Synthesis of trifluoromethyl derivatives of pyrrole. Reaction of α,β-unsaturated trifluoromethyl ketones with sodium cyanide

V. G. Nenajdenko, S. V. Druzhinin, and E. S. Balenkova*

Department of Chemistry, M. V. Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax: +7 (095) 932 8846. E-mail: nen@acylium.chem.msu.ru

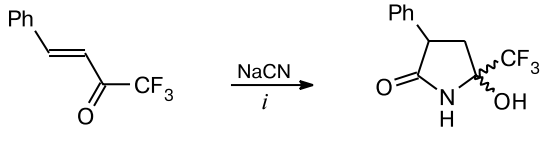
An efficient preparative procedure was developed for the synthesis of 5-hydroxy-5-trifluoromethyl-2-pyrrolidones by the reaction of α,β-unsaturated trifluoromethyl ketones with sodium cyanide. Dehydration of these reaction products under mild conditions afforded previously unknown 5-trifluoromethyl-3-pyrrolin-2-ones.

Key words: unsaturated trifluoromethyl ketones, cyanides, Michael reaction, pyrrole, cyclization.

Different classes of trifluoromethyl-substituted heterocyclic compounds often exhibit a wide range of physiological activity. Many of these compounds find use as pharmaceuticals. Most of known approaches to the synthesis of trifluoromethyl-containing heterocycles have substantial drawbacks associated with the use of difficultly accessible starting compounds which are often highly toxic and inconvenient to handle. In this connection, the development of procedures for the synthesis of heterocyclic compounds based on trifluoromethyl enones[1,2] is of considerable interest.

The conjugated addition of the cyanide ion to different Michael acceptors, including α,β-unsaturated ketones, often serves as a convenient route for the regio- and stereoselective introduction of a one-carbon fragment into various molecules. Many examples of the 1,4-addition of the cyanide ion to α,β-unsaturated ketones were reported.[3—7] We studied the reaction of 1,1,1-trifluoro-4-phenylbut-3-en-2-one (**1a**) as a model compound with NaCN. No reaction in anhydrous THF took place. In aqueous alcohols (MeOH, EtOH) and THF acidified with AcOH, the reaction afforded a mixture of diastereomers of 5-hydroxy-3-phenyl-5-trifluoromethylpyrrolidin-2-one (**2a**) (~1 : 1) (Scheme 1).

Scheme 1

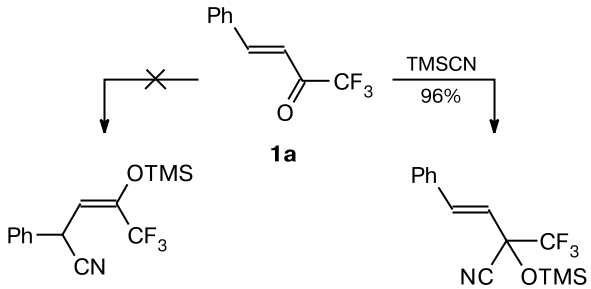


1a **2a**

i. MeOH—water, refluxing.

We expected that the reaction of enone **1a** with trimethylsilyl cyanide (TMSCN) in anhydrous conditions would give rise to a silyl derivative of the 1,4-addition product of the cyanide ion to the enone (Scheme 2). However, it appeared that no Michael adduct was produced at −10 °C in anhydrous THF; instead, the 1,2-addition product, *viz.*, trimethylsilyl ether of cyanohydrin **3**, was prepared in nearly quantitative yield.

Scheme 2



1a **3**

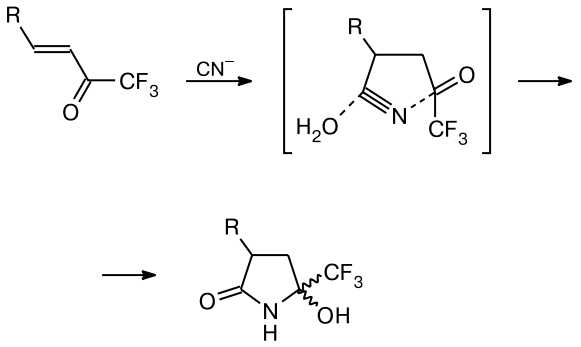
This result is consistent with the results of the study,[8] which demonstrated that the reaction of trimethylsilyl cyanide with α,β-unsaturated compounds proceeds predominantly as the 1,2-addition. For the preparation of 1,4-addition products, which can undergo subsequent cyclization, Lewis acids or elevated temperature are required.[9]

