Benzamidines in cyclocondensation with hexafluoroacetone and methyl trifluoropyruvate acyl- and ethoxycarbonylimines

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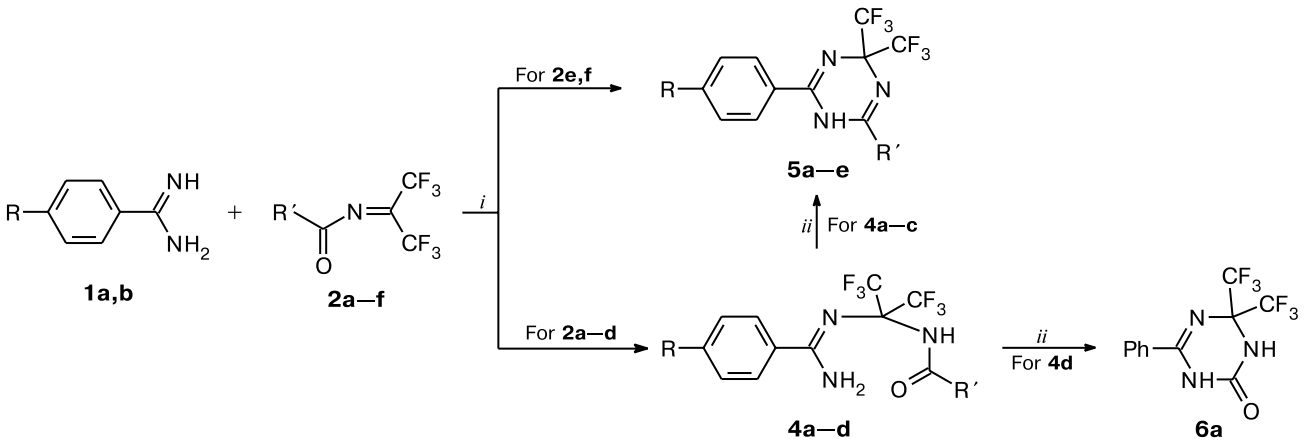
The reactions of hexafluoroacetone and methyl trifluoropyruvate acyl- and ethoxycarbonylimines with benzamidines afford fluoro-containing heterocycles of four structural types: dihydrotriazines, dihydrotriazinones, imidazoles, and imidazooxazoles.

Key words: benzamidines, acylimines, ethoxycarbonylimines, hexafluoroacetone, methyl trifluoropyruvate, dihydrotriazines, dihydrotriazinones, imidazolines, imidazooxazole, cyclocondensation, heterocyclization.

Benzamidines are successfully used as 1,3-bis-nucleophiles in syntheses of nitrogen-containing heterocycles, including fluoro-containing heterocycles, by cyclocondensation with various bis-electrophilic agents, for instance, 3-oxocarboxylates,[1,2] 1,3-dicarbonyl compounds,[3] unsaturated carbonyl compounds,[4] and ethyl pentafluorobutyrate.[5]

In this work, we present data on the cyclocondensation of benzamidines **1** with hexafluoroacetone acyl- and ethoxycarbonylimines **2** and methyl trifluoropyruvate acyl- and ethoxycarbonylimines **3**, which serve as bis-electrophilic agents, as we have shown previously.[6,7] Benzamidines **1**, similarly to other amino-containing compounds, react exothermically with imines **2** and **3** to form five different reaction products, depending on the nature of compounds **1**, **2**, and **3**. For example, the reactions of benzamidines **1a,b** with imines **2a—d** in benzene at 20 °C afford stable acyclic adducts of the iminic N atom of benzamidines **1a,b** at the azomethine bond of compounds **2a—d** in 72—85% yields (Scheme 1). This is

Scheme 1



Reagents and conditions: *i*. PhH, 20 °C, 1 h; *ii*. Et_3N, DMF, Δ, 1 h.

