3-Substituted 2-trifluoromethylimidazo[1,2-*a*]pyridines

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3-Fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridines were obtained by reactions of hexafluoroacetone 2-pyridylimines with trimethyl phosphite and studied in reactions with sodium methoxide. This gave the corresponding 3-methoxy-2-trifluoromethylimidazo[1,2-*a*]pyridines.

Key words: hexafluoroacetone, 2-aminopyridines, hexafluoroacetone 2-pyridylimines, trimethyl phosphite, 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridines, 3-methoxy-2-trifluoromethylimidazo[1,2-*a*]pyridines, sodium methoxide, heterocyclization, nucleophilic substitution.

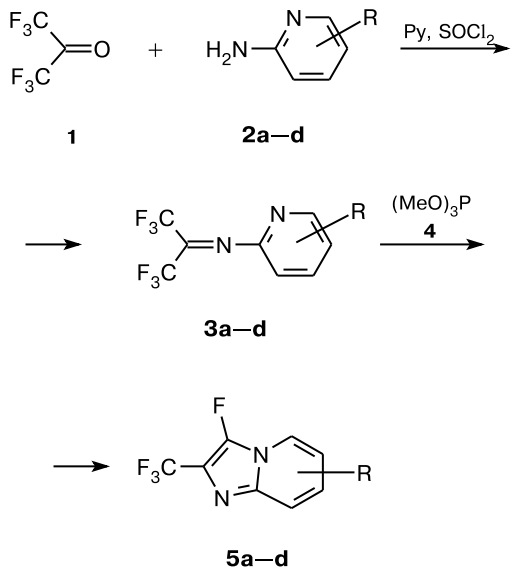
Among imidazoheterocyclic derivatives, compounds have been found that exhibit cardiac stimulant,[1] arrhythmic,[1] or neurotropic[2,3] activities, exert cytoprotective and antitumor action,[4] and that are promising for treating Alzheimer´s disease.[5] Therefore, development of new methods for the formation of imidazoheterocyclic systems is quite a topical and promising task. A key method for the synthesis of imidazo[1,2-*a*]pyridines is heterocyclization of α-bromoketones and 2-aminopyridines.[5,6] The purpose of this study was to develop an approach to the synthesis of new imidazopyridine derivatives, namely, substituted 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridines.

This study was initiated in view of our earlier data[7] on intramolecular cyclization of 2-pyridylimines of methyl trifluoropyruvate under the action of trimethyl phosphite to give imidazolecarboxylic acids and the data on heterocyclization of hexafluoroacetone acylimines under the action of tin dichloride[8—13] and zinc[14,15] to give fluorine-containing oxazoles. All these transformations were accompanied by defluorination of the trifluoromethyl group.

The synthetic algorithm for the preparation of 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridines presented in Scheme 1 comprises a series of consecutive transformations: imination of hexafluoroacetone (**1**) with substituted 2-aminopyridines **2a—d** to give hexafluoroacetone 2-pyridylimines **3a—d** and reaction of the latter with trimethyl phosphite **4** resulting in imidazopyridines **5a—d**.

Hexafluoroacetone 2-pyridylimines **3a—d** were obtained in 63—71% yields by successive addition of equimolar amounts of compound **1**, pyridine, and $SOCl_2$ at 20 °C to a benzene solution (or suspension) of 2-aminopyridines **2a—d**; the reaction was completed within 1.5—2 h. In the ^{19}F NMR spectra of imines, the signals of nonequivalent trifluoromethyl groups as quartets at

Scheme 1



2, 3: R = 3-Me (**a**); 4-Me (**b**); 6-Me (**c**); 5-Br (**d**)
5: R = 8-Me (**a**); 7-Me (**b**); 5-Me (**c**); 6-Br (**d**)

7—9 ppm and 13—15 ppm with spin-spin coupling constant of 7—8 Hz are characteristic. On refluxing in acetonitrile with an equimolar amount of trimethyl phosphite **4**, imines **3a—d** undergo heterocyclization to give 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridines **5a—d** as crystalline solids in 69—81% yields. The composition and structure of the products were proven by elemental analysis and ^1H and ^{19}F NMR spectra. Characteristic ^{19}F NMR signals are doublets of the trifluoromethyl group at 16—17 ppm with spin-spin coupling constants of 10—11 Hz and quar-

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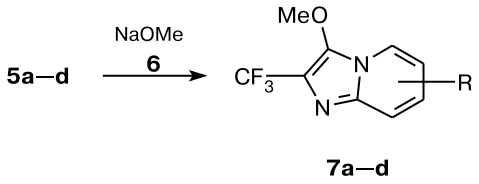
tets of fluorine atoms at −68 to −73 ppm with spin-spin coupling constants of 10—11 Hz.