We hypothesized that cyclization giving rise to hydroxypyrrolidinone proceeds due to enhanced electrophilicity of the trifluoroacetyl group, which intramolecularly coordinates the CN group and favors so rapid addition of water that the reaction cannot be stopped in the step of formation of the Michael adduct (Scheme 3).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2332—2337, November, 2003.

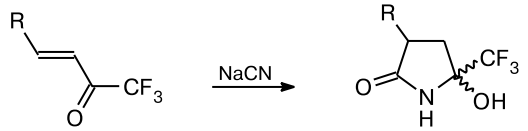
1066-5285/03/5211-2467 $25.00 © 2003 Plenum Publishing Corporation

Scheme 3



We carried out the reactions of α,β-unsaturated trifluoromethyl ketones **1b—h** with NaCN (Scheme 4). This process is of a general character and affords 3-substituted 5-hydroxy-5-trifluoromethylpyrrolidin-2-ones **2b—h** in high yields. The latter are formed as mixtures of diastereomers in approximately equal ratios. Generally, the reactions were completed in 5—10 h. However, refluxing for 2—3 days was required in the case of ketones **1g** and **1h** containing the strong electron-donating indolyl substituents. Individual diastereomers were isolated by chromatography on silica gel. The structure of one of the individual diastereomers of **2a** was confirmed by X-ray diffraction analysis. It was demonstrated that the molecules in the crystal are linked by intermolecular hydrogen bonds between the hydroxy and carbonyl groups (Fig. 1).

Scheme 4



1b—h **2b—h**

R = 4-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 3-$MeOC_6H_4$ (**d**), 2,5-$(MeO)_2C_6H_3$ (**e**), 2-thienyl (**f**), indol-3-yl (**g**), 2-methylindol-3-yl (**h**)

The resulting products hold promise as building blocks for the synthesis of various pyrrole and pyrrolidine derivatives as well as structurally rigid analogs of γ-aminobutyric acid (GABA) containing the trifluoromethyl group.

The results of our study agree well with the results obtained in the study[10] of the reaction of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1i**) with NaN_3 in aqueous EtOH and the subsequent transformation of a mixture of the reaction products under the action of NaCN yielding a mixture of diastereomers of 3-ethoxy-5-hydroxy-5-trifluoromethyl-2-pyrrolidone (**2i**) (Scheme 5). However,

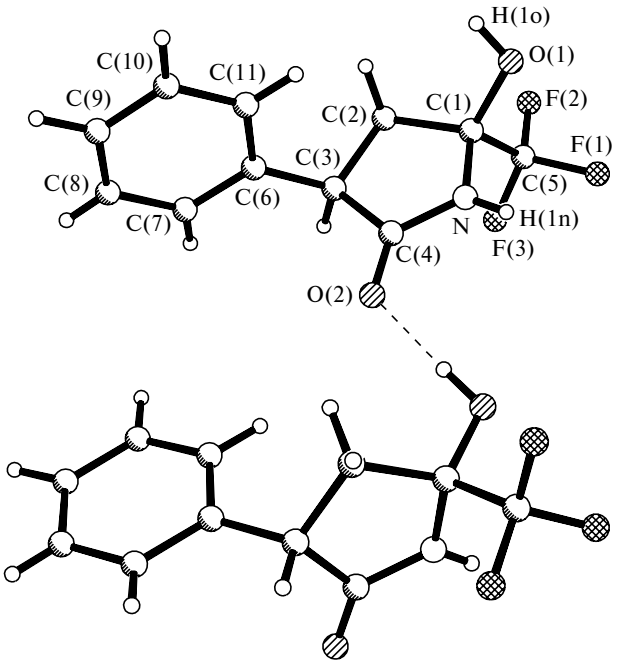
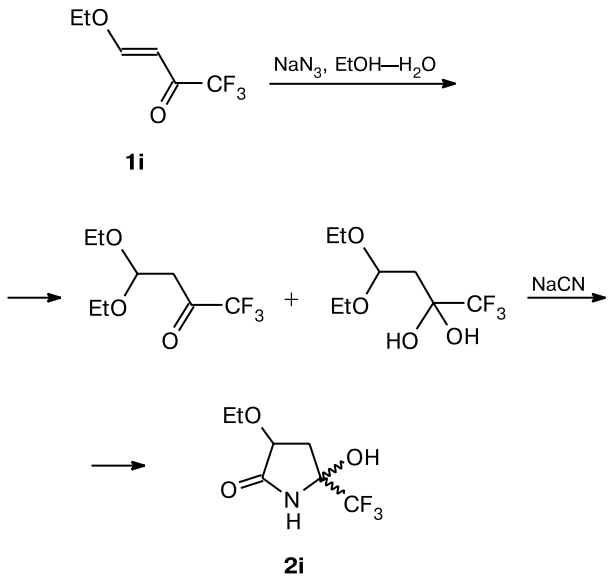


