer, a gas bubbler, and a reflux condenser connected to a Tishchenko (Drechsel) bottle to monitor the gas outflow. Freon 22 ($CHClF_2$) was then passed through the reaction mixture with stirring at 60-70°C for 3 h, then 46% NaOH solution (a further 150 ml) was poured in, and Freon 22 passed for a further 2 h. The mixture was cooled, the precipitate of mineral salt was filtered off, carefully squeezed out, and washed with ether (3 × 120 ml). The aqueous dioxan filtrate was poured into water and ice (1.6 liter), the organic layer was extracted with ether, the ether layer washed with 10% sodium hydroxide solution, then with water to a neutral reaction, and dried over anhydrous sodium sulfate. The ether was distilled off, and the residue redistilled in vacuum collecting the fraction of bp 139-143°C (12 mm Hg). Yield was 73 g (38.6%), n_D = 1.4812. Found, %: F 29.7. $C_{10}H_8F_4O_3$. Calculated, %: F 30.2.

2,4-Bis(difluoromethoxy)acetophenone 2,4-Dinitrophenylhydrazone, mp 109-111°C (from ethanol). PMR spectrum: 3.05 (3H, s, CH_3); 6.71 (1H, t, $OCHF_2$); 6.88 (1H, t, $OCHF_2$); 7.24-9.24 ppm (6H, m, arom.). Found, %: F 17.8. $C_{16}H_{12}F_4N_4O_6$. Calculated, %: F 17.6.

4-(Difluoromethoxy)acetophenone (III) was synthesized according to the procedure in [9].

α-Bromo-4-(difluoromethoxy)acetophenone (V). Bromine (13 ml, 0.255 mole) was added dropwise with stirring over 30 min to a solution of 4-(difluoromethoxy)acetophenone (III) (46.5 g, 0.25 mole) in a mixture of dioxan (40 ml) and ether (100 ml). The reaction mixture was then poured into water (400 ml), the organic layer separated, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated in vacuum and the residue crystallized from hexane. Yield was 51 g (77%), mp 63-64°C.

α-Bromo-2,4-bis(difluoromethoxy)acetophenone (VI) was obtained analogously to compound (V) from 2,4-bis-(difluoromethoxy)acetophenone (IV) (63 g, 0.25 mole) and bromine (13 ml, 0.255 mole). Yield was 76 g (92%). Bp 117-120°C (1 mm Hg), n_D = 1.5142.

2-Amino-1-[4-(difluoromethoxy)benzoylmethyl]-4,5-dihydro-3H-pyrrolium bromide (VIII). A chloroform solution of 2-amino-4,5-dihydro-3H-pyrrole (2.94 g, 0.035 mole) was added dropwise with stirring to a solution of α-bromo-4-(difluoromethoxy)acetophenone (V) (9.28 g, 0.035 mole) in chloroform (80 ml). The formation of colorless crystals was observed after 1-2 min accompanied by heating of the reaction mixture. After stirring for 2 h, the precipitate formed was filtered off and washed with ether. Yield was 9.0 g (73.3%), mp 208-210°C (from propan-2-ol). PMR spectrum: 2.44 (2H, m, CH_2); 3.29 (2H, t, CH_2); 3.95 (2H, t, CH_2); 5.24 (2H, s, CH_2); 6.73 (1H, t, $OCHF_2$); 7.30 and 7.67 ppm (4H, d.d, C_6H_4). Found, %: N 8.04; F 10.7. $C_{13}H_{15}BrF_2N_2O_2$. Calculated, %: N 8.02; F 10.9.

2-Amino-1-[2,4-bis(difluoromethoxy)benzoylmethyl]-4,5-dihydro-3H-pyrrolium bromide (IX) was obtained analogously to compound (VIII). Yield was 64%, mp 162°C (from propan-2-ol). PMR spectrum: 2.43 (2H, m, CH_2); 3.27 (2H, t, CH_2); 3.96 (2H, t, CH_2); 5.25 (2H, s, CH_2); 6.67 (1H, t, $OCHF_2$); 6.86 (1H, t, $OCHF_2$); 7.08-8.17 ppm (3H, m, arom.). Found, %: N 6.67; F 18.5. $C_{14}H_{15}BrF_4N_2O_3$. Calculated, %: N 6.75; F 18.3.

2-[2',4'-Bis(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole Hydrobromide (X). Salt (IX) (2.08 g, 0.005 mole) in water (100 ml) containing 48% hydrobromic acid (2-3 drops) was boiled under reflux for 5 h. The reaction

mixture was then evaporated to dryness on a water bath. The dry residue was purified by crystallization from propan-2-ol. Yield was 1.54 g (77.6%), mp 90-92°C. PMR spectrum: 2.98 (2H, m, CH_2); 3.43 (2H, m, CH_2); 4.46 (2H, t, CH_2); 6.61 (1H, t, $OCHF_2$); 6.74 (1H, t, $OCHF_2$); 7.63 (1H, s, 3-H); 7.25-7.47 ppm (3H, t, arom.). Found, %: N 6.92; F 19.2. $C_{14}H_{13}BrF_4N_2O_2$. Calculated, %: N 7.05; F 19.1.