The 3-fluoro substituent in the imidazole ring was fairly reactive with respect to potent nucleophiles. Thus on refluxing **5a—d** in acetonitrile with an equimolar amount of sodium methoxide (**6**), the fluorine atom in **5a—d** was quantitatively replaced by a methoxy group yielding 3-methoxy-2-trifluoromethylimidazo[1,2-*a*]pyridines **7a—d** (Scheme 2).

Scheme 2



7: R = 8-Me (**a**); 7-Me (**b**); 5-Me (**c**); 6-Br (**d**)

Substituted 3-methoxy-2-trifluoromethylimidazo-[1,2-*a*]pyridines **7a—d** are crystalline solids formed in 87—92% yields, their composition and structure were proven by elemental analysis and ^{1}H NMR spectroscopy. The singlets of methoxy groups at 4.0—4.2 ppm confirm the proposed structure **7**.

Thus, transformations of the trifluoromethyl group in hexafluoroacetone 2-pyridylimines induced by nucleophilic reagents, trimethyl phosphite and sodium methoxide, is a convenient synthetic approach to previously unknown 3-substituted 2-trifluoromethylimidazo[1,2-*a*]pyridines.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200.13 and 188.29 MHz relative to $SiMe_4$ (internal standard) and CF_3COOH (external standard), respectively. Melting points were determined in a glass capillary. Hexafluoroacetone (**1**), substituted 2-aminopyridines **2a—d**, and trimethyl phosphite (**4**) (Aldrich) were used as received.

***N*-[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]-3-methylpyridine-2-amine (3a), *N*-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-4-methylpyridine-2-amine (3b), *N*-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-6-methylpyridine-2-amine (3c), *N*-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-5-bromopyridine-2-amine (3d) (general procedure).** Hexafluoroacetone (16.6 g, 0.1 mol), pyridine (31.2 g, 0.2 mol), and $SOCl_2$ (12.0 g, 0.1 mol) were added successively to a solution (or suspension) of 2-aminopyridine **3a—d** (0.1 mol) in benzene (100 mL). The reaction mixture was stirred for 2 h and filtered, the filtrate was concentrated, and the residue was fractionated.

Table 1. Yields, melting points and elemental analysis data for compounds **3a—d**, **5a—d**, and **7a—d**

Compound	Yield (%)	M.p./°C B.p./°C (*p*/Torr)	Found / Calculated (%)			Molecular formula
			C	H	N	
3a	63	60—61 (10)	42.17 42.20	2.45 2.36	10.81 10.94	$C_9H_6F_6N_2$
3b	67	70—71 (15)	42.28 42.20	2.27 2.36	11.07 10.94	$C_9H_6F_6N_2$
3c	71	7—75 (20)	42.32 42.20	2.48 2.36	10.86 10.94	$C_9H_6F_6N_2$
3d	68	52—54 (3)	23.84 23.93	1.07 0.94	8.61 8.73	$C_8H_3BrF_6N_2$
5a	81	61—63	49.68 49.55	2.85 2.77	12.99 12.84	$C_9H_6F_4N_2$
5b	75	139—140	49.47 49.55	2.63 2.77	12.71 12.84	$C_9H_6F_4N_2$
5c	69	110—112	49.49 49.55	2.61 2.77	12.69 12.84	$C_9H_6F_4N_2$
5d	77	88—89	33.82 33.95	1.13 1.01	9.76 9.90	$C_8H_3BrF_4N_2$
7a	92	55—57	52.07 52.18	3.81 3.94	12.04 12.17	$C_{10}H_9F_3N_2O$
7b	89	Oil	52.02 52.18	3.78 3.94	12.01 12.17	$C_{10}H_9F_3N_2O$
7c	91	61—62	52.31 52.18	4.11 3.94	12.29 12.17	$C_{10}H_9F_3N_2O$
7d	87	74—75	36.51 36.64	1.91 2.05	9.32 9.49	$C_9H_6BrF_3N_2O$

Table 2. ^{1}H and ^{19}F NMR spectra of compounds **3a—d**, **5a—d** and **7a—d** in DMSO-d_6

