Three-component condensation of 5-aminoimidazole derivatives with aldehydes and Meldrum´s acid. Synthesis of 3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones

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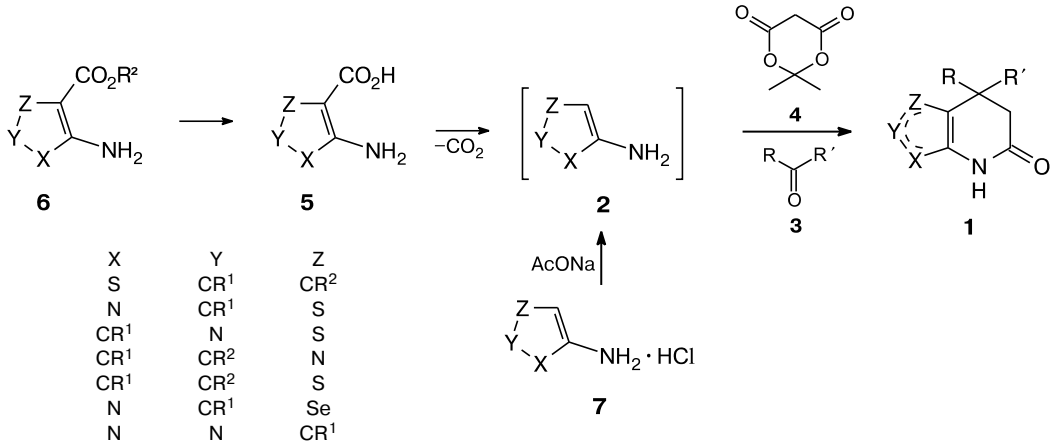
A convenient method for the synthesis of the earlier unknown substituted 3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones was developed based on a three-component condensation of 5-aminoimidazole derivatives, aldehydes, and Meldrum´s acid. Unstable aminoimidazole derivatives were readily formed *in situ* by decarboxylation of 5-amino-4-imidazolecarboxylic acids in acidic medium at room temperature, whose sodium salts were obtained by the alkaline hydrolysis of the corresponding, readily available esters.

Key words: 5-amino-4-imidazolecarboxylic acids, three-component condensation, Meldrum´s acid, 5-aminoimidazoles, decarboxylation, 3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones.

Earlier,[1—8] we have developed a general approach to the synthesis of fused heterocyclic systems **1** containing a dihydropyridin-2-one fragment based on the condensation of labile heterocyclic amines **2** with carbonyl compounds **3** and the Meldrum´s acid **4** (Scheme 1). The unstable aminoheterocycles **2** were generated directly in the reaction medium either from vicinal aminocarboxylic acids **5** obtained by the alkaline hydrolysis of the corresponding, readily available esters **6**, or as a result of neutralization of stable hydrochlorides **7** with anhydrous sodium acetate.

In the present work, we broadened the approach developed on the synthesis of the earlier unknown substituted 3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones **8** (X = Z = = N, Y = CH). The free forms of 5-aminoimidazoles are known to be extremely unstable.[9] We suggested to use as their precursors sodium salts **9**, obtained by alkaline hydrolysis of the corresponding esters **10** (Scheme 2). We showed that the reaction carried out in acetic acid at room temperature during 24 h resulted in the synthesis of the earlier unknown imidazopyridinones **8** in 54—80% yields (Table 1). An increase in the reaction temperature led to

Scheme 1



X	Y	Z
S	CR^1	CR^2
N	CR^1	S
CR^1	N	S
CR^1	CR^2	N
CR^1	CR^2	S
N	CR^1	Se
N	N	CR^1

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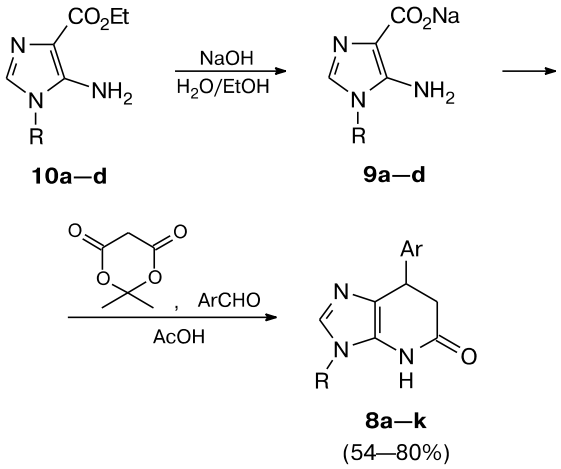
Scheme 2

