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Synthesis of *N*-(5-Pyrazolyl) Schiff Bases Derived from Aryl Trifluoromethyl Ketones

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Abstract—5-Amino-1-aryl-4-methylpyrazoles readily add to methyl 1-aryl-2,2,2-trifluoroethylidenecarbamates to give the corresponding methyl 1-aryl-2,2,2-trifluoro-1-(5-pyrazolylamino)ethylcarbamates which undergo fragmentation at elevated temperature in the presence of an organic base to afford *N*-(5-pyrazolyl)-1-aryl-2,2,2-trifluoroethanimines.

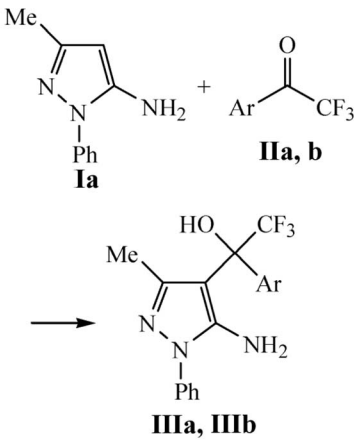
N-Aryl-substituted 1-aryl-2,2,2-trifluoroethanimines are usually prepared by the aza-Wittig reaction of the corresponding ketones with triphenylphosphazoarenes [1]. Also, a procedure was reported [2] for the synthesis of 1,*N*-diphenyl-2,2,2-trifluoroethanimine via direct reaction of trifluoroacetophenone with aniline over zeolite as neutral water acceptor [2]. We have found no published data on Schiff bases derived from aryl trifluoromethyl ketones with a heterocyclic substituent on the nitrogen atom. In the present communication we report on the synthesis of *N*-(5-pyrazolyl)-1-aryl-2,2,2-trifluoroethanimines which attract interest, apart from other aspects, from the viewpoint of their subsequent heterocyclizations as new 2-azadiene systems. It should be noted that structurally related *N*-(5-pyrazolyl)amidines have found application in the synthesis of pyrazolo[3,4-*b*]pyrrolo[3,4-*d*]pyridines according to the hetero-Diels–Alder scheme [3].

5-Aminopyrazoles are known to react with carbonyl compounds both at the amino group and at the C^4 atom of the pyrazole ring, depending on the nature of the carbonyl component and reaction conditions. For example, condensation of 5-aminopyrazoles with aromatic aldehydes yielded *N*-pyrazolyl-substituted imines [4, 5]; when the reaction was carried out under microwave irradiation, the corresponding bispyrazolyl aldehyde imines and products of their subsequent transformations were also isolated [6]. The reaction of 5-aminopyrazoles with cyclic ketones was accompanied by formation of 5-amino-4-cycloalkenylpyrazoles [7], and their reaction with isatin afforded 3-(5-aminopyrazol-3-yl)-3-hydroxy-2,3-dihydroindol-2-ones [8].

While studying the reaction of 5-amino-3-methyl-1-phenylpyrazole (**Ia**) with aryl trifluoromethyl ketones **IIa** and **IIb**, we have found that this process occurs at the electron-rich C^4 atom of the pyrazole ring rather than at the amino group. As a result, 5-amino-4-(1-aryl-1-hydroxy-2,2,2-trifluoroethyl)pyrazoles **IIIa** and **IIIb** were obtained (Scheme 1).

Drach *et al*. previously showed [9] that products of addition of primary aliphatic, aromatic, and heterocyclic amines to some acyl derivatives of benzophenone imine are unstable and that they decompose to give the corresponding N-substituted benzophenone imines even at room temperature. Taking these data into account, we made an attempt to use methyl 1-aryl-2,2,2-trifluoro-ethylidenecarbamates **IVa**–**IVc** [10]

Scheme 1.



II, **III**, Ar = Ph (**a**), 4-$MeOC_6H_4$ (**b**).