1: R = H (**a**), Me (**b**)
2: R′ = Me (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), EtO (**d**), $PhCH_2$ (**e**), $PhOCH_2$ (**f**)
4: R = H, R′ = Me (**a**); R = H, R′ = Ph (**b**); R = Me, R′ = 4-ClC_6H_4 (**c**); R = H, R′ = EtO (**d**)
5: R = H, R′ = Me (**a**); R = H, R′ = Ph (**b**); R = Me, R′ = 4-ClC_6H_4 (**c**); R = H, R′ = $PhCH_2$ (**d**); R = H, R′ = $PhOCH_2$ (**e**)

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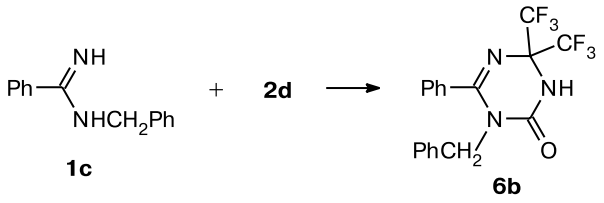
confirmed by the signal from the NH_2 group (a singlet with the 2 H intensity at δ 5.75—6.80) in the ^1H NMR spectra of products **4a—d**.

Refluxing of compounds **4a—d** in DMF (1 h) in the presence of catalytic amounts of Et_3N produces the corresponding dihydrotriazines **5a—c** or dihydrotriazinone **6a** (in the case of **4d**) in 61—77% yields.

We detected no acyclic products like compound **4** upon the reaction of phenyl- and phenoxyacetylimines **2e**,**f** with benzamidines, because dihydrotriazines **5d,e** are formed immediately (see Scheme 1).

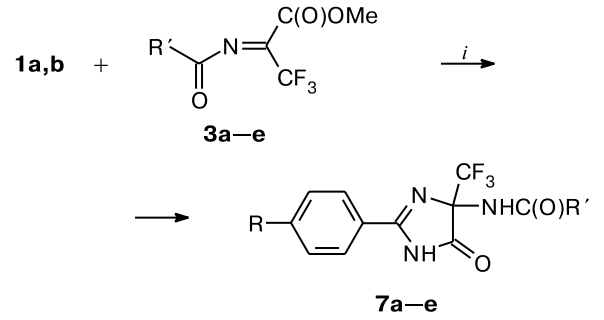
No acyclic products were either detected upon the reaction of *N*-benzylbenzamidine (**1c**) with imine **2d**, and dihydrotriazinone **6b** was obtained (Scheme 2).

Scheme 2



Unlike imines **2**, imines **3** serve as 1,2-bis-electrophiles in the reaction with benzamidines **1a,b** to form dihydroimidazoles **7a—e** (Scheme 3) in 65—79% yields (despite two acyl groups in molecule **3**, which does not exclude a possibility of formation of both five- and six-membered cycles in the reactions).

Scheme 3

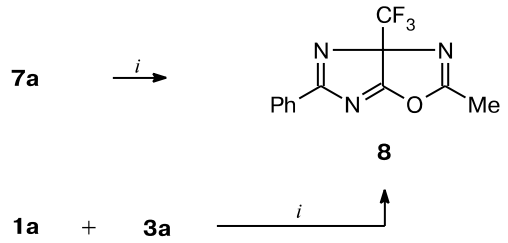


Reagents and conditions: *i*. PhH, 20 °C, 1 h.

R = H (**a—c**, **e**), Me (**d**);
R′ = Me (**a**), Et (**b**), 4-ClC_6H_4 (**c**), 2-FC_6H_4 (**d**), EtO (**e**)

Dihydrotriazines **5a—e**, dihydrotriazinones **6a**,**b**, and dihydroimidazoles **7a—e** are crystalline solids, whose compositions and structures were confirmed by elemental analysis and NMR spectroscopy. The ^{19}F NMR spectra of these compounds contain characteristic signals: the signals of the geminal CF_3 groups at δ −1.8 to −0.5 for triazines **5a—e** and triazinones **6a**,**b** and the signal of the CF_3 group at δ 0.5—1.7 for imidazolinones **7a—e**. The structure of compound **7a** was confirmed by the chemical transformation. Its refluxing in DMF in the presence of catalytic amounts of Et_3N produces imidazooxazole **8** in 82% yield. The latter was also obtained directly from an equimolar mixture of compounds **1a** and **3a** by its refluxing in DMF (Scheme 4).

Scheme 4



Reagents and conditions: *i*. DMF, Et_3N, Δ, 2 h.

Thus, the studied transformations of benzamidines in the reactions with hexafluoroacetone and methyl trifluoropyruvate acyl- and ethoxycarbonylimines made it possible to propose preparative methods for the syntheses of earlier unknown fluoro-containing heterocycles of four structural types: dihydrotriazines, dihydrotriazinones, dihydroimidazoles, and imidazooxazoles. The synthesis of the latter is the first example of cascade cyclocondensation of polyfluoroketone acylimines in reactions with bis-nucleophiles.

