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Reactions of Methyl 3,3,3-Trifluoro-2-(pyridin-2-ylimino)-propanoates with Mono- and Difunctional Nucleophiles

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Abstract—Reactions of methyl 3,3,3-trifluoro-2-(pyridin-2-ylimino)propanoates with such nucleophiles and 1,3-binucleophiles as methanol, *p*-toluidine, phenylhydrazine, diethyl phosphonate, 2-aminobut-2-enenitrile, benzamidine, and 4,5-dihydro-1,3-thiazol-2-amine led to the formation of various acyclic 2-substituted methyl 3,3,3-trifluoro-2-(pyridin-2-ylamino)propanoates and trifluoromethyl-containing heterocyclic N-substituted 2-aminopyridine derivatives: 4,5-dihydro-1*H*-pyrroles, 4,5-dihydro-1*H*-imidazol-5-ones, and 2,3-dihydro-6*H*-imidazo[2,1-*b*][1,3]thiazol-5-ones.

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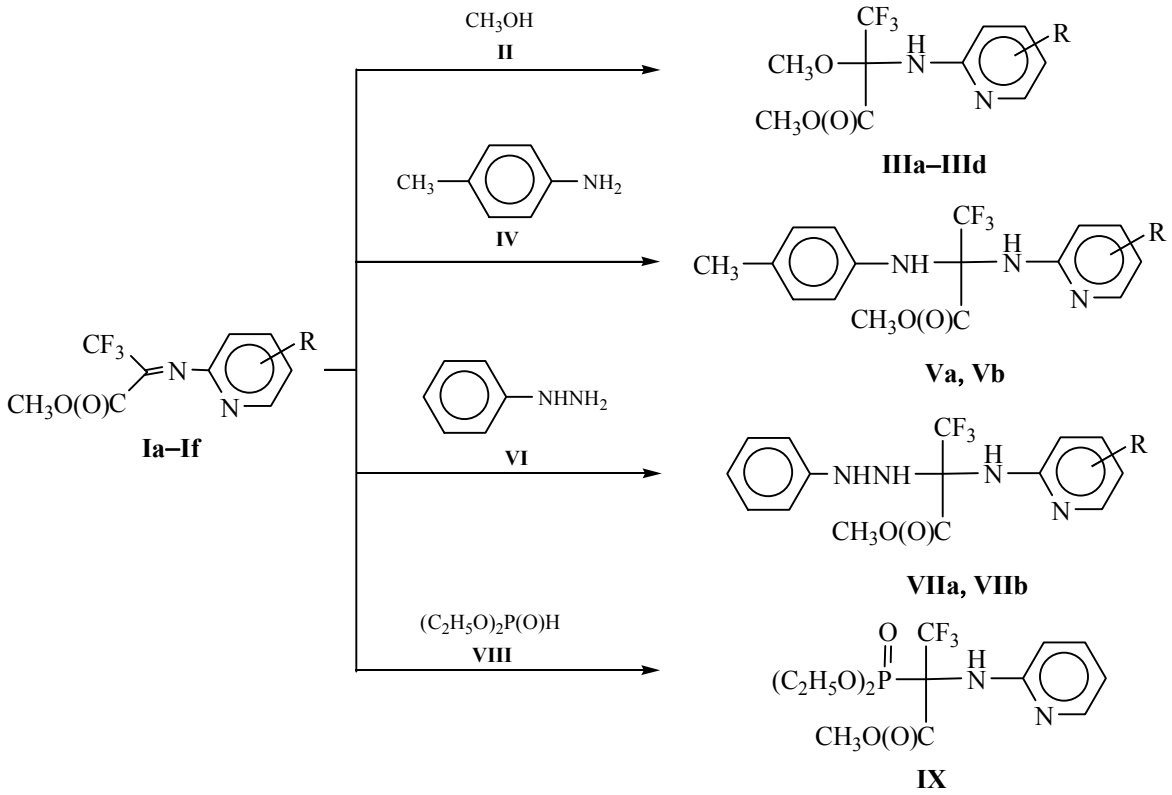
We previously studied transformations of Schiff bases derived from hexafluoroacetone and methyl 3,3,3-trifluoro-2-oxopropanoate in reactions with difunctional nucleophiles and proposed synthetic approaches to novel trifluoromethyl-substituted heterocyclic compounds [1–4]. In continuation of these studies in the present work we examined reactions of previously synthesized [5] methyl 3,3,3-trifluoro-2-(pyridin-2-ylimino)propanoates **Ia**–**If** with various nucleophiles and 1,3-binucleophiles. These reactions led to the formation of trifluoromethyl-containing N-substituted (including heterocyclic) 2-aminopyridine derivatives. It should be emphasized that pharmacophoric 2-aminopyridine moiety is a structural fragment of various medical agents [6] and that substituted 2-aminopyridines constitute a fairly wide series of biologically active substances; in particular, they act as histamine H_1 receptor antagonists [7] and thrombin inhibitors [8, 9].