2-(4′-Difluoromethoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine Hydrobromide (XI). A solution of 2-amino-3,4,5,6-tetrahydropyridine (0.98 g, 0.01 mole) in chloroform (15 ml) was added with stirring to a solution of α-bromo-4-(difluoromethoxy)acetophenone (V) (2.65 g, 0.01 mole) in chloroform (20 ml). After stirring for 2 h, the solvent was carefully poured off and the residual oil washed with ether. After removing the ether, water (100 ml) containing hydrobromic acid (2-3 drops) was poured in, and the mixture boiled under reflux for 5 h. The reaction mixture was then evaporated to dryness on a water bath. Yield was 1.48 g (43%), mp 212-213°C (from propan-2-ol). PMR spectrum: 2.22 (4H, m, CH_2CH_2); 3.23 (2H, t, CH_2); 4.28 (2H, t, CH_2); 6.56 (1H, t, $OCHF_2$); 7.24 (1H, s, 3-H); 7.32 and 7.68 ppm (4H, d.d, C_6H_4). Found, %: F 10.9. $C_{14}H_{15}BrF_2N_2O$. Calculated, %: F 11.0.

2-(4′-Hydroxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole Hydrobromide (XII). Salt (VIII) (1.745 g, 0.005 mole) in water (100 ml) containing 48% hydrobromic acid (5 ml) was boiled under reflux for 5 h. The reaction mixture was then evaporated to dryness on a water bath. Yield was 0.88 g (63%), mp 275-277°C (from propan-2-ol). PMR spectrum: 2.96 (2H, m, CH_2); 3.40 (2H, t, CH_2); 4.41 (2H, t, CH_2); 7.13 and 7.58 (4H, d.d, C_6H_4); 7.38 ppm (1H, s, 3-H). Found, %: Br 28.2. $C_{12}H_{13}BrN_2O$. Calculated, %: Br 28.5.

2-(4′-Hydroxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine hydrobromide (XIII) was obtained analogously to compound (XI), with the difference that 48% hydrobromic acid (5 ml) was used as catalyst. Yield was 38%, mp 289-290°C (from propan-2-ol). PMR spectrum: 2.22 (4H, m, CH_2CH_2); 3.22 (2H, t, CH_2); 4.26 (2H, t, CH_2); 7.29 (1H, s, 3-H); 7.12 and 7.59 ppm (4H, d.d, C_6H_4). Found, %: Br 26.9. $C_{13}H_{15}BrN_2O$. Calculated, %: Br 27.1.

2-(4′-Difluoromethoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole (XIV). Salt (VIII) (3.49 g, 0.01 mole) in water (100 ml) containing 48% hydrobromic acid (2-3 drops) was boiled under reflux for 5 h. After cooling, 10% sodium hydroxide solution (15 ml) was poured in. The resulting crystals were filtered off, washed with water, and dried. Yield was 1.3 g (54%), mp 117-118°C (from hexane). PMR spectrum: 2.99 (2H, m, CH_2); 3.37 (2H, t, CH_2); 4.42 (2H, t, CH_2); 6.55 (1H, t, $OCHF_2$); 7.31 and 7.61 (4H, d.d, C_6H_4); 7.45 ppm (1H, s, 3-H). Found, %: C 62.4; H 4.7; F 15.6; N 11.1. $C_{13}H_{12}F_2N_2O$. Calculated, %: C 62.4; H 4.8; F 15.2; N 11.2.

2-(4′-Difluoromethoxyphenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (XV). A 10% solution of sodium hydroxide (10 ml) was added to a solution of salt (XI) (1.73 g, 0.005 mole) in water (100 ml). The crystals formed were filtered off, washed with water, and dried. Yield was 1.15 g (87%), mp 135-136°C (from hexane). PMR spectrum ($CDCl_3$, TMS): 1.96 (4H, m, CH_2CH_2); 2.91 (2H, t, CH_2); 3.96 (2H, t, CH_2); 6.50 (1H, t, $OCHF_2$); 7.03 (1H, s, 3-H); 7.08 and 7.72 ppm (4H, d.d, C_6H_4). Found, %: C 63.2; H 5.21; F 14.2; N 10.3. $C_{14}H_{14}F_2N_2O$. Calculated, %: C 63.6; H 5.30; F 14.4; N 10.6.

