N-Substituted imines of methyl trifluoropyruvate in the synthesis of 5-amino-5-trifluoromethylhydantoins

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Cyclocondensation of *N*-substituted imines of methyl trifluoropyruvate with monosubstituted ureas afforded novel 5-amino-5-trifluoromethylhydantoins.

Key words: hydantoins, imidazolidine-2,4-diones, *N*-substituted imines, methyl trifluoropyruvate, fluoro-containing ureas, cyclocondensation.

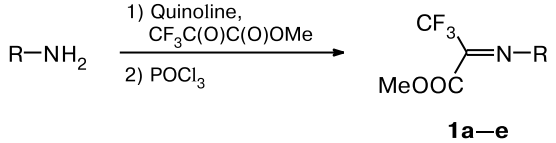
Hydantoins (imidazolidine-2,4-diones) are nitrogen-containing heterocycles, which are widely used in medicinal (anticonvulsants[1] and anticancer drugs[2]) and agrochemical practice (fungicides[3] and herbicides[4]). The biological activities of many various hydantoins have been studied to date.[5]

General methods for the synthesis of these compounds involve reactions of α-amino acids with alkyl or aryl isocyanates, as well as reactions of *N*-substituted ureas with alkyl α-halo carboxylates; these transformations have been studied with a sufficiently great number of acids, ureas, and isocyanates.[6] At the same time, the problem of the applicability of the known methods to the synthesis of 5-aminohydantoins, which are cyclic derivatives of α-amino acids and are of interest as potential biologically active substances, remains open.

Here we report on the synthesis of novel 5-amino-5-trifluoromethylhydantoins from *N*-substituted imines of methyl trifluoropyruvate **1** and monosubstituted ureas **2**. This investigation was motivated by data on the cyclocondensation of acylimines of methyl trifluoropyruvate with C,N-binucleophiles of the enamine type[7] and with N,N-binucleophiles of the amidine type.[8]

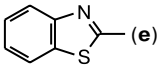
The starting *N*-substituted imines of methyl trifluoropyruvate **1a**—**e** were prepared in 69—76% yields by successive addition of equimolar amounts of quinoline, methyl trifluoropyruvate, and $POCl_3$ to a suspension of an appropriate amide in benzene (Scheme 1).

Scheme 1



1a—e

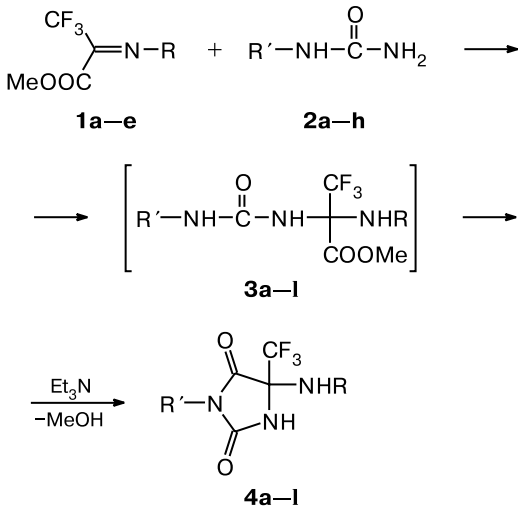
R = Ac (**a**), Bz (**b**), 4-$FC_6H_4C(O)$ (**c**), 4-$ClC_6H_4C(O)$ (**d**),



(**e**)

Imines **1a**—**e** reacted with ureas **2a**—**h** to give adducts **3** (Scheme 2), the reaction conditions being varied with the imine nature. For instance, the reactions of imines **1a**—**d** with ureas **2a**—**h** were exothermic, while for the

Scheme 2



2	R′	**2**	R′	**2**	R′	**2**	R′
a	Me	**c**	Ph	**e**	2-Furfuryl	**g**	4-MeC_6H_4
b	Bu	**d**	Bn	**f**	4-FC_6H_4	**h**	*cyclo*-C_6H_{11}