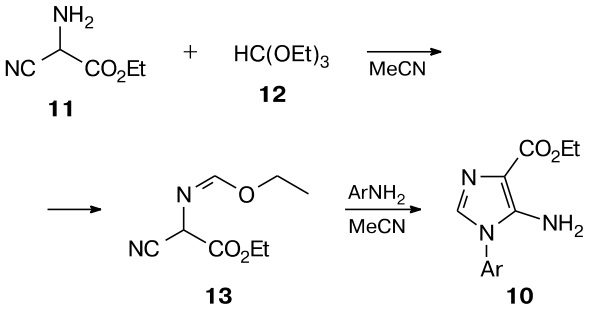


9, 10: R = Ph (**a**), 4-MeO-C_6H_4 (**b**), 3-CF_3-C_6H_4 (**c**), 3-Cl-C_6H_4 (**d**)

resinification of the reaction mixture and decrease in the yields of the target compounds.

It should be noted that the preparation of the starting vicinal amino esters **10** posed a certain problem. The synthesis of esters **10** containing an aryl substituent on the ring nitrogen atom was described in the literature.[10—12] It is based on the reaction of labile 2-amino-2-cyanoacetic ester **11** with ethyl orthoformate **12** and subsequent condensation with anilines (Scheme 3).

Scheme 3



However, from our point of view this approach is not preparatively useful because of high reactivity of imino ester **13**, which is the reason, in particular, for a possibility of the condensation of the latter with the starting 2-amino-2-cyanoacetate **11**, leading to various side products.[12]

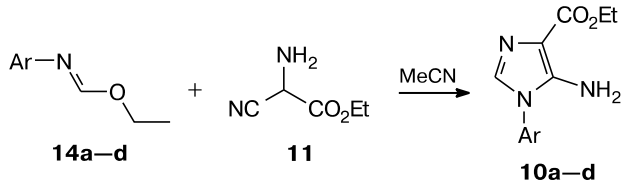
We elaborated a convenient general method for the preparation of 5-amino-4-imidazolecarboxylic esters **10** with the aryl substituent on the ring nitrogen atom. The literature describes an approach to the synthesis of 5-aminoimidazole derivatives based on the reaction of cyclic imidates with 2-aminocyanoacetamide.[13] We suggested that

Table 1. Yields, melting points, and elemental analysis data for compounds **8a—k**

Compound	R	Ar	M.p./°C	Yield	Found / Calculated (%)			Molecular formula
					C	H	N	
8a	Ph	3,4-$(MeO)_2$-C_6H_3	211—212	80	68.51 68.75	5.60 5.48	12.28 12.03	$C_{20}H_{19}N_3O_3$
8b	Ph	Ph	221—222	72	74.50 74.72	5.34 5.23	14.37 14.52	$C_{18}H_{15}N_3O$
8c	Ph	4-MeO-C_6H_4	201—202	78	71.68 71.46	5.25 5.37	13.31 13.16	$C_{19}H_{17}N_3O_2$
8d	4-MeO-C_6H_4	3-Cl-C_6H_4	233—234	61	64.72 64.50	4.66 4.56	11.73 11.88	$C_{19}H_{16}ClN_3O_2$
8e	4-MeO-C_6H_4	3,4-OCH_2O-C_6H_3	239—240	70	65.90 66.11	4.83 4.72	11.69 11.56	$C_{20}H_{17}N_3O_4$
8f	3-Cl-C_6H_4	3,4-$(MeO)_2$-C_6H_3	220—221	56	62.36 62.58	4.82 4.73	10.75 10.95	$C_{20}H_{18}ClN_3O_3$
8g	3-Cl-C_6H_4	3-Cl-C_6H_4	203—204	66	60.11 60.35	3.79 3.66	11.91 11.73	$C_{18}H_{13}Cl_2N_3O$
8h	3-Cl-C_6H_4	3,4-OCH_2O-C_6H_3	222—223	79	62.29 62.05	3.96 3.84	11.25 11.42	$C_{19}H_{14}ClN_3O_3$
8i	3-CF_3-C_6H_4	3,4-$(MeO)_2$-C_6H_3	224—225	54	60.66 60.43	4.46 4.35	9.92 10.07	$C_{21}H_{18}F_3N_3O_3$
8j	3-CF_3-C_6H_4	3-Cl-C_6H_4	212—213	55	58.01 58.25	3.45 3.34	10.58 10.73	$C_{19}H_{13}ClF_3N_3O$
8k	3-CF_3-C_6H_4	3,4-OCH_2O-C_6H_3	227—228	63	60.06 59.85	3.43 3.52	10.61 10.47	$C_{20}H_{14}F_3N_3O_3$