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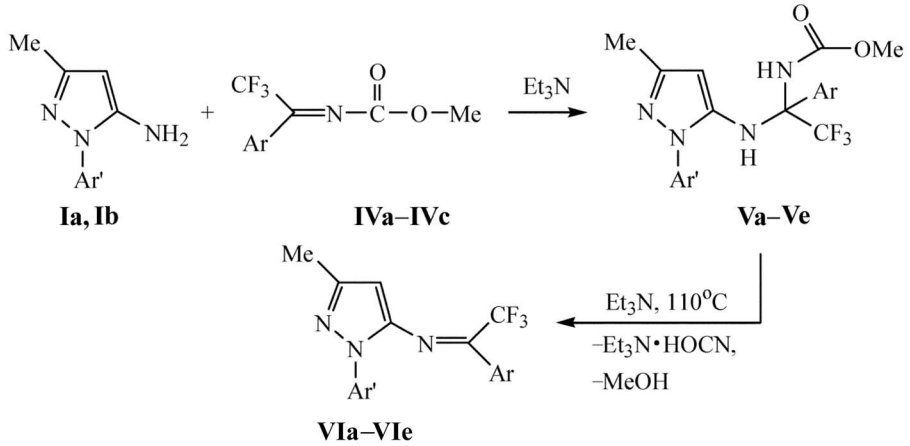
Scheme 2.

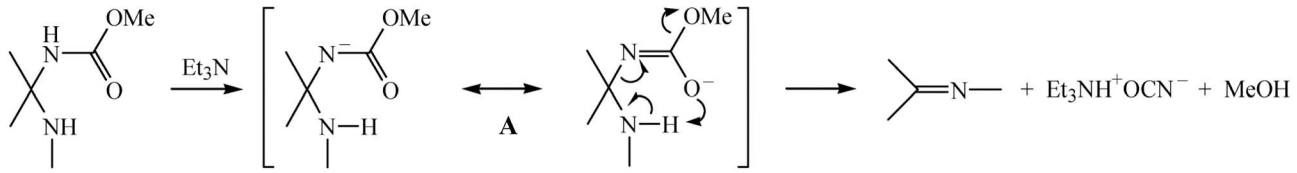


Ia, Ib **IVa–IVc** **Va–Ve**

VIa–VIe

I, Ar = 3-ClC_6H_4 (**b**); IV, Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-$MeOC_6H_4$ (**c**); **V, VI**, Ar = Ar' = Ph (**a**), Ar = Ph, Ar' = 3-ClC_6H_4 (**b**), Ar = 4-MeC_6H_4, Ar' = Ph (**c**), 3-ClC_6H_4 (**d**), Ar = 4-$MeOC_6H_4$, Ar' = Ph (**e**).

Scheme 3.



as starting compounds for the synthesis of *N*-(5-pyrazolyl) ketone imines.

We have found that *N*-ethylidenecarbamates **IVa**–**IVc** react with 5-aminopyrazoles **Ia** and **Ib** at 18–20°C in the presence of a catalytic amount of triethylamine to give products **Va**–**Ve** having an aminal structure (Scheme 2). Compounds **Vc** and **Ve** were isolated in the pure state. Their IR spectra contained absorption bands at 1710 and 3335–3340 cm^{-1}, which belong to stretching vibrations of the carbonyl and NH groups. In the ^1H NMR spectra of these compounds, the 4-H proton of the pyrazole ring appeared as a singlet at δ 5.83 ppm, indicating that the reaction with *N*-ethylidenecarbamates **IV** occurred at the exocyclic amino group of pyrazoles **I**. This conclusion does not contradict the ^{19}F NMR spectra where resonance signals from fluorine atoms were observed at δ_F –77.7 ppm, i.e., in the region typical of a trifluoromethyl group attached to the carbon atom in an N–C–N triad [11]. Taking into account our previous data [12] on the ability of the closest structural analogs of **V**, *N*-methoxycarbonyl-*N*'-(5-pyrazolyl)trihaloacetamidines, to undergo intramolecular cyclocondensation to 6-trihalomethyl-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-ones at elevated temperature, we expected a similar transformation to occur with compounds **V**. However, these compounds remained unchanged on prolonged heating (12–15 h) in boiling toluene, which may be due to reduced electrophilicity of the carbonyl group in the carbamate moiety of aminals **V**, as compared to amidine derivatives. On the other hand, heating of solutions of **V** in boiling toluene in the presence of an equimolar amount of triethylamine for 10 h resulted in their fragmentation with formation of *N*-(5-pyrazolyl) ketone imines **VIa**–**VIe** in 55–63% yield.