3, **4**	R	R′	**3**, **4**	R	R′
a	Ac	Me	**g**	4-$ClC_6H_4C(O)$	Bu^i
b	Ac	Bn	**h**	4-$ClC_6H_4C(O)$	2-Furfuryl
c	Bz	Me	**i**	Benzothiazolyl	Ph
d	Bz	Bn	**j**	Benzothiazolyl	4-MeC_6H_4
e	4-$FC_6H_4C(O)$	4-FC_6H_4	**k**	Benzothiazolyl	*cyclo*-C_6H_{11}
f	4-$FC_6H_4C(O)$	Bn	**l**	Benzothiazolyl	Bn

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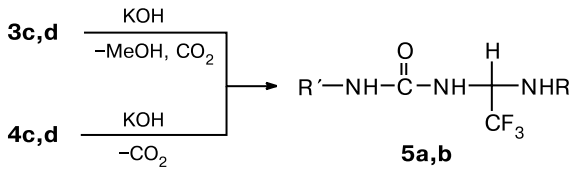
reactions of imine **1e** with ureas **2c,d,g,h** to be completed, heating at 60—80 °C for ~10—20 min was required. Hydantoins **4a,b,e—l** were obtained in 82—96% yields without isolation of intermediate adducts **3a,b,e—l**. Adducts **3c,d** were isolated; their high-yielding cyclization into hydantoins **4c,d** through elimination of MeOH occurred in boiling benzene in the presence of catalytic amounts of Et_3N for 3—4 h or on heating in DMF at 90 °C.

Hydantoins **4** are crystalline substances; their compositions and structures were confirmed by elemental analysis and NMR spectroscopy. The ^{1}H NMR spectra of hydantoins **4** show signals for the NH protons at δ 9—10, the signal for the exocyclic NH proton is shifted downfield by ~0.2 ppm compared to adducts **3**. In the ^{19}F NMR spectra of hydantoins **4**, the signals for the CF_3 group are shifted upfield (δ 0.5—–0.9) compared to adducts **3**.

When refluxed in DMF in the presence of 1 *M* KOH, adducts **3** underwent decarbomethoxylation to ureas **5a,b** (Scheme 3). Under analogous conditions, hydantoins **4c,d** were also converted into products **5a,b**.

Scheme 3



5: R = Bz, R′ = Me (**a**); R = Bz, R′ = Bn (**b**)

In the ^{1}H NMR spectra of ureas **5**, the signal for the proton of the CH—CF_3 fragment appears as a characteristic sextet at δ 6.3 ($J_{H,H} = J_{H,F} = 7$ Hz). The signals for the CF_3 group at δ ~2.5 (d, $J_{H,F} = 7$ Hz) in the ^{19}F NMR spectra of these compounds confirmed the proposed structure.

Thus, the cyclocondensation of *N*-substituted imines of methyl trifluoropyruvate with monosubstituted ureas opens up broad possibilities for the synthesis of novel 5-amino-5-trifluoromethylimidazolidine-2,4-diones and various aminals of trifluoroacetaldehyde.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer. Melting points were determined in glass capillaries. Commercial monosubstituted ureas **2** (Aldrich, Lancaster) were used.

Methyl 2-acetylimino-3,3,3-trifluoropropionate (1a). Quinoline (25.8 g, 0.2 mol), methyl trifluoropyruvate (15.6 g, 0.1 mol), and $POCl_3$ (15.4 g, 0.1 mol) were successively added to a suspension of acetamide (5.9 g, 0.1 mol) in benzene (50 mL). The reaction mixture was stirred for 1 h and filtered. The solvent was removed and the residue was fractionated. The yield of imine **1a** was 14.5 g (74%), b.p. 77—78 °C (20 Torr). Found (%): C, 36.32; H, 3.35. $C_6H_6F_3NO_3$. Calculated (%): C, 36.56; H, 3.07. ^{1}H NMR ($CDCl_3$), δ: 2.35 (s, 3 H, Ac); 4.00 (s, 3 H, MeO). ^{19}F NMR ($CDCl_3$), δ: 7.60 (s).

Methyl 2-benzoylimino-3,3,3-trifluoropropionate (1b) was obtained analogously from benzamide (12.1 g, 0.1 mol). The yield was 18.6 g (72%), b.p. 102—103 °C (2 Torr). Found (%): C, 51.22; H, 2.85. $C_{11}H_8F_3NO_3$. Calculated (%): C, 50.98; H, 3.11. ^{1}H NMR ($CDCl_3$), δ: 4.10 (s, 3 H, MeO); 7.40 (m, 3 H, CH_{Ar}); 7.90 (m, 2 H, CH_{Ar}). ^{19}F NMR ($CDCl_3$), δ: 7.20 (s).