Experimental

^1H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer. Melting points were determined in a glass capillary. Acyl- and ethoxycarbonylimines **2a—d** and **3a—e** were synthesized according to known procedures.[8,9]

Amides 4a—d (general procedure). Acylimine **2a—d** (10 mmol) was added to a solution of benzamidine **1** (10 mmol) in benzene (20 mL), and the mixture was stirred for 1 h. Benzene was evaporated, and the residue was crystallized from a benzene—hexane (1 : 1) mixture. The yields, melting points, and spectral characteristics of compounds **4a—d** are presented in Tables 1 and 2.

Triazines 5a—c (general procedure). Amides **4a—c** (5 mmol) and Et_3N (0.1 mL) were refluxed in DMF (10 mL) for 2 h. The reaction mixture was poured into water (50 mL), and the precipitate that formed was filtered off and crystallized from 50% EtOH. The yields, melting points, and spectral characteristics of compounds **5a—c** are presented in Tables 1 and 2.

Triazines 5d,e (general procedure). Acylimine **2e** or **2f** (10 mmol) was added to a solution of benzamidine **1a** (10 mmol)

Table 1. Yields, melting points, and elemental analysis data for compounds **4a—d**, **5a—e**, **6a,b**, **7a—e**, and **8**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula
			C	H	N	
N-[1-(Benzimidoylamino)-2,2,2-trifluoro-1-trifluoromethylethyl]acetamide (**4a**)	85	157—158	44.19 44.05	3.24 3.39	12.99 12.84	$C_{12}H_{11}F_6N_3O$
N-[1-(Benzimidoylamino)-2,2,2-trifluoro-1-trifluoromethylethyl]benzamide (**4b**)	72	121—122	52.62 52.45	3.19 3.37	10.92 10.79	$C_{17}H_{13}F_6N_3O$
N-[1-(Benzimidoylamino)-4-chloro-2,2,2-trifluoro-1-trifluoromethylethyl]benzamide (**4c**)	75	165—166	49.55 49.39	3.06 3.22	9.79 9.60	$C_{18}H_{14}ClF_6N_3O$
N-[1-(Benzimidoylamino)-2,2,2-trifluoro-1-trifluoromethylethyl] ethyl carbamate (**4d**)	81	136—138	43.89 43.71	3.88 3.67	11.89 11.76	$C_{13}H_{13}F_6N_3O_2$
2-Methyl-4,4-bis(trifluoromethyl)-6-phenyl-1,4-dihydro[1,3,5]triazine (**5a**)	77	167—168	46.80 46.61	2.79 2.93	13.75 13.59	$C_{12}H_9F_6N_3$
4,4-Bis(trifluoromethyl)-2-(4-chlorophenyl)-6-phenyl-1,4-dihydro[1,3,5]triazine (**5b**)	64	175—177	55.17 54.99	2.89 2.99	11.49 11.32	$C_{17}H_{11}F_6N_3$
4,4-Bis(trifluoromethyl)-2,6-diphenyl-1,4-dihydro[1,3,5]triazine (**5c**)	61	200—201	51.67 51.51	2.97 2.88	10.19 10.01	$C_{18}H_{12}ClF_6N_3$
2-Benzyl-4,4-bis(trifluoromethyl)-6-phenyl-1,4-dihydro[1,3,5]triazine (**5d**)	77	95—97	56.28 56.11	3.57 3.40	11.09 10.91	$C_{18}H_{13}F_6N_3$
4,4-Bis(trifluoromethyl)-2-phenoxy-6-phenyl-1,4-dihydro[1,3,5]triazine (**5e**)	72	112—113	53.99 53.87	3.11 3.27	10.59 10.47	$C_{18}H_{13}F_6N_3$
4,4-Bis(trifluoromethyl)-6-phenyl-1,4-dihydro-1*H*-[1,3,5]triazin-2-one (**6a**)	68	155—157	42.59 42.46	2.42 2.27	13.69 13.50	$C_{11}H_7F_6N_3O$
1-Benzyl-4,4-bis(trifluoromethyl)-6-phenyl-1,4-dihydro-1*H*-[1,3,5]triazin-2-one (**6b**)	79	143—144	53.98 53.87	3.09 3.27	10.59 10.47	$C_{18}H_{13}F_6N_3O$
N-(5-Oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)acetamide (**7a**)	77	183—184	50.69 50.53	3.35 3.53	14.89 14.73	$C_{12}H_{10}F_3N_3O_2$
N-(5-Oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)propionamide (**7b**)	65	238—240	52.29 52.18	4.22 4.04	14.21 14.04	$C_{13}H_{12}F_3N_3O_2$
4-Chloro-*N*-(5-oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl)benzamide (**7c**)	68	183—184	53.60 53.43	2.79 2.90	11.19 11.01	$C_{17}H_{11}ClF_3N_3O$
2-Fluoro-*N*-[2-(4-methylphenyl)-5-oxo-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl]benzamide (**7d**)	78	212—214	57.16 57.00	3.26 3.45	11.19 11.08	$C_{18}H_{13}F_4N_3O_2$
N-(5-Oxo-2-phenyl-4-trifluoromethyl-4,5-dihydro-1*H*-imidazol-4-yl) ethyl carbamate (**7e**)	71	212—213	49.69 49.53	3.89 3.84	13.48 13.33	$C_{13}H_{12}F_3N_3O_3$
2-Methyl-5-phenyl-3a-trifluoromethyl-3a*H*-imidazo[4,5-*d*]oxazole (**8**)	82	222—224	53.77 53.94	3.18 3.02	15.91 15.73	$C_{12}H_8F_3N_3O$