Like *N*-acyl- and *N*-sulfonyl-substituted Schiff bases [10, 11], *N*-(pyridin-2-yl) imines **I** reacted with oxygen-, nitrogen-, and phosphorus-centered nucleophiles, but these reactions required more severe conditions. As nucleophiles we used methanol (**II**), *p*-toluidine (**IV**), phenylhydrazine (**VI**), and diethyl phosphonate (**VIII**). Nucleophiles **IV** and **VI** reacted with Schiff bases **I** at room temperature, and the reactions were accompanied by heat evolution. Addition of less nucleophilic compounds **II** and **VIII** at the C=N bond of compounds **I** was complete when the reaction mixture (reactant ratio 1 : 1) was heated in boiling benzene over a period of 30 min.

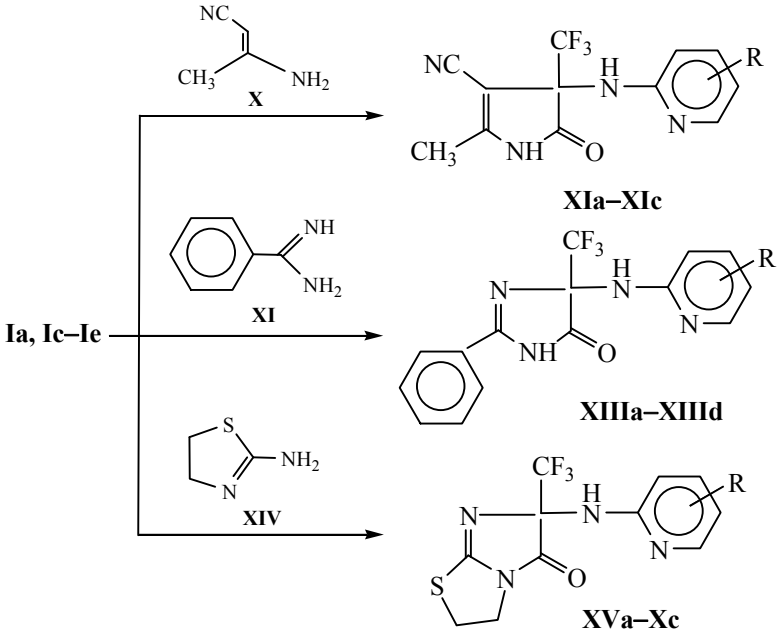
N-Substituted 2-aminopyridines **IIIa**–**IIId**, **Va**, **Vb**, **VIIa**, **VIIb**, and **IX** thus obtained (Scheme 1) were isolated in 76–95% yield as crystalline substances, and their structure was confirmed by elemental analyses (Table 1) and NMR spectra (Table 2). The ^{1}H NMR spectra of the products characteristically contained a singlet from the NH proton at δ 7.22–7.99 ppm (**IIIa**–**IIId**, **Va**, **Vb**, **VIIa**, **VIIb**), while compound **IX** displayed a doublet at δ 7.13 ppm due to coupling with the phosphorus nucleus (J_{HP} = 9.1). In the ^{19}F NMR spectra of these compounds we observed singlets from the trifluoromethyl group at δ_F 0.78–2.95 ppm (**IIIa**–**IIId**, **Va**, **Vb**, **VIIa**, **VIIb**) or a doublet (**IX**) at δ_F 11.84 ppm (J_{FP} = 5.2 Hz).