Methyl 3,3,3-trifluoro-2-(4-fluorobenzoylimino)propionate (1c) was obtained analogously from 4-fluorobenzamide (13.9 g, 0.1 mol). The yield was 19.1 g (69%), b.p. 111—113 °C (2 Torr). Found (%): C, 47.01; H, 2.35. $C_{11}H_7F_4NO_3$. Calculated (%): C, 47.67; H, 2.55. ^{1}H NMR ($CDCl_3$), δ: 3.90 (s, 3 H, MeO); 7.10—7.20, 8.00—8.10 (both m, 2 H each, CH_{Ar}). ^{19}F NMR ($CDCl_3$), δ: 7.41 (s, 3 F, CF_3); –38.20 (m, 1 F, CF_{Ar}).

Methyl 2-(4-chlorobenzoylimino)-3,3,3-trifluoropropionate (1d) was obtained analogously from 4-chlorobenzamide (15.5 g, 0.1 mol). The yield was 22.4 g (76%), b.p. 138—140 °C (2 Torr). Found (%): C, 44.72; H, 2.16. $C_{11}H_7ClF_3NO_3$. Calculated (%): C, 45.00; H, 2.40. ^{1}H NMR ($CDCl_3$), δ: 4.15 (s, 3 H, MeO); 7.30, 7.85 (both d, 2 H each, CH_{Ar}, $J_{H,H} = 8.0$ Hz). ^{19}F NMR ($CDCl_3$), δ: 7.32 (s).

Methyl 2-(benzothiazol-2-ylimino)-3,3,3-trifluoropropionate (1e) was obtained analogously from 2-aminobenzothiazole (15.0 g, 0.1 mol). The yield was 22.1 g (73%), m.p. 143—145 °C. Found (%): C, 45.56; H, 2.23. $C_{11}H_7F_3N_2O_2S$. Calculated (%): C, 45.84; H, 2.45. ^{1}H NMR ($CDCl_3$), δ: 3.95 (s, 3 H, MeO); 7.10, 7.25 (both m, 1 H each, CH_{Ar}); 7.60 (m, 2 H, CH_{Ar}). ^{19}F NMR ($CDCl_3$), δ: 6.33 (s).

Methyl 2-benzoylamino-3,3,3-trifluoro-2-(3-methylureido)propionate (3c). Imine **1b** (1.30 g, 5 mmol) was added to a suspension of *N*-methylurea **2a** (0.37 g, 5 mmol) in benzene (5 mL). The reaction mixture was stirred for 1 h. The solvent was removed and the residue was recrystallized from benzene—hexane (1 : 1). The yield was 1.05 g (63%).

Methyl 2-benzoylamino-2-(3-benzylureido)-3,3,3-trifluoropropionate (3d) was obtained analogously from *N*-benzylurea **2d** (0.75 g, 5 mmol) and imine **1b** (1.30 g, 5 mmol). The yield was 1.51 g (74%).

Melting points, spectroscopic characteristics, and elemental analysis data for compounds **3c,d** are given in Tables 1 and 2.

5-Acetylamino-3-methyl-5-trifluoromethylimidazolidine-2,4-dione (4a). A solution of imine **1a** (1.0 g, 5.1 mmol) and *N*-methylurea **2a** (0.38 g, 5.2 mmol) in DMF (5 mL) and Et_3N (0.05 g, 0.5 mmol) were heated at 90 °C for 3 h and then diluted with water (100 mL). The precipitate that formed was filtered off and recrystallized from benzene—hexane (1 : 1). The yield was 0.99 g (82%).

5-Benzoylamino-3-methyl-5-trifluoromethylimidazolidine-2,4-dione (4c). ***A.*** A solution of propionate **3c** (0.5 g, 1.5 mmol) and Et_3N (0.05 g, 0.5 mmol) in benzene (5 mL) was refluxed for 3 h. The solvent was removed and the residue was recrystallized from benzene—hexane (1 : 1). The yield was 0.35 g (77%).