a similar reaction of readily available and stable *N*-aryl-substituted imino esters **14** with 2-aminocyanoacetic ester **11** would lead to imidazoles **10**. In fact, compounds **10** were obtained in good yields as a result of such a condensation (Scheme 4).

Scheme 4



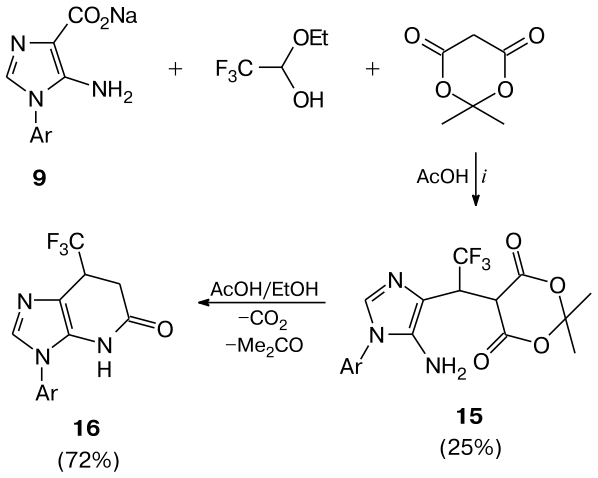
10, 14: Ar = Ph (**a**); 4-MeO-C_6H_4 (**b**); 3-CF_3-C_6H_4 (**c**); 3-Cl-C_6H_4 (**d**)

An important problem to be solved during the present investigation was the isolation and confirmation of the structure of a key intermediate product **15** (Scheme 5) of the three-component condensation under study. We have chosen trifluoroacetic aldehyde hemiacetal as an aldehyde component to effect these studies, since the presence of a trifluoromethyl group significantly simplified confirmation of the structure of intermediate **15** by NMR spectroscopy. The three-component condensation of salts **9**, the Meldrum´s acid, and trifluoroacetic aldehyde hemiacetal at room temperature in acetic acid during 3 h allowed us to obtain the intermediate compound **15** in moderate yield, which was isolated and completely characterized by NMR spectroscopy, mass spectrometry, and elemental analysis. The ^{1}H NMR spectrum of the compound obtained exhibits the signal pattern for the methine proton characteristic of the splitting on the fluorine atoms of the trifluoromethyl group with the spin-spin coupling constant of 12 Hz, that unambiguously confirms the structure of compound **15**. The subsequent cyclization of compound **15** upon heating in alcohol in the presence of excess acetic acid led to the target imidazopyridinone **16** (Scheme 5).

To sum up, taking 5-aminoimidazole derivatives as examples we for the first time synthesized the intermediate **15**, whose intramolecular cyclization with elimination of the CO_2 and acetone molecules led to the target bicyclic products. The isolation of compound **15** and its transformation to imidazopyridinone **16** confirmed the scheme suggested by us earlier[1—8] for the three-component condensation of heterocyclic amines with aldehydes and Meldrum´s acid.