Compounds **I** reacted with highly reactive 1,3-binucleophiles, 2-aminobut-2-enenitrile (**X**), benzamidine (**XII**), and 4,5-dihydro-1,3-thiazol-2-amine (**XIV**) following the cycloaddition pattern, i.e., nucleophile addition at the C=N bond and subsequent intramolecular cyclization with elimination of methanol molecule. As a result of these transformations we isolated the corresponding 4,5-dihydro-1*H*-pyrrole-3-carbonitriles **XIa**–**XIc**, 4,5-dihydro-1*H*-imidazol-5-ones **XIIIa**–**XIIId**, and 2,3-dihydro-6*H*-imidazo[2,1-*b*][1,3]thiazol-5-ones **XVa**–**XVc**. Our



I, R = H (**a**), 3-Me (**b**), 4-Me (**c**), 5-Me (**d**), 6-Me (**e**), 5-Cl (**f**); **III**, R = H (**a**), 3-Me (**b**), 4-Me (**c**), 5-Cl (**d**); **V**, **VII**, R = H (**a**), 4-Me (**b**).

attempts to perform cyclocondensations of Schiff bases **I** with leass nucleophilic N-substituted ureas, 6-aminouracils, and 3-substituted aminocyclohexenones (which are typical of analogous *N*-acyl, *N*-phosphoryl, and *N*-sulfonyl derivatives [12–15]) were unsuccessful, and the initial compounds were recovered from the reaction mixtures. Presumably, the reason is reduced electrophilicity of the C=N bond in **I**.



XI, **XIII**, **XV**, R = H (**a**), 4-Me (**b**), 5-Me (**c**); **XIIId**, R = 6-Me.

Table 1. Yields, melting points, and elemental analyses of compounds **III**, **V**, **VII**, **IX**, **XI**, **XIII**, and **XV**

Compound no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	91	122–124	45.28	4.32	10.76	$C_{10}H_{11}F_3N_2O_3$	45.46	4.20	10.60
IIIb	88	68–70	47.36	4.83	10.19	$C_{11}H_{13}F_3N_2O_3$	47.49	4.71	10.07
IIIc	86	96–98	47.33	4.85	10.21	$C_{11}H_{13}F_3N_2O_3$	47.49	4.71	10.07
IIId	94	81–83	40.11	3.26	9.51	$C_{10}H_{10}ClF_3N_2O_3$	40.22	3.38	9.38
Va	95	105–107	56.52	4.62	12.26	$C_{16}H_{16}F_3N_3O_2$	56.64	4.75	12.38
Vc	85	114–116	57.63	5.29	11.73	$C_{17}H_{18}F_3N_3O_2$	57.79	5.13	11.89
VIIa	78	81–83	52.81	4.31	16.58	$C_{15}H_{15}F_3N_4O_2$	52.94	4.44	16.46
VIIb	83	96–98	54.11	4.72	15.95	$C_{16}H_{17}F_3N_4O_2$	54.24	4.84	15.81
IX	76	56–57	43.92	5.07	7.45	$C_{14}H_{20}F_3N_2O_5P$	43.76	5.25	7.29
XIa	81	242–244	51.22	3.35	19.73	$C_{12}H_9F_3N_4O$	51.07	3.21	19.85
XIb	78	202–204	52.56	3.89	18.77	$C_{13}H_{11}F_3N_4O$	52.71	3.74	18.91
XIc	76	216–218	52.83	3.58	18.73	$C_{13}H_{11}F_3N_4O$	52.71	3.74	18.91
XIIIa	82	208–210	56.12	3.31	17.35	$C_{15}H_{11}F_3N_4O$	56.25	3.46	17.49
XIIIb	71	201–203	57.61	3.78	16.61	$C_{16}H_{13}F_3N_4O$	57.49	3.92	16.76
XIIIc	78	201–203	57.65	3.75	16.59	$C_{16}H_{13}F_3N_4O$	57.49	3.92	16.76
XIIId	85	206–208	57.33	3.81	16.92	$C_{16}H_{13}F_3N_4O$	57.49	3.92	16.76
XVa	79	217–219	43.56	3.14	18.69	$C_{11}H_9F_3N_4OS$	43.71	3.00	18.53
XVb	76	248–250	45.28	3.64	17.85	$C_{12}H_{11}F_3N_4OS$	45.57	3.51	17.71
XVc	84	242–244	45.43	3.38	17.59	$C_{12}H_{11}F_3N_4OS$	45.57	3.51	17.71