B. A solution of imine **1b** (1.0 g, 3.8 mmol), *N*-methylurea **2a** (0.28 g, 3.8 mmol), and Et_3N (0.05 g, 0.5 mmol) in DMF (5 mL) was heated at 90 °C for 3 h and then diluted with water (100 mL). The precipitate that formed was filtered off and recrystallized from benzene—hexane (1 : 1). The yield was 0.96 g (75%).

Table 1. Yields, melting points, and elemental analysis data for compounds **3c,d**, **4a—l**, and **5a,b**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)			Molecular formula
			C	H	N	
3c	63	177—178	46.89 46.85	4.48 4.23	12.48 12.61	$C_{13}H_{14}F_3N_3O_4$
3d	74	119—121	55.79 55.75	4.08 4.43	10.08 10.26	$C_{19}H_{18}F_3N_3O_4$
4a	82	245—247	35.29 35.16	3.08 3.37	17.63 17.57	$C_7H_8F_3N_3O_3$
4b	87	110—117	49.38 49.53	3.95 3.84	13.52 13.33	$C_{13}H_{12}F_3N_3O_3$
4c	77 75*	176—178	47.70 47.85	3.33 3.35	13.83 13.95	$C_{12}H_{10}F_3N_3O_3$
4d	91 88*	143—144	57.14 57.30	3.54 3.74	11.05 11.14	$C_{18}H_{14}F_3N_3O_3$
4e	89	195—197	51.30 51.14	2.53 2.52	10.62 10.52	$C_{17}H_{10}F_5N_3O_3$
4f	90	128—129	54.58 54.69	3.22 3.31	10.33 10.63	$C_{18}H_{13}F_4N_3O_3$
4g	92	158—159	47.89 47.69	3.90 4.00	11.39 11.12	$C_{15}H_{15}ClF_3N_3O_3$
4h	93	153—154	47.59 47.84	2.52 2.76	10.36 10.46	$C_{16}H_{11}ClF_3N_3O_4$
4i	96	227—229	52.29 52.04	2.52 2.83	14.12 14.28	$C_{17}H_{11}F_3N_4O_2S$
4j	93	213—215	53.39 53.20	3.47 3.22	13.84 13.79	$C_{18}H_{13}F_3N_4O_2S$
4k	91	205—206	51.44 51.25	4.34 4.30	14.24 14.06	$C_{17}H_{17}F_3N_4O_2S$
4l	88	142—144	53.59 53.20	3.52 3.22	13.82 13.79	$C_{18}H_{13}F_3N_4O_2S$
5a	71 78*	255—257	48.19 48.00	4.47 4.39	15.44 15.27	$C_{11}H_{12}F_3N_3O_2$
5b	69 74*	239—241	58.39 58.12	4.47 4.59	11.84 11.96	$C_{17}H_{16}F_3N_3O_2$

* According to procedure ***B***.

Table 2. ^1H and ^{19}F NMR spectra of compounds **3c,d**, **4a—l**, and **5a,b** in DMSO-d_6

Compound	δ (*J*/Hz)	
	^1H	^{19}F
3c	2.60 (d, 3 H, MeN, $J_{H,H}$ = 7.0); 3.85 (s, 3 H, MeO); 6.35 (q, 1 H, NHMe, $J_{H,H}$ = 7.0); 7.45 (m, 4 H, CH_{Ar} + NH); 7.90 (m, 2 H, CH_{Ar}); 8.90 (s, 1 H, NH)	2.47 (s)
3d	3.80 (s, 3 H, MeO); 4.20 (m, 2 H, CH_2N); 6.90—7.20 (m, 6 H, CH_{Ar}); 7.40 (m, 4 H, CH_{Ar} + NH); 7.85 (m, 2 H, CH_{Ar}); 8.90 (s, 1 H, NH)	2.68 (s)
4a	1.95 (s, 3 H, MeC); 2.95 (s, 3 H, MeN); 9.00, 9.37 (both s, 1 H each, NH)	0.31 (s)
4b	1.95 (s, 3 H, MeC); 4.60 (m, 2 H, AB system, CH_2N, *J* = 14.0); 7.10—7.25 (m, 5 H, CH_{Ar}); 9.20, 9.45 (both s, 1 H each, NH)	–0.23 (s)
4c	3.00 (s, 3 H, Me); 7.45 (m, 3 H, CH_{Ar}); 7.90 (m, 2 H, CH_{Ar}); 9.15, 9.70 (both s, 1 H each, NH)	0.29 (s)
4d	4.70 (m, 2 H, AB system, CH_2); 7.20—7.60 (m, 8 H, CH_{Ar}); 7.90 (m, 2 H, CH_{Ar}); 9.20, 9.70 (both s, 1 H each, NH)	–0.16 (s)