The synthesized products **8** are the solid crystalline compounds, whose structure was confirmed by the elemental analysis data and ^{1}H NMR spectroscopy. The ^{1}H NMR spectra of the products exhibit signals characteristic of the protons of the methine fragment in the region δ 4.15—4.30 and of the nonequivalent protons of the methylene group in the region δ 2.60—3.12, which is in

Scheme 5



Ar = 4-MeO-C_6H_4

i. 20 °C, 3 h.

good agreement with the literature data reported for analogous objects.[1—8]

In conclusion, we have developed a convenient method for the synthesis of the earlier unknown substituted 3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones, which was based on a three-component condensation of 5-aminoimidazoles, aldehydes, and Meldrum´s acid. Sodium salts of 5-amino-4-imidazolecarboxylic acids were shown to serve as synthetic equivalents of 5-aminoimidazoles. It was found that the reaction proceeded through the formation of an intermediate, whose subsequent cyclization led to the target products.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance II 300 (300 MHz) spectrometer in DMSO-d_6. Mass spectra were obtained on a FINNIGAN MAT INCOS 50 instrument (direct injection, electron impact, 70 eV). Melting points were measured on a Boetius heating stage and were not corrected.

Reagents and solvents used in the work were commercially available (Acros Organics) and used without additional purification.

Ethyl 2-aminocyanoacetate (11)[14] and imino esters 14a (R = Ph),[15] 14b (R = 4-$MeOC_6H_4$),[16] 14c (R = 3-$CF_3C_6H_4$ obtained similarly to 14a), and 14d (R = 3-ClC_6H_4)[17] were obtained according to the methods described in the literature.[14—17]

Ethyl 5-amino-1-phenyl-1*H*-imidazole-4-carboxylate (10a). A mixture of aminocyanoacetate **11** (12.8 g, 0.1 mmol) and imino ester (14.9 g, 0.1 mmol) **14a** in acetonitrile (75 mL) was refluxed for 30 min, then, the reaction mixture was cooled, a precipitate formed was filtered off and washed with ethanol on the filter. The yield was 15.1 g (65%). M.p. 203—204 °C. ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, CH_3, J = 7.1 Hz); 4.22 (q, 2 H, CH_2, J = 7.1 Hz); 5.91 (s, 2 H, NH_2); 7.35 (s, 1 H, CH);

7.43—7.62 (m, 5 H, C_6H_5). Found (%): C, 62.54; H, 5.58; N, 18.32. $C_{12}H_{13}N_3O_2$. Calculated (%): C, 62.33; H, 5.67; N, 18.17. Esters **10b**—**d** were obtained similarly.

Ethyl 5-amino-1-(4-methoxyphenyl)-1*H*-imidazole-4-carboxylate (10b). The yield was 63%. M.p. 223—224 °C. ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, CH_3, J = 7.1 Hz); 3.82 (s, 3 H, OCH_3); 4.22 (q, 2 H, CH_2, J = 7.1 Hz); 5.83 (s, 2 H, NH_2); 7.11 (d, 2 H, C_6H_4, J = 8.1 Hz); 7.28 (s, 1 H, CH); 7.39 (d, 2 H, C_6H_4, J = 8.1 Hz). Found (%): C, 60.01; H, 5.67; N, 18.24. $C_{13}H_{15}N_3O_3$. Calculated (%): C, 59.76; H, 5.79; N, 16.08.

Ethyl 5-amino-1-(3-trifluoromethylphenyl)-1*H*-imidazole-4-carboxylate (10c). The yield was 57%. M.p. 190—191 °C. ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, CH_3, J = 7.1 Hz); 4.22 (q, 2 H, CH_2, J = 7.1 Hz); 6.08 (s, 2 H, NH_2); 7.45 (s, 1 H, CH); 7.75—7.93 (m, 4 H, C_6H_4). Found (%): C, 51.97; H, 3.93; N, 14.18. $C_{13}H_{12}F_3N_3O_2$. Calculated (%): C, 52.18; H, 4.04; N, 14.04.

Ethyl 5-amino-1-(3-chlorophenyl)-1*H*-imidazole-4-carboxylate (10d). The yield was 68%. M.p. 199—200 °C. ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, CH_3, J = 7.1 Hz); 4.22 (q, 2 H, CH_2, J = 7.1 Hz); 6.01 (s, 2 H, NH_2); 7.40 (s, 1 H, CH); 7.43—7.70 (m, 4 H, C_6H_4). Found (%): C, 54.02; H, 4.66; N, 15.03. $C_{12}H_{12}ClN_3O_2$. Calculated (%): C, 54.25; H, 4.55; N, 15.81.