Table 2. ^1H and ^{19}F NMR spectra of the synthesized compounds in DMSO-d_6

Compound	δ_H (J/Hz)	δ_F (s)
4a	2.12 (s, 3 H, Me); 6.71 (br.s, 2 H, NH_2); 7.46 (m, 3 H, H arom.); 7.81 (d, 2 H, H arom., J = 8.2); 8.42 (s, 1 H, NH)	5.26
4b	6.80 (br.s, 2 H, NH_2); 7.42 (m, 2 H, H arom.); 7.48 (m, 3 H, H arom.); 7.55 (t, 1 H, H arom., J = 7.5); 7.84 (m, 4 H, H arom.); 8.74 (s, 1 H, NH)	3.05
4c	2.38 (s, 3 H, Me); 6.67 (br.s, 2 H, NH_2); 7.11, 7.32, 7.70, 7.83 (all d, 2 H each, H arom., J = 8.0); 8.65 (s, 1 H, NH)	5.81
4d	1.31 (t, 3 H, Me, J = 6.9); 4.19 (q, 2 H, CH_2, J = 6.9); 5.43 (s, 1 H, NH); 5.75 (br.s, 2 H, NH_2); 7.45 (m, 3 H, H arom.); 7.83 (d, 2 H, H arom., J = 8.0)	1.86
5a	2.20 (s, 3 H, Me); 7.52 (m, 3 H, H arom.); 7.95 (d, 2 H, H arom., J = 8.0); 10.58 (s, 1 H, NH)	−1.51
5b	7.35, 7.52 (both m, 3 H each, H arom.); 7.82, 8.03 (both d, 2 H each, H arom., J = 8.0); 11.09 (s, 1 H, NH)	−1.0
5c	2.45 (s, 3 H, Me); 7.30, 7.52, 7.92, 8.13 (all d, 2 H each, H arom., J = 8.2); 11.09 (s, 1 H, NH)	−1.0

(*to be continued*)

Table 2 (*continued*)