(*to be continued*)

Table 2 (*continued*)

Compound	δ (*J*/Hz)	
	^{1}H	^{19}F
4e	7.10—7.30 (m, 4 H, CH_{Ar}); 7.40—7.50, 8.00—8.10 (both m, 2 H each, CH_{Ar}); 9.60, 10.00 (both s, 1 H each, NH)	−35.10, −29.00 (both m, 1 F each); 0.53 (s, 3 F)
4f	4.70 (m, 2 H, AB system, CH_2); 7.10—7.45 (m, 7 H, CH_{Ar}); 7.90—8.10 (m, 2 H, CH_{Ar}); 9.30, 9.80 (both s, 1 H each, NH)	−29.30 (m, 1 F); 0.33 (s, 3 F)
4g	0.90 (d, 6 H, Me, J = 7.0); 2.05 (m, 1 H, CH); 3.30 (d, 2 H, CH_2, J = 8.0); 7.35 (d, 2 H, CH_{Ar}, J = 8.0); 7.90 (d, 2 H, CH_{Ar}, J = 7.0); 9.10, 9.70 (both s, 1 H each, NH)	0.15 (s)
4h	4.70 (m, 2 H, AB system, CH_2); 6.27 (m, 2 H, CH of furan); 7.30—7.40 (m, 3 H, CH_{Ar} + CH of furan); 7.90 (m, 2 H, CH_{Ar}); 9.25, 9.80 (both s, 1 H each, NH)	0.21 (s)
4i	7.00—7.70 (m, 9 H, CH_{Ar}); 9.55, 9.70 (both s, 1 H each, NH)	−0.33 (s)
4j	2.45 (s, 3 H, Me); 7.05—7.40 (m, 7 H, CH_{Ar}); 7.65 (m, 1 H, CH_{Ar}); 9.40, 9.60 (both s, 1 H each, NH)	−0.36 (s)
4k	1.00—1.40 (m, 3 H, CH_{Alk}); 1.60—2.20 (m, 7 H, CH_{Alk}); 3.90 (m, 1 H, CHN); 7.10, 7.20 (both t, 1 H each, CH_{Ar}, $J_{H,H}$ = 7.2); 7.40, 7.65 (both d, 1 H each, CH_{Ar}, $J_{H,H}$ = 7.2); 9.10, 9.45 (both s, 1 H each, NH)	−0.89 (s)
4l	4.65 (m, 2 H, CH_2, $J_{A,B}$ = 12.0); 7.00—7.60 (m, 9 H, CH_{Ar}); 9.30, 9.50 (both s, 1 H each, NH)	−0.57 (s)
5a	2.65 (d, 3 H, MeN, $J_{H,H}$ = 7.0); 6.30 (quint, 1 H, $CHCF_3$, $J_{H,H}$ = 7.0, $J_{H,F}$ = 7.0); 6.40 (q, 1 H, N<u>H</u>Me, $J_{H,H}$ = 7.0); 6.60 (d, 1 H, CHN<u>H</u>, $J_{H,H}$ = 7.0); 7.45 (m, 3 H, CH_{Ar}); 7.90 (m, 2 H, CH_{Ar}); 9.00 (d, 1 H, BzN<u>H</u>, $J_{H,H}$ = 7.0)	0.30 (d, $J_{H,F}$ = 7.0)
5b	4.23 (m, 2 H, CH_2); 6.25 (sext, 1 H, $CHCF_3$, $J_{H,F}$ = 7.0, $J_{H,H}$ = 7.0); 6.72 (d, 1 H, N<u>H</u>CH, $J_{H,H}$ = 7.0); 6.90 (t, 1 H, N<u>H</u>CH_2, $J_{H,H}$ = 7.0); 7.05—7.50 (m, 8 H, CH_{Ar}); 7.90 (m, 2 H, CH_{Ar}); 9.02 (d, 1 H, BzN<u>H</u>, $J_{H,H}$ = 7.0)	0.45 (d, $J_{H,F}$ = 7.0)