Table 2. ^{1}H and ^{19}F NMR spectra of compounds **III**, **V**, **VII**, **IX**, **XI**, **XIII**, and **XV**

Compound no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm	^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm
IIIa	3.35 s (3H, CH_3O), 3.71 s (3H, CH_3O), 6.65 t (1H, CH_{Ar}, *J* 7.6 Hz), 6.88 d (1H, CH_{Ar}, *J* 7.6 Hz), 7.44 t (1H, CH_{Ar}, *J* 7.6 Hz), 7.75 s (1H, NH), 7.93 d (1H, CH_{Ar}, *J* 7.6 Hz)	0.88 s
IIIb	2.22 s (3H, CH_3), 3.33 s (3H, CH_3O), 3.58 s (3H, CH_3O), 6.21 d (1H, CH_{Ar}, *J* 7.2 Hz), 6.58 t (1H, CH_{Ar}, *J* 7.2 Hz), 7.22 s (1H, NH), 7.74 d (1H, CH_{Ar}, *J* 7.2 Hz)	0.85 s
IIIc	2.24 s (3H, CH_3), 3.31 s (3H, CH_3O), 3.67 s (3H, CH_3O), 6.48 d (1H, CH_{Ar}, *J* 7.3 Hz), 6.63 s (1H, CH_{Ar}), 7.58 s (1H, NH), 7.75 d (1H, CH_{Ar}, *J* 7.0 Hz)	0.87 s
IIId	3.34 s (3H, CH_3O), 3.72 s (3H, CH_3O), 6.89 d (1H, CH_{Ar}, *J* 8.8 Hz), 7.42 d (1H, CH_{Ar}, *J* 8.8 Hz), 7.91 s (1H, CH_{Ar}), 7.99 s (1H, NH)	0.78 s
Va	2.14 s (3H, CH_3), 3.85 s (3H, CH_3O), 5.64 s (1H, NH), 6.48 t (1H, CH_{Ar}, *J* 7.2 Hz), 6.71 m (5H, CH_{Ar}), 7.25 t (1H, CH_{Ar}, *J* 7.2 Hz), 7.79 d (1H, CH_{Ar}, *J* 7.2 Hz), 7.91 s (1H, NH)	2.58 s
Vb	2.13 s (6H, CH_3 + CH_3), 3.68 s (3H, CH_3O), 5.60 s (1H, NH), 6.28 d (1H, CH_{Ar}, *J* 7.3 Hz), 6.39 s (1H, CH_{Ar}), 6.73 m (4 H, CH_{Ar}), 7.64 d (1H, CH_{Ar}, *J* 7.3 Hz), 7.77 s (1 H, NH)	2.68 s
VIIa	3.70 s (3H, CH_3O), 5.83 s (2H, NH), 6.62 m (2H, CH_{Ar}), 6.86 m (3H, CH_{Ar}), 7.02 m (2H, CH_{Ar}), 7.45 t (1H, CH_{Ar}, *J* 7.7 Hz), 7.60 s (1H, NH), 7.95 d (1H, CH_{Ar}, *J* 7.7 Hz)	2.95 s
VIIb	2.24 s (3H, CH_3), 3.67 s (3H, CH_3O), 5.72 s (1H, NH), 5.81 s (1H, NH), 6.45 d (1H, CH_{Ar}, *J* 7.3 Hz), 6.58 t (1H, CH_{Ar}, *J* 7.1 Hz), 7.67 s (1H, CH_{Ar}), 6.79 d (2H, CH_{Ar}, *J* 7.1 Hz), 6.99 t (2H, CH_{Ar}, *J* 7.1 Hz), 7.41 s (1H, NH), 7.81 d (1H, CH_{Ar}, *J* 7.3 Hz)	2.92 s
IX	1.34 t (6H, CH_3CH_2O), 2.23 s (3H, CH_3), 3.65 s (3H, CH_3O), 4.22 m (4H, CH_3CH_2O), 6.43 d (1H, CH_{Ar}, *J* 5.2 Hz), 6.70 s (1H, CH_{Ar}), 7.13 d (1H, NH, *J* 9.1 Hz), 7.76 d (1H, CH_{Ar}, *J* 5.2 Hz)	11.84 d (CF_3, *J* 5.2 Hz)
XIa	2.16 s (3H, CH_3), 7.54 t (1H, CH_{Ar}, *J* 7.1 Hz), 6.82 d (1H, CH_{Ar}, *J* 7.1 Hz), 7.44 t (1H, CH_{Ar}, *J* 7.1 Hz), 7.88 m (2H, CH_{Ar} + NH), 11.09 s (1H, NH)	2.46 s