The structure of compounds **VIa**–**VIe** is consistent with their IR and ^1H and ^{19}F NMR spectra (see table). In particular, the IR spectra contained absorption bands due to stretching vibrations of the C=N bonds at 1655–1665 cm^{-1}. In the ^1H NMR spectra, the pyrazole 4-H signal was observed at δ 5.06–5.17 ppm, and fluorine nuclei of the trifluoromethyl group gave signals in the region δ_F –70.2 to –70.6 ppm [13]. We presume that the observed thermal transformation in the presence of triethylamine involves intermediate mesomeric anion **A** whose fragmentation occurs via a six-membered transition state (Scheme 3).

EXPERIMENTAL

The IR spectra of samples pelleted with KBr were recorded on a UR-20 instrument. The ^1H NMR spectra of solutions in DMSO-d_6 were measured on a Varian VXR-300 spectrometer (300 MHz) relative to tetramethylsilane as internal reference. The ^{19}F NMR spec-

Yields, melting points, IR and ^1H and ^{19}F NMR spectra, and elemental analyses of *N*-(5-pyrazolyl)-1-aryl-2,2,2-trifluoroethanimines **VIa**–**VIe**

Compd. no.	Yield, %	mp, °C	IR spectrum, $\nu_{C=N}$, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)	^{19}F NMR spectrum, δ_F, ppm
VIa	63	101–102	1665	2.07 s (3H, CH_3), 5.03 s (1H, 4-H), 7.35–7.60 m (10H)	–70.3
VIb	55	87–88	1650	2.08 s (3H, CH_3), 5.04 s (1H, 4-H), 7.38–7.62 m (8H), 7.75 s (1H	–70.3
VIc	60	109–110	1660	2.11 s (3H, CH_3), 2.46 s (3H, CH_3), 5.08 s (1H, 4-H), 7.27 d (2H, *J* = 8.1), 7.28–7.35 m (3H), 7.44 t (2H, *J* = 7.8), 7.62 d (2H, *J* = 8.1	–70.6
VId	61	137–138	1655	2.09 s (3H, CH_3), 2.44 s (3H, C**H**$_3C_6H_4$), 5.13 s (1H, 4-H), 7.30–7.37 m (4H), 7.49 t (1H, *J* = 8.1), 7.62 d (1H, *J* = 8.1), 7.73 br.s (1H)	–70.2
VIe	59	149–150	1660	2.12 s (3H, CH_3), 3.87 s (3H, OCH_3), 5.17 s (1H, 4-H), 7.07 d (2H, *J* = 8.7), 7.34–7.37 m (3H), 7.46 t (2H, *J* = 7.8), 7.59 d (2H, *J* = 7.5)	–70.1

Compd no.	Found, %			Formula	Calculated		
	C	H	F		C	H	F
VIa	65.97	4.39	17.40	$C_{18}H_{14}F_3N_3$	65.65	4.28	17.31
VIb	59.70	3.51	15.93	$C_{18}H_{13}C1F_3N_3$	59.43	3.60	15.67
Vlc	66.15	4.85	16.62	$C_{19}H_{16}F_3N_3$	66.46	4.70	16.60
VId	60.07	4.19	15.46	$C_{19}H_{15}C1F_3N_3$	60.40	4.00	15.09
Vle	63.17	4.53	16.07	$C_{19}H_{16}F_3N_30$	63.51	4.49	15.86

tra were obtained on the same instrument operating at 282 MHz; DMSO-d_6 was used as solvent, and trichlorofluoromethane, as internal reference.

5-Amino-4-(1-aryl-2,2,2-trifluoro-1-hydroxyethyl)-3-methyl-1-phenylpyrazoles IIIa and IIIb. Aminopyrazole **Ia**, 0.5 g (0.029 mol), and 4–5 crystals of iodine were added to a solution of 0.029 mol of ketone **IIa** or **IIb** in 20 ml of toluene. The mixture was heated for 10 h under reflux and cooled, 5 ml of hexane was added, and the precipitate was filtered off and recrystallized ethanol.

5-Amino-3-methyl-1-phenyl-4-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)pyrazole (IIIa). Yield 65%, mp 215°C. ^1H NMR spectrum, δ, ppm: 1.34 s (3H, CH_3), 5.11 br.s (2H, NH_2), 7.21 s (1H, OH), 7.29 t (1H, H_{arom}, *J* = 7.5 Hz), 7.31–7.57 m (9H, H_{arom}). ^{19}F NMR spectrum: δ_F –75.2 ppm, s. Found, %: F 16.28; N 12.17. $C_{18}H_{16}F_3N_3O$. Calculated, %: F 16.41; N 12.10.