Fig. 1. Structure of compound **2a** according to X-ray diffraction data.

this process has drawbacks, such as many steps involved and a rather low yield of the target product.

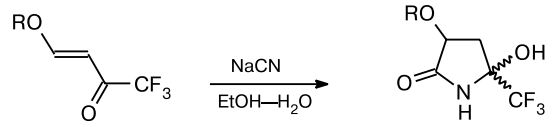
Scheme 5



1i **2i**

At the same time, our investigations demonstrated that 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1i**) and 4-butoxy-1,1,1-trifluorobut-3-en-2-one (**1j**) can be directly used (without preliminary treatment with sodium azide) in the reaction with NaCN giving rise to known[10] products **2i,j** (Scheme 6).

Scheme 6

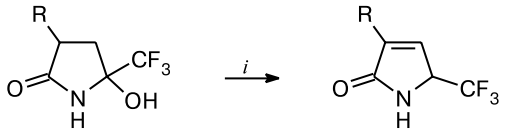


1i,j **2i,j**

R = Et (**i**), Bu (**j**)

We studied dehydration of hydroxypyrrolidones **2a—f,h** by refluxing in toluene in the presence of catalytic amounts of *para*-toluenesulfonic acid, which was accompanied by the migration of the double bond that formed to position 3 giving rise to substituted 3-pyrrolin-2-ones (**4a—f,h**) (Scheme 7). The resulting pyrrolinones find wide use in the synthesis of natural and physiologically active compounds. In particular, analogs of these compounds[11] serve as cytostatics for treatment of prostatic cancer.

Scheme 7



1a—f,h **4a—f,h**

i. TsOH (cat.), toluene, refluxing.

The dehydration product of indol-3-yl derivative **2g** was not isolated because the reaction mixture underwent resinification.

It is known that 3-pyrrolin-2-ones is a more stable tautomeric form of 2-hydroxypyrroles and are subject to *O*-alkylation and *O*-acylation. We examined the possibility of implementation of certain reactions typical of 3-pyrrolin-2-ones devoid of the trifluoromethyl group using 3-phenyl-5-trifluoromethyl-3-pyrrolin-2-one (**4a**) as a model compound.[12,13] However, our attempts failed.

To summarize, we studied the reaction of α,β-unsaturated trifluoromethyl ketones with sodium cyanide and developed an efficient preparative procedure for the synthesis of 5-hydroxy-5-trifluoromethyl-2-pyrrolidones based on this reaction. Dehydration of the latter under mild conditions affords 5-trifluoromethyl-3-pyrrolin-2-ones.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$, CD_3CN, and $(CD_3)_2SO$ with Me_4Si as the internal standard. The IR spectra were measured on a UR-20 spectrometer in Nujol mulls. The TLC analysis was performed on Silufol UV-254 plates; visualization was carried out with an acidified solution of $KMnO_4$ and iodine vapor. Unsaturated ketones were synthesized according to known procedures.[14] Compound **3** was prepared according to a procedure analogous to that described earlier.[11]