Table 2. (Contd.)

Compound no.	^{1}H NMR spectrum (DMSO-d_6), δ, ppm	^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm
XIb	2.18 s (3H, CH_3), 2.21 s (3H, CH_3), 6.49 d (1H, CH_{Ar}, *J* 6.8 Hz), 6.65 s (1H, CH_{Ar}), 6.63 s (1H, NH), 7.69 d (1H, CH_{Ar}, *J* 6.8 Hz), 10.88 s (1H, NH)	2.45 s
XIc	2.19 s (3H, CH_3), 6.45 d (1H, CH_{Ar}, *J* 6.9 Hz), 6.71 d (1H, CH_{Ar}, *J* 6.9 Hz), 7.29 t (1H, CH_{Ar}, *J* 6.9 Hz), 7.76 s (1H, NH), 10.99 s (1H, NH)	2.58 s
XIIIa	6.55 t (1H, CH_{Ar}, *J* 7.0 Hz), 6.88 d (1H, CH_{Ar}, *J* 7.0 Hz), 7.49 m (4H, CH_{Ar}), 8.05 d (1H, CH_{Ar}, *J* 7.0 Hz), 11.94 s (1H, NH)	0.23 s
XIIIb	2.25 s (3H, CH_3), 6.38 d (1H, CH_{Ar}, *J* 5.8 Hz), 6.68 s (1H, CH_{Ar}), 7.51 m (3H, CH_{Ar}), 7.65 s + d (2H, CH_{Ar} + NH, *J* 5.8 Hz), 8.04 m (2H, CH_{Ar}), 11.87 s (1H, NH)	0.09 s
XIIIc	2.11 s (3H, CH_3), 6.79 d (1H, CH_{Ar}, *J* 8.4 Hz), 7.23 d (1H, CH_{Ar}, *J* 8.4 Hz), 7.52 m (3H, CH_{Ar}), 7.57 s (1H, NH), 7.63 s (1H, CH_{Ar}), 8.04 d (1H, CH_{Ar}, *J* 6.7 Hz), 11.89 s (1H, NH)	0.21 s
XIIId	2.11 s (3H, CH_3), 6.34 d (1H, CH_{Ar}, *J* 6.9 Hz), 6.65 d (1H, CH_{Ar}, *J* 6.9 Hz), 7.33 t (1H, CH_{Ar}, *J* 6.9 Hz), 7.54 m (3H, CH_{Ar}), 7.76 s (1H, NH), 8.03 d (2H, CH_{Ar}, *J* 7.1 Hz), 11.83 s (1H, NH)	0.34 s
XVa	3.73 m (3H, CH_2N + CH_2S), 4.02 m (1H, CH_2S), 6.75 t (1H, CH_{Ar}, *J* 7.3 Hz), 6.79 d (1H, CH_{Ar}, *J* 7.3 Hz), 7.38 t (1H, CH_{Ar}, *J* 7.3 Hz), 7.88 m (2H, CH_{Ar} + NH)	0.44 s
XVb	2.21 s (1H, CH_3), 3.71 m (3H, CH_2N + CH_2S), 4.01 m (1H, CH_2S), 6.42 d (1H, CH_{Ar}, *J* 7.2 Hz), 6.61 s (1H, CH_{Ar}), 7.77 m (2H, CH_{Ar} + NH)	0.46 s
XVc	2.24 s (3H, CH3), 3.76 m (3H, CH_2N + CH_2S), 3.99 m (1H, CH_2S), 6.43 d (1H, CH_{Ar}, *J* 7.2 Hz), 6.61 d (1H, CH_{Ar}, *J* 7.2 Hz), 7.28 t (1H, CH_{Ar}, *J* 7.2 Hz), 7.84 s (1H, NH)	0.42 s