Synthesis of 3,7-diaryl-3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-ones (8a—k) (general procedure). A mixture of the corresponding ester **10** (5 mmol) and NaOH (0.4 g, 10 mmol) in ethanol (3 mL) and water (3 mL) was refluxed for 4 h, then, the solution was cooled, a salt formed was filtered off and washed with ethanol on the filter. The salt obtained was further used without additional purification. A mixture of the previously obtained salt (4 mmol), Meldrum´s acid (0.64 g, 4.4 mmol), and the corresponding aldehyde (4.2 mmol) in acetic acid (12 mL) was kept for 24 h at room temperature, then, the solvent was evaporated *in vacuo*, the residue was recrystallized from aqueous ethanol. Characteristics of compounds **8a**—**k** are given in Tables 1 and 2.

5-{1-[5-Amino-1-(4-methoxyphenyl)-1*H*-imidazol-4-yl]-2,2,2-trifluoroethyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (15). A mixture of ester **10b** (1.3 g, 5 mmol) and NaOH (0.4 g,

Table 2. ^{1}H NMR spectra (DMSO-d_6) of compounds **8a**—**k**

Compound	H—C—H	H—C—H (dd, 1 H)	CH	δ, J/Hz			NH
				R	CH_{imide}	Ar	
8a	2.65 (J = 7.1, J = 16.1)	3.07 (J = 7.1, J = 16.1)	4.15 (J = 7.1, J = 7.1)	7.41—7.62 (m, 6 H)		4.71 (s, 6 H, 2 OMe); 6.69 (m, 1 H, C_6H_3); 6.89 (m, 2 H, C_6H_3)	10.11
8b	2.65 (J = 7.1, J = 16.1)	3.12 (J = 7.1, J = 16.1)	4.23 (J = 7.1, J = 7.1)	7.41—7.62 (m, 6 H)		7.18—7.38 (m, 5 H)	10.12
8c	2.62 (J = 7.1, J = 16.1)	3.08 (J = 7.1, J = 16.1)	4.17 (J = 7.1, J = 7.1)	7.41—7.62 (m, 6 H)		6.87 (d, 2 H, C_6H_4, J = 8); 6.12 (d, 2 H, C_6H_4, J = 8); 4.71 (s, 3 H, OMe)	10.12
8d	2.66 (J = 7.1, J = 16.1)	3.10 (J = 7.1, J = 16.1)	4.28 (J = 7.1, J = 7.1)	7.04—7.51 (m, 9 H); 4.81 (s, 3 H, OMe)			10.15
8e	2.60 (J = 7.1, J = 16.1)	3.05 (J = 7.1, J = 16.1)	4.15 (J = 7.1, J = 7.1)	4.81 (s, 3 H, OMe); 7.09 (d, 2 H, C_6H_4, J = 8.1); 7.40 (d, 2 H, C_6H_4, J = 8.1)	7.49 (s, 1 H)	5.98 (s, 2 H, OCH_2O); 6.65 (d, 1 H, C_6H_3); 6.76 (s, 1 H, C_6H_3); 6.83 (d, 1 H, C_6H_3)	10.09
8f	2.65 (J = 7.1, J = 16.1)	3.07 (J = 7.1, J = 16.1)	4.18 (J = 7.1, J = 7.1)	7.42—7.68 (m, 5 H)		3.72 (s, 6 H, 2 OMe); 6.65 (m, 1 H, C_6H_3); 6.88 (m, 2 H, C_6H_3)	10.25
8g	2.70 (J = 7.1, J = 16.1)	3.10 (J = 7.1, J = 16.1)	4.30 (J = 7.1, J = 7.1)	7.42—7.70 (m, 5 H)		7.18—7.40 (m, 4 H, C_6H_4)	10.32
8h	2.60 (J = 7.1, J = 16.1)	3.05 (J = 7.1, J = 16.1)	4.16 (J = 7.1, J = 7.1)	7.42—7.72 (m, 5 H)		5.98 (s, 2 H, OCH_2O); 7.65 (d, 1 H, C_6H_3); 7.76 (s, 1 H, C_6H_3); 7.83 (d, 1 H, C_6H_3)	10.24
8i	2.67 (J = 7.1, J = 16.1)	3.09 (J = 7.1, J = 16.1)	4.18 (J = 7.1, J = 7.1)	7.72—7.93 (m, 4 H, C_6H_4)	7.69 (s, 1 H)	3.72 (s, 6 H, 2 OMe); 6.68 (d, 1 H, C_6H_3, J = 7.1);6.88 (d, 2 H, C_6H_3, J = 7.1)	10.30
8j	2.70 (J = 7.1, J = 16.1)	3.10 (J = 7.1, J = 16.1)	4.30 (J = 7.1, J = 7.1)	7.75—7.95 (m, 4 H, C_6H_4)	7.70 (s, 1 H)	7.19—7.40 (m, 4 H, C_6H_4)	10.38
8k	2.60 (J = 7.1, J = 16.1)	3.08 (J = 7.1, J = 16.1)	4.19 (J = 7.1, J = 7.1)	7.75—7.92 (m, 4 H, C_6H_4)	7.70 (s, 1 H)	5.98 (s, 2 H, OCH_2O); 7.65 (d, 1 H, C_6H_3); 7.76 (s, 1 H, C_6H_3); 7.83 (d, 1 H, C_6H_3)	10.30