Compound	NMR spectra, δ (*J*/Hz)	
	^{1}H	^{19}F
3a	2.17 (s, 3 H, Me); 7.13 (dd, 1 H, $J_1 = 7.5$, $J_2 = 5.4$); 7.57 (d, 1 H, $J = 7.5$); 8.22 (d, 1 H, $J = 5.4$)	8.07, 13.64 (both d, $J = 6.1$)
3b	2.42 (s, 3 H, Me); 6.83 (s, 1 H); 7.04, 8.33 (both d, 1 H, $J = 5.4$)	7.78, 14.63 (both q, $J = 7.2$)
3c	2.53 (s, 3 H, Me); 6.76, 7.06 (both d, 1 H, $J = 8.1$); 7.65 (t, 1 H, $J = 8.1$)	7.91, 14.99 (both q, $J = 7.1$)
3d	7.05 (d, 1 H, $J = 9.1$); 8.03 (dd, 1 H, $J_1 = 9.1$, $J_2 = 2.1$); 8.66 (d, 1 H, $J = 2.1$)	7.94, 14.74 (both q, $J = 7.2$)
5a	2.69 (s, 3 H, Me); 7.06 (t, 1 H, $J = 6.7$); 7.22 (d, 1 H, $J = 6.7$); 8.13 (d, 1 H, $J = 6.7$)	−71.75 (q, 1 F, $J = 10.2$); 16.88 (d, 3 F, $J = 10.2$)
5b	2.54 (s, 3 H, Me); 7.01 (d, 1 H, $J = 7.2$); 7.39 (s, 1 H); 8.23 (d, 1 H, $J = 7.2$)	−73.27 (q, 1 F, $J = 10.1$); 16.81 (d, 3 F, $J = 10.1$)
5c	2.93 (d, 3 H, Me, J =6.4); 6.88 (d, 1 H, $J = 6.8$); 7.34 (dd, 1 H, $J_1 = 9.5$, $J_2 = 6.8$); 7.51 (br.d, 1 H, $J_1 = 9.5$)	−68.12 (q, 1 F, $J = 10.5$); 16.65 (d, 3 F, CF_3, $J = 10.5$)
5d	7.44 (dd, 1 H, CH_{Ar}, $J_1 = 10.9$, $J_2 = 1.9$); 7.59 (d, 1 H, CH_{Ar}, $J = 10.9$); 8.62 (s, 1 H, CH_{Ar})	−70.72 (qd, $J = 10.5$, $J = 1.5$); 16.67 (d, 3 F, $J = 10.5$)
7a	2.51 (s, 3 H, Me); 4.06 (s, 3 H, MeO); 6.85 (t, 1 H, $J = 6.6$); 7.04 (d, 1 H, $J = 6.6$); 8.00 (d, 1 H, $J = 6.6$)	17.86 (s, CF_3)
7b	2.38 (s, 3 H, Me); 4.04 (s, 3 H, MeO); 6.76 (dd, 1 H, $J_1 = 7.9$, $J_2 = 1.1$); 7.21 (d, 1 H, $J = 1.1$); 8.04 (d, 1 H, $J = 7.9$)	17.72 (s, CF_3)
7c	2.96 (s, 3 H, Me); 4.18 (s, 3 H, MeO); 6.78 (d, 1 H, $J = 6.6$); 7.28 (t, 1 H, $J = 6.6$); 7.46 (d, 1 H, $J = 6.6$)	17.34 (s, CF_3)
7d	4.11 (s, 3 H, MeO); 7.36 (d, 1 H, $J = 9.8$); 7.52 (d, 1 H, $J = 9.8$); 8.47 (s, 1 H)	17.63 (s, CF_3)

3-Fluoro-8-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (5a), 3-fluoro-7-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (5b), 3-fluoro-5-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (5c), 6-bromo-3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridine (5d) (general procedure). Trimethyl phosphite (**4**) (1.24 g, 0.01 mol) was added with stirring to a solution of hexafluoroacetone 2-pyridylimine **3a—d** (0.01 mol) in CH_3CN (20 mL). After completion of the exothermal reaction, the reaction mixture was refluxed for 1 h and poured into water (50 mL), the mixture was neutralized with a 5% solution of K_2CO_3, and the precipitate was filtered off, and recrystallized from 50% EtOH.

3-Methoxy-8-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (7a), 3-methoxy-7-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (7b), 3-methoxy-5-methyl-2-trifluoromethylimidazo[1,2-*a*]pyridine (7c), 6-bromo-3-methoxy-2-trifluoromethylimidazo[1,2-*a*]pyridine (7d) (general procedure). A solution of 3-fluoro-2-trifluoromethylimidazo[1,2-*a*]pyridine **5a—d** (0.01 mol) and $NaOCH_3$ (**6**) (0.6 g, 0.011 mol) in CH_3CN (20 mL) was refluxed for 1 h and poured into water (50 mL). The precipitate was filtered off and recrystallized from 50% EtOH.

The yields, boiling points, and spectral characteristics of compounds **3a—d**, **5a—d**, and **7a—d** are summarized in Tables 1 and 2.

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