Compound	δ_H (J/Hz)	δ_F (s)
5d	2.12 (s, 2 H, CH_2); 7.12—7.52 (m, 8 H, H arom.); 7.86 (d, 2 H, H arom., J = 8.0); 10.68 (s, 1 H, NH)	−1.13
5e	4.76 (s, 2 H, CH_2); 6.82—7.06 (m, 3 H, H arom.); 7.24 (m, 2 H, H arom.); 7.44 (m, 3 H, H arom.); 7.96 (d, 2 H, H arom., J = 8.0); 11.02 (s, 1 H, NH)	−0.51
6a	7.45 (m, 3 H, H arom.); 8.03 (d, 2 H, H arom., J = 8.0); 9.18, 10.84 (both s, 1 H each, NH)	−1.80
6b	4.85 (s, 2 H, CH_2); 6.89, 7.18 (both d, 2 H each, H arom., J = 8.1); 7.39 (m, 6 H, H arom.); 9.82 (s, 1 H, NH)	−1.24
7a	1.97 (s, 3 H, Me); 7.53 (m, 3 H, H arom.); 8.05 (d, 2 H, H arom., J = 8.0); 9.38, 12.0 (both s, 1 H each, NH)	0.47
7b	1.31 (t, 3 H, Me, J = 6.8); 2.24 (q, 2 H, CH_2, J = 6.8); 7.45 (m, 3 H, H arom.); 8.04 (d, 2 H, H arom., J = 8.0); 9.10, 11.86 (both s, 1 H each, NH)	0.49
7c	7.36 (m, 3 H, H arom.); 7.52 (m, 2 H, H arom.); 7.93, 8.13 (both d, 2 H each, H arom., J = 8.2); 9.73, 12.11 (both s, 1 H each, NH)	1.73
7d	2.38 (s, 3 H, Me); 7.11—7.39 (m, 4 H, H arom.); 7.53 (m, 1 H, H arom.); 7.75 (t, 1 H, H arom., J = 8.0); 8.00 (d, 2 H, H arom., J = 8.0); 9.32, 12.07 (both s, 1 H each, NH)	0.88, −32.94*
7e	1.25 (t, 3 H, Me, J = 7.0); 4.06 (q, 2 H, CH_2, J = 7.0); 7.52 (m, 3 H, H arom.); 8.11 (d, 2 H, H arom., J = 8.2); 8.76, 12.05 (both s, 1 H each, NH)	0.58
8	1.94 (s, 3 H, Me); 7.52 (m, 3 H, H arom.); 8.08 (d, 2 H, H arom., J = 8.2)	1.01

* M (1 F).

in benzene (20 mL), and the mixture was stirred for 1 h. Benzene was evaporated, and the residue was crystallized from a benzene—hexane (1 : 1) mixture. The yields, melting points, and spectral characteristics of compounds **5d,e** are presented in Tables 1 and 2.

Triazinone 6a was synthesized by the ring closure of compound **4d** under the conditions for the synthesis of compounds **5a—c** (see Tables 1 and 2).

Triazinone 6b was synthesized by the reaction of *N*-benzylamidine **1c** and imine **2d** under the conditions for the synthesis of compounds **5d,e** (see Tables 1 and 2).

Imidazolones 7a—e (general procedure). Acylimine **3** (10 mmol) was added to a solution of amidine **1** (10 mmol) in benzene (20 mL), and the mixture was stirred for 1 h. Benzene was evaporated, and the residue was crystallized from benzene—hexane (1 : 1) mixture. The yields, melting points, and spectral characteristics of compounds **7a—e** are presented in Tables 1 and 2.

Compound 8. Imidazolone **7a** (1.43 g, 5 mmol) and Et_3N (0.1 mL) were refluxed in DMF (10 mL) for 2 h. The reaction mixture was poured into water (50 mL), and the precipitate that formed was filtered off and recrystallized from 50% EtOH. The yield was 1.1 g (82%). The physicochemical characteristics of compound **8** are presented in Tables 1 and 2.

References

1. J. Lazar and G. Bemath, *J. Heterocycl. Chem.*, 1990, **27**, 1885.
2. J.-J. Wang, B.-Z. Yin, G.-J. Jiang, and K. Imafuku, *J. Heterocycl. Chem.*, 1990, **27**, 1181.
3. K. Takagi, A. Bajnali, and M. Hubert-Habart, *Heterocycles*, 1990, **31**, 1105.
4. A. L. Weis, *Synthesis*, 1985, 528.
5. H.-P. Guan, Q.-S. Hu, and C.-M. Hu, *Synthesis*, 1996, 997.
6. V. B. Sokolov, A. Yu. Aksinenko, and I. V. Martynov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2001, 1064 [*Russ. Chem. Bull.*, *Int. Ed.*, 2001, **50**, 1113].
7. V. B. Sokolov and A. Yu. Aksinenko, *Izv. Akad. Nauk*, *Ser. Khim.*, 2003, 2053 [*Russ. Chem. Bull.*, *Int. Ed.*, 2003, **52**, 2167].
8. O. V. Korenchenko, V. B. Sokolov, A. Yu. Aksinenko, and I. V. Martynov, *Izv Akad. Nauk SSSR, Ser. Khim.*, 1990, 373 [*Bull. Acad. Sci. USSR*, *Div. Chem. Sci.*, 1990, **39**, 313 (Engl. Transl.)].
9. S. N. Osipov, V. B. Sokolov, A. F. Kolomiets, I. V. Martynov, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 1185 [*Bull. Acad. Sci. USSR*, *Div. Chem. Sci.*, 1987, **36**, 1038 (Engl. Transl.)].

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