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

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. 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 and monosubstituted ureas. This investigation was motivated by data on the cyclocondensation of acylimines of methyl trifluoropyruvate with C,N-binucleophiles of the enamine type and with N,N-binucleophiles of the amidine type.

The starting N-substituted imines of methyl trifluoropyruvate were prepared in 69—76% yields by successive addition of equimolar amounts of quinoline, methyl trifluoropyruvate, and POCl₃ to a suspension of an appropriate amide in benzene (Scheme 1).

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 1**

\[
\begin{align*}
1a-e & \quad 2a-h \\
\text{MeOOC} & \quad \text{R} \quad \text{R}^\prime \quad \text{N} \quad \text{H} \quad \text{C} \quad \text{C} \quad \text{MeOOC} \\
\end{align*}
\]

\[
\begin{align*}
\text{CF}_3 & \quad \text{N} \quad \text{R} \\
\text{MeOOC} & \quad \text{R} \quad \text{R}^\prime \\
\end{align*}
\]

**Scheme 2**

\[
\begin{align*}
\text{MeOOC} & \quad \text{R} \quad \text{N} \quad \text{R}^\prime \\
\text{CF}_3 & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeOOC} & \quad \text{R} \quad \text{N} \quad \text{R}^\prime \\
\text{CF}_3 & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{R} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeOOC} & \quad \text{R} \quad \text{N} \quad \text{R}^\prime \\
\text{CF}_3 & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{H} \quad \text{N} \quad \text{R} \\
\end{align*}
\]

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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—I were obtained in 82—96% yields without isolation of intermediate adducts 3a,b,e—I. 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 Et3N 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 1H 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 19F NMR spectra of hydantoins 4, the signals for the CF3 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 decarbamoylhydrolysis to ureas 5a,b (Scheme 3). Under analogous conditions, hydantoins 4c,d were also converted into products 5a,b.

**Scheme 3**

![Scheme 3](image)

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

In the 1H NMR spectra of ureas 5, the signal for the proton of the CH—CF3 fragment appears as a characteristic sextet at δ 6.3 (JH,H = JH,F = 7 Hz). The signals for the CF3 group at δ ~2.5 (d, JH,F = 7 Hz) in the 19F 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 trifluoroacetaldheyde.

**Experimental**

1H and 19F 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 POCl3 (15.4 g, 0.1 mol) were successively added to a suspension of acetic acid (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, 3.51; C8H6F3NO3. Calculated (%): C, 36.56; H, 3.07.

1H NMR (CDCl3), δ: 2.35 (s, 3 H, Ac); 4.00 (s, 3 H, MeO). 19F NMR (CDCl3), 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. C9H6F3NO3. Calculated (%): C, 50.98; H, 3.11. 1H NMR (CDCl3), δ: 4.10 (s, 3 H, MeO); 7.40 (m, 3 H, CHAr); 7.90 (m, 2 H, CHAr). 19F NMR (CDCl3), 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. C10H6F4NO3. Calculated (%): C, 46.77; H, 2.55. 1H NMR (CDCl3), δ: 3.90 (s, 3 H, MeO); 7.10—7.20, 8.00—8.10 (both m, 2 H each, CHAr). 19F NMR (CDCl3), δ: 7.41 (s, 3 F, CF3); –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. C10H6ClF3NO3. Calculated (%): C, 45.00; H, 2.40. 1H NMR (CDCl3), δ: 4.15 (s, 3 H, MeO); 7.30, 7.85 (both d, 2 H each, CHAr, JH,H = 8.0 Hz). 19F NMR (CDCl3), δ: 7.32 (s).

Methyl 2-(benzothiazol-2-yl)-3,3,3-trifluoropropionate (1e) was obtained analogously from 2-aminobenzothiazole (15.0 g, 0.1 mol). The yield was 22.1 g (73%), b.p. 145—145 °C. Found (%): C, 45.56; H, 2.23. C11H6ClF3NO3. Calculated (%): C, 45.84; H, 2.45. 1H NMR (CDCl3), δ: 3.95 (s, 3 H, MeO); 7.10, 7.25 (both m, 1 H each, CHAr); 7.60 (m, 2 H, CHAr). 19F NMR (CDCl3), 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-Acetamido-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 Et3N (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-Benzamido-3-methyl-5-trifluoromethylimidazolidine-2,4-dione (4c). A. A solution of propionate 3e (0.5 g, 1.5 mmol) and Et3N (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 Et3N (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%).