2-[2′,4′-Bis(difluoromethoxy)phenyl]-6,7-dihydro-5H-pyrrolo[1,2-*a*]imidazole (XVI) was obtained analogously to compound (XV) from salt (IX). Yield was 84%, mp 95-96°C (from hexane). PMR spectrum ($CDCl_3$, TMS): 2.63 (2H, m, CH_2); 2.91 (2H, t, CH_2); 4.02 (2H, t, CH_2); 6.52 (2H, t, 2 × $OCHF_2$); 6.90-8.20 (3H, m, C_6H_3); 7.41 ppm (1H, s, 3-H). Found, %: C 49.8; H 3.89; F 23.7; N 8.73. $C_{14}H_{12}F_4N_2O_2$. Calculated, %: C 53.2; H 3.80; F 24.0; N 8.86.

3-Carbamoyl-1-(4′-difluoromethoxyphenacyl)pyridinium Bromide (XVII). A solution of haloketone (V) (2.65 g, 0.01 mole) in acetone (30 ml) was poured into a solution of nicotinamide (1.22 g, 0.01 mole) in acetone (50 ml). Next day, the crystals formed were filtered off, washed with ether, and dried. Yield was 2.4 g (62%), mp 206-208°C (from methanol). PMR spectrum (DMSO, HMDS): 6.44 (2H, s, NCH_2CO); 7.42 (1H, t, $OCHF_2$); 7.38 and 8.08 (4H, d.d, C_6H_4); 8.16 (1H, d, 4-H); 8.32 (1H, t, 5-H); 9.02 (2H, m, $CONH_2$); 9.41 ppm (1H, s, 2-H). Found, %: N 7.15. $C_{15}H_{13}BrF_2N_2O_3$. Calculated, %: N 7.24.

2-Bromo-1-(4′-difluoromethoxyphenacyl)pyridinium Bromide (XVIII). A mixture of 2-bromopyridine (0.216 g, 0.0015 mole) and haloketone (V) (0.398 g, 0.0015 mole) was kept on a boiling water bath for 5 h. After cooling, the reaction mixture was rubbed with ether, the solid filtered off, and dried. Yield was 0.175 g (28%), mp 138-140°C (from propan-2-ol). PMR spectrum (DMSO, HMDS): 5.49 (2H, s, NCH_2CO); 6.31 (1H, t, 4-H); 6.43 (1H, d, 3-H); 7.45 (1H, t, $OCHF_2$); 7.35 and 8.13 (4H, d.d, C_6H_4); 7.51 (1H, t, 5-H); 7.67 ppm (1H, d, 6-H). Found, %: N 3.79. $C_{14}H_{11}Br_2F_2NO_2$. Calculated, %: N 3.64.

1-(4-Difluoromethoxyphenacyl)-2-methylpyridinium bromide (XIX) was obtained analogously to compound (XVIII) from equimolar quantities of α-picoline and haloketone (V). Yield was 42%, mp 172-174°C (from propan-2-ol). PMR spectrum (DMSO, HMDS): 2.65 (2H, s, CH_3); 6.48 (2H, s, NCH_2CO); 7.44 (1H, t, $OCHF_2$); 7.39 and 8.12 (4H, d.d, C_6H_4); 8.02

(1H, t, 4-H); 8.14 (1H, d, 3-H); 8.56 (1H, t, 5-H); 8.87 ppm (1H, d, 6-H). Found, %: N 4.02. $C_{15}H_{14}BrF_2NO_2$. Calculated, %: N 3.91.

1-(4′-Difluoromethoxyphenacyl)-4-(N-β-hydroxyethylcarbamoyl)pyridinium bromide (XX) was obtained analogously to compound (XVII) from equimolar quantities of isonicotinic acid N-(β-hydroxyethyl)amide and haloketone (V). Yield was 59%, mp 180-182°C (from methanol). PMR spectrum (DMSO, HMDS): 3.49-3.75 (4H, m, CH_2CH_2); 4.56 (1H, t, OH); 6.43 (2H, s, NCH_2CO); 7.41 (1H, t, $OCHF_2$); 7.39 and 8.09 (4H, d.d, C_6H_4); 8.45 and 9.06 (4H, d.d, p-C_5H_4N); 9.24 ppm (1H, t, NH). Found, %: N 7.15. $C_{14}H_{17}BrF_2N_2O_4$. Calculated, %: N 7.09.

4-(N-Benzylcarbamoyl)-1-(4′-difluoromethoxyphenacyl)pyridinium bromide (XXI) was obtained analogously to compound (XVII) from equimolar quantities of isonicotinic acid N-benzylamide and haloketone (V). Yield was 76%, mp 224-226°C (from methanol). PMR spectrum: 4.78 (2H, s, $NCH_2C_6H_5$); 5.25 (2H, s, NCH_2CO); 6.73 (1H, t, $OCHF_2$); 7.39 (5H, s, C_6H_5); 7.30 and 7.68 (4H, d.d, C_6H_4); 8.58 and 8.96 ppm (4H, d.d, C_5H_4N). Found, %: F 8.35. $C_{22}H_{19}BrF_2N_2O_3$. Calculated, %: F 8.21.

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