4,5-Dihydro-1*H*-pyrrole-3-carbonitriles **XIa**–**XIc**, 4,5-dihydro-1*H*-imidazol-5-ones **XIIIa**–**XIIId**, and 2,3-dihydro-6*H*-imidazo[2,1-*b*][1,3]thiazol-5-ones **XVa**–**XVc** were isolated in 69–85% yield as crystalline substances whose structure was confirmed by elemental analyses (Table 1) and NMR data (Table 2). The endocyclic NH proton resonated in the ^{1}H NMR spectra of these compounds in the region δ 8–12 ppm, while fluorine nuclei in the trifluoromethyl group gave rise to singlets in the region δ_F 0.09–2.58 ppm of the ^{19}F NMR spectra.

Thus we have proposed a novel synthetic approach to 2-aminopyridine derivatives modified at the amino group with various trifluoromethyl-containing (including five-membered heterocyclic) fragments via transformations of methyl 3,3,3-trifluoro-2-(pyridin-2-ylimino)propanoates by the action of oxygen-, nitrogen-, and phosphorus-centered nucleophiles and 1,3-C,N- and N,N-binucleophiles.

EXPERIMENTAL

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer at 200.13 and 188.29 MHz, respectively; the chemical shifts were measured relative to tetramethylsilane (^{1}H, internal reference) or CF_3COOH (^{19}F, external reference). The melting points were determined using glass capillaries. Initial Schiff bases **Ia**–**If** were synthesized according to the procedure described in [1]; methanol (**II**), *p*-toluidine (**IV**), phenylhydrazine (**VI**), diethyl phosphonate (**VIII**), 2-aminobut-2-enenitrile (**IX**), benzamidine (**XI**), and 4,5-dihydro-1,3-thiazol-2-amine (**XIII**) were commercial products (from Aldrich) which were used without additional purification.

Methyl 3,3,3-trifluoro-2-methoxy-2-(pyridin-2-yl-amino)propanoate (IIIa), methyl 3,3,3-trifluoro-2-methoxy-2-(3-methylpyridin-2-ylamino)propanoate (IIIb), methyl 3,3,3-trifluoro-2-methoxy-2-(4-methylpyridin-2-ylamino)propanoate (IIIc), and methyl 2-(5-chloropyridin-2-ylamino)-3,3,3-trifluoro-2-methoxypropanoate (IIId) *(general procedure).* Methanol, 0.01 mol, was added under stirring at 20°C to a solution of 0.01 mol of Schiff base **Ia**–**Ic** or **If** in 10 ml of benzene. The mixture was heated for 30 min under reflux, cooled, and evaporated, and the residue was crystallized from hexane. The yields, melting points, elemental analyses, and NMR spectra of compounds **IIIa**–**IIId** are given in Tables 1 and 2.