5-Amino-3-methyl-1-phenyl-4-[2,2,2-trifluoro-1-hydroxy-1-(4-methoxyphenyl)ethyl]pyrazole (IIIb). Yield 53%, mp 248–250°C. ^1H NMR spectrum, δ, ppm: 1.38 s (3H, CH_3), 3.80 s (3H, OCH_3), 5.14 br.s (2H, NH_2), 6.94 d (2H, H_{arom}, *J* = 8.7 Hz), 7.14 br.s (1H, OH), 7.29 t (1H, H_{arom}, *J* = 7.5 Hz), 7.44–7.47 m (4H, H_{arom}), 7.57 d (2H, H_{arom}, *J* = 7.5 Hz). ^{19}F NMR spectrum; δ_F –75.5 ppm, s. Found, %: F 14.92; N 11.05. $C_{19}H_{18}F_3N_3O_2$. Calculated, %: F 15.10; N 11.14.

Methyl 1-aryl-2,2,2-trifluoro-1-(5-pyrazolylamino)ethylcarbamates Vc and Ve. 5-Aminopyrazole **Ia**, 5 mmol, and 2–3 drops of triethylamine were added to a solution of 5 mmol of *N*-ethylidene carbamate **IVb** or **IVc** in 15 ml of toluene. The mixture was stirred for 3–4 h (until initial aminopyrazole **Ia** dissolved completely) and was left to stand for 2 days at 18–20°C. The precipitate of carbamate **Vc** or **Ve** was filtered off, and an additional portion of the product was isolated by partial evaporation of the filtrate. The portions were combined and recrystallized from ethanol.

Methyl 2,2,2-trifluoro-1-(5-pyrazolylamino)-1-(4-tolyl)ethylcarbamate (Vc). Yield 87%, mp 158–159°C. IR spectrum, ν, cm^{-1}: 1710 (C=O), 3335 (NH). ^1H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 2.33 s (3H, CH_3), 3.56 s (3H, OCH_3), 5.34 s (1H, NH), 5.83 s

(1H, 4-H), 7.17 d (2H, H_{arom}, J = 8.1 Hz), 7.35 t (1H, H_{arom}, J = 7.4 Hz), 7.62 d (2H, H_{arom}, J = 8.0 Hz), 8.58 s (1H, NH). ^{19}F NMR spectrum: δ_F –77.7 ppm, s. Found, %: C 60.63; H 4.83; F 13.30. $C_{21}H_{21}F_3N_4O_2$. Calculated, %: C 60.28; H 5.06; F 13.62.

Methyl 2,2,2-trifluoro-1-(4-methoxyphenyl)-1-(5-pyrazolylamino)ethylcarbamate (Ve). Yield 85%, mp 166–167°C. IR spectrum, ν, cm^{-1}: 1710 (C=O), 3340 (NH). ^1H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 3.58 s (3H, OCH_3), 3.79 s (3H, OCH_3), 5.28 s (1H, NH), 5.83 s (1H, CH), 6.89 d (2H, H_{arom}, J = 8.7 Hz), 7.35 t (1H, H_{arom}, J = 7.4 Hz), 7.50 m (4H, H_{arom}), 7.62 d (2H, H_{arom}, J = 8.7 Hz), 8.55 s (1H, NH). ^{19}F NMR spectrum: δ_F –77.7 ppm, s. Found, %: C 57.79; H 4.87; F 13.45. $C_{21}H_{21}F_3N_4O_3$. Calculated, %: C 58.06; H 4.87; F 13.12.

***N*-(1-Aryl-3-methylpyrazol-5-yl)-1-aryl-2,2,2-trifluoroethanimines VIa–VIe** (see table)**.** Triethylamine, 0.5 g (5 mmol), was added to the reaction mixture containing carbamate **Va–Ve**, obtained as described above from 5 mmol of *N*-ethylidene carbamate **IVa**–**IVc** and aminopyrazole **Ia** or **Ib**. The mixture was heated for 10 h at the boiling point, and a white material (mp > 300°C) deposited on the walls of the reflux condenser due to sublimation. This material was identified as $Et_3NH^+ \cdot OCN^-$ [14]. The mixture was evaporated, and the oily residue was ground with hexane and crystallized from anhydrous 2-propanol.

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