Synthesis of 3-substituted 5-hydroxy-5-trifluoromethylpyrrolidin-2-ones (2a—j) (general procedure). Enone **1a—j** (0.5 g) was dissolved in a mixture of MeOH (10 mL) and water (2 mL) and then NaCN (1.1 equiv.) was added. The resulting mixture was refluxed until the reaction was completed (TLC control, 5 : 1 hexane—ethyl acetate). The solutions were concentrated. The residue was dissolved in ethyl acetate and passed through a layer of silica gel. The eluent was concentrated and the resulting mixture of diastereomers was separated by chromatography (hexane—ethyl acetate, 3 : 1). The characteristics of compounds **2i** and **2j** are identical with those published earlier.[10]

5-Hydroxy-3-phenyl-5-trifluoromethylpyrrolidin-2-one (2a), the yield of a mixture of diastereomers was 392 mg (64%). IR, ν/cm^{-1}: 1710 (C=O), 3170 (O—H), 3270 (N—H). Found (%): C, 53.83; H, 4.03. $C_{11}H_{10}F_3NO_2$. Calculated (%): C, 53.88; H, 4.11.

Diastereomer 1, 175 mg (28.5%), m.p. 174 °C, R_f = 0.51 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.16 (dd, 1 H, CH_2, J = 14.7 Hz, J = 8.9 Hz); 2.92 (dd, 1 H, CH_2, J = 14.4 Hz, J = 9.9 Hz); 3.72 (t, 1 H, CH, J = 9.2 Hz); 7.21—7.38 (m, 5 H, C_6H_5); 7.43 (br.s, 1 H, OH); 9.21 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.9 (C(3)); 47.2 (C(4)); 84.3 (q, C(5), J = 32.2 Hz); 127.6, 129.0, 129.1, 140.2 (C_6H_5); 126.9 (q, CF_3, J = 284.0 Hz); 175.3 (C=O).

Diastereomer 2, 90 mg (16%), m.p. 193 °C, R_f = 0.37 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.33 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.23 Hz); 2.59 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 3.95 (t, 1 H, CH, J = 9.6 Hz); 7.18—7.35 (m, 5 H, C_6H_5); 7.37 (br.s, 1 H, OH); 9.26 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.7 (C(3)); 45.7 (C(4)); 84.2 (q, C(5), J = 32.2 Hz); 124.0 (q, CF_3, J = 284.0 Hz); 127.7, 128.8, 129.3, 139.7 (C_6H_5); 177.6 (C=O).

5-Hydroxy-3-(4-tolyl)-5-trifluoromethylpyrrolidin-2-one (2b), the yield of a mixture of diastereomers was 360 mg (60%). IR, ν/cm^{-1}: 1710 (C=O), 3170 (O—H), 3270 (N—H). Found (%): C, 55.38; H, 4.66. $C_{12}H_{12}F_3NO_2$. Calculated (%): C, 55.60; H, 4.67.

Diastereomer 1, 110 mg (22%), m.p. 104—105 °C, R_f = 0.47 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.18 (dd, 1 H, CH_2, J = 13.7 Hz, J = 9.2 Hz); 2.28 (s, 3 H, Me); 2.93 (dd, 1 H, CH_2, J = 14.4 Hz, J = 9.9 Hz); 3.68 (t, 1 H, CH, J = 9.2 Hz); 7.13 (d, 2 H, H(3′), H(5′), 4-MeC_6H_4, J = 7.5 Hz); 7.21 (d, 2 H, H(2′), H(6′), 4-MeC_6H_4, J = 7.5 Hz); 7.44 (br.s, 1 H, OH); 9.19 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 20.8 (Me); 38.9 (C(3)); 47.0 (C(4)); 84.3 (q, C(5), J = 32.2 Hz); 124.5 (q, CF_3, J = 285.4 Hz); 129.0, 129.7, 136.9, 137.2 (4-MeC_6H_4); 175.3 (C=O).