5-Benzoylamino-3-benzyl-5-trifluoromethylimidazolidine-2,4-dione (4d) was obtained analogously according to procedures ***A*** and ***B***.

5-Acetylamino-3-benzyl-5-trifluoromethylimidazolidine-2,4-dione (4b), 5-(4-fluorobenzoylamino)-3-(4-fluorophenyl)-5-trifluoromethylimidazolidine-2,4-dione (4e), 3-benzyl-5-(4-fluorobenzoylamino)-5-trifluoromethylimidazolidine-2,4-dione (4f), 5-(4-chlorobenzoylamino)-3-isobutyl-5-trifluoromethylimidazolidine-2,4-dione (4g), 5-(4-chlorobenzoylamino)-3-furfuryl-5-trifluoromethylimidazolidine-2,4-dione (4h), 5-(1,3-benzothiazol-2-ylamino)-3-phenyl-5-trifluoromethylimidazolidine-2,4-dione (4i), 5-(1,3-benzothiazol-2-ylamino)-3-(4-methylphenyl)-5-trifluoromethylimidazolidine-2,4-dione (4j), 5-(1,3-benzothiazol-2-ylamino)-3-cyclohexyl-5-trifluoromethylimidazolidine-2,4-dione (4k), and 5-(1,3-benzothiazol-2-ylamino)-3-benzyl-5-trifluoromethylimidazolidine-2,4-dione (4l) were obtained as described for compound **4a**. The yields, melting points, and spectroscopic characteristics of compounds **4a—l** are given in Tables 1 and 2.

N*-[2,2,2-Trifluoro-1-(3-methylureido)ethyl]benzamide (5a).** A 1 *M* solution of KOH (1 mL) was added to a solution of compound **3c** (0.5 g, 1.5 mmol) (procedure ***A) or compound **4c** (0.5 g, 1.6 mmol) (procedure ***B***) in DMF (5 mL). The reaction mixture was refluxed for 3 h and then diluted with water (50 mL). The precipitate that formed was filtered off and recrystallized from 50% EtOH. The yields were 0.29 g (71%) (procedure ***A***) and 0.31 g (78%) (***B***).

N*-[1-(3-Benzylureido)-2,2,2-trifluoroethyl]benzamide (5b)** was obtained analogously according to procedures ***A and ***B***. The yields, melting points, and spectroscopic characteristics of compounds **5a,b** are given in Tables 1 and 2.

References

1. W. J. Brouillette, V. P. Jestkov, M. L. Brown, and M. S. Akhtar, *J. Med. Chem.*, 1994, **37**, 3289.
2. R. F. Struck, M. C. Kirk, L. S. Rice, and W. J. Suling, *J. Med. Chem*., 1986, **29**, 1319.
3. C. J. Mappes, E. H. Pommer, C. Rentzea, and B. Zeeh, US Pat. 4 198 423, 1980; *Chem. Abstrs*, 1980, **93**, 71784.
4. H. Ohta, T. Jikihara, K. Wakabayashi, and T. Fujita, *Pestic. Biochem. Physiol.*, 1980, **14**, 153.
5. C. Avendano Lopez and G. Gonsalez Trigo, *Adv. Heterocycl. Chem.*, 1985, **38**, 177.
6. E. Ware, *Chem. Rev.*, 1950, **46**, 403.
7. 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].
8. V. B. Sokolov, A. Yu. Aksinenko, T. A. Epishina, T. V. Goreva, A. N. Pushin, and I. V. Martynov, *Izv. Akad. Nauk, Ser. Khim.*, 2005, 1619 [*Russ. Chem. Bull., Int. Ed.*, 2005, **54**, 1667].

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