10 mmol) in ethanol (3 mL) and H_2O (3 mL) was refluxed for 4 h, then, the solution was cooled, a salt formed was filtered off and washed with ethanol on the filter. A mixture of the salt obtained (4 mmol), Meldrum´s acid (0.64 g, 4.4 mmol), and trifluoroacetic aldehyde hemiacetal (0.86 g, 6 mmol) in acetic acid (15 mL) was stirred for 3 h at room temperature until a precipitate was completely dissolved, then, concentrated until the weight was constant, the residue obtained was recrystallized from aq. ethanol. The yield was 0.43 g (25%). M.p. 201—203 °C. ^{1}H NMR (DMSO-d_6), δ: 1.55 (s, 6 H, 2 CH_3); 4.82 (s, 3 H, OMe); 5.18 (q, 1 H, CH—CF_3, J = 12.1 Hz); 5.52 (s, 2 H, NH_2); 7.16 (d, 2 H, C_6H_4, J = 8.1 Hz); 7.58 (d, 2 H, C_6H_4, J = 8.1 Hz); 8.61 (s, 1 H, CH_{imid}); 15.79 (s, 1 H, CH_{meldr}). Found (%): C, 52.53; H, 4.51; N, 10.01. $C_{18}H_{18}F_3N_3O_5$. Calculated (%): C, 52.30; H, 4.39; N, 10.17. MS (EI, 70 eV) m/z: 413 $[M]^+$.

3-(4-Methoxyphenyl)-7-trifluoromethyl-3,4,6,7-tetrahydroimidazo[4,5-*b*]pyridin-5-one (16). Acetic acid (0.24 g, 4 mmol) was added to a solution of compound **15** (0.41 g, 1 mmol) in ethanol (2 mL), the mixture was refluxed for 2 h, then another portion of acetic acid (0.24 g, 4 mmol) was added followed by reflux for 6 h. The solution was cooled and diluted with water (10 mL). A precipitate formed was filtered off and washed with water on the filter. The yield was 0.22 g (72%). M.p. 225—227 °C. ^{1}H NMR (DMSO-d_6), δ: 2.59 (m, 1 H, H—C—H); 3.15 (m, 1 H, H—C—H); 3.88 (m, 1 H, CH—CF_3); 7.09 (d, 2 H, C_6H_4, J = 8.1 Hz); 7.38 (d, 2 H, C_6H_4, J = 8.1 Hz); 7.51 (s, 1 H, CH_{imid}); 10.21 (s, 1 H, NH). Found (%): C, 54.25; H, 4.01; N, 13.65. $C_{14}H_{12}F_3N_3O_2$. Calculated (%): C, 54.02; H, 3.89; N, 13.50.

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