Methyl 3,3,3-trifluoro-2-(4-methylphenylamino)-2-(pyridin-2-ylamino)propanoate (Va), methyl 3,3,3-trifluoro-2-(4-methylphenylamino)-2-(4-methylpyridin-2-ylamino)propanoate (Vb), methyl 3,3,3-trifluoro-2-(2-phenylhydrazino)-2-(pyridin-2-ylamino)propanoate (VIIa), and methyl 3,3,3-trifluoro-2-(4-methylpyridin-2-ylamino)-2-(2-phenylhydrazino)propanoate (VIIb) *(general procedure).* *p*-Toluidine (**IV**) or phenylhydrazine (**VI**), 0.01 mol, was

added under stirring at 20°C to a solution of 0.01 mol of compound **Ia** or **Ic** in 10 ml of benzene. The mixture was stirred for 1 h and evaporated, and the residue was crystallized from hexane. The yields, melting points, elemental analyses, and NMR spectra of compounds **Va**, **Vb**, **VIIa**, and **VIIb** are given in Tables 1 and 2.

Methyl 2-(diethoxyphosphoril)-3,3,3-trifluoro-2-(pyridin-2-ylamino)propanoate (IX). Diethyl phosphonate (**VIII**), 1.38 g, was added under stirring at 20°C to a solution of 2.32 g of Schiff base **Ia** in 10 ml of benzene. The mixture was heated for 30 min under reflux, cooled and evaporated, and the residue was crystallized from hexane. The yield, melting point, elemental analysis, and NMR spectra of compound **IX** are given in Tables 1 and 2.

2-Methyl-5-oxo-4-(pyridin-2-ylamino)-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (XIa), 2-methyl-4-(4-methylpyridin-2-ylamino)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (XIb), 2-methyl-4-(5-methylpyridin-2-ylamino)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-pyrrole-3-carbonitrile (XIc), 2-phenyl-4-(pyridin-2-ylamino)-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-5-one (XIIIa), 4-(4-methylpyridin-2-ylamino)-2-phenyl-5-trifluoromethyl-4,5-dihydro-1*H*-imidazol-5-one (XIIIb), 4-(5-methylpyridin-2-ylamino)-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-5-one (XIIIc), 4-(6-methylpyridin-2-ylamino)-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-5-one (XIIId), 6-(pyridin-2-ylamino)-6-trifluoromethyl-2,3-dihydro-6*H*-imidazo[2,1-*b*][1,3]thiazol-5-one (XVa), 6-(4-methylpyridin-2-ylamino)-6-trifluoromethyl-2,3-dihydro-6*H*-imidazo[2,1-*b*][1,3]thiazol-5-one (XVb), and 6-(5-methylpyridin-2-ylamino)-6-trifluoromethyl-2,3-dihydro-6*H*-imidazo-[2,1-*b*][1,3]thiazol-5-one (XVc) *(general procedure).* A solution of 0.01 mol of the corresponding Schiff base **I** and 0.01 mol of 2-aminobut-2-enenitrile (**X**), benzamidine (**XII**), or 4,5-dihydro-1,3-thiazol-2-amine (**XIV**) in 10 ml of dimethylformamide was stirred for 1 h at 20°C and was then heated for 2 h at 90–100°C. The mixture was cooled and poured into 50 ml of water, and the precipitate was filtered off and recrystallized from 50% ethanol. The yields, melting points, elemental analyses, and NMR spectra of compounds **XIa**–**XIc**, **XIIIa**–**XIIId**, and **XVa**–**XVc** are given in Tables 1 and 2.

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