Diastereomer 2, 90 mg (17%), m.p. 193 °C, R_f = 0.37 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.26 (s, 3 H, Me); 2.28 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 2.55 (dd, 1 H, CH_2, J = 13.7 Hz, J = 9.9 Hz); 3.88 (t, 1 H, CH_2, J = 9.6 Hz); 7.06 (d, 2 H, H(3), H(5), 4-MeC_6H_4, J = 7.9 Hz); 7.13 (d, 2 H, H(2), H(6), 4-MeC_6H_4, J = 7.9 Hz); 7.36 (br.s, 1 H, OH); 9.23 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 20.8 (Me); 38.7 (C(3)); 45.2 (C(4)); 84.5 (q, C(5), J = 32.2 Hz);

124.5 (q, CF_3, J = 285.7 Hz); 128.7, 129.9, 136.7, 136.9 (4-MeC_6H_4); 177.7 (C=O).

5-Hydroxy-3-(3-tolyl)-5-trifluoromethylpyrrolidin-2-one (2c), the yield of a mixture of diastereomers was 520 mg (83%). IR, ν/cm^{-1}: 1700 (C=O), 3170 (O—H), 3280 (N—H). Found (%): C, 55.85; H, 5.04. $C_{12}H_{12}F_3NO_2$. Calculated (%): C, 55.60; H, 4.67.

Diastereomer 1, 230 mg (38%), m.p. 160 °C, R_f = 0.5 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.16 (dd, 1 H, CH_2, J = 14.0 Hz, J = 8.9 Hz); 2.29 (s, 3 H, Me); 2.93 (dd, 1 H, CH_2, J = 14.4 Hz, J = 9.9 Hz); 3.67 (t, 1 H, CH, J = 9.2 Hz); 7.08 (t, 1 H, H(5), 3-MeC_6H_4, J = 5.1 Hz); 7.11 (d, 1 H, H(2), 3-MeC_6H_4, J = 4.5 Hz); 7.22 (t, 1 H, H(6), 3-MeC_6H_4, J = 7.5 Hz); 7.46 (br.s, 1 H, OH); 9.23 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 21.0 (Me); 38.8 (C(3)); 47.3 (C(4)); 84.2 (q, C(5), J = 32.2 Hz); 126.2, 128.2, 129.0, 129.7, 138.2, 140.1 (3-MeC_6H_4); 127.0 (q, CF_3, J = 285 Hz); 175.4 (C=O).

Diastereomer 2, 135 mg (22%), m.p. 153 °C, R_f = 0.35 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.28 (s, 3 H, Me); 2.31 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 2.56 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.9 Hz); 3.89 (t, 1 H, CH, J = 9.2 Hz); 7.08 (t, 1 H, H(5), 3-MeC_6H_4, J = 5.1 Hz); 6.94—7.03 (m, 2 H, H(5), H(6), 3-MeC_6H_4); 7.06 (d, 1 H, H(2), 3-MeC_6H_4, J = 7.5 Hz); 7.21 (t, 1 H, H(4), C_6H_4Me, J = 7.5 Hz); 7.37 (br.s, 1 H, OH); 9.27 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 21.1 (Me); 38.6 (C(3)); 45.6 (C(4)); 84.1 (q, C(5), J = 32.1 Hz); 125.8, 128.3, 129.2, 129.5, 138.4, 139.6 (3-MeC_6H_4); 126.8 (q, CF_3, J = 284.0 Hz); 176.57 (C=O).

5-Hydroxy-3-(3-methoxyphenyl)-5-trifluoromethylpyrrolidin-2-one (2d), the yield of a mixture of diastereomers was 400 mg (67%). IR, ν/cm^{-1}: 1700 (C=O), 3170 (O—H), 3280 (N—H). Found (%): C, 52.62; H, 4.54. $C_{12}H_{12}F_3NO_3$. Calculated (%): C, 52.37; H, 4.39.

Diastereomer 1, 250 mg (42%), m.p. 170 °C, R_f = 0.34 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.17 (dd, 1 H, CH_2, J = 14.4 Hz, J = 8.6 Hz); 2.92 (dd, 1 H, CH_2, J = 14.7 Hz, J = 9.9 Hz); 3.70 (t, 1 H, CH, J = 9.2 Hz); 3.74 (s, 3 H, OMe); 6.83 (dd, 1 H, H(2), 3-$MeOC_6H_4$, J = 8.2 Hz, J = 2.0 Hz); 6.89—6.93 (m, 2 H, H(4), H(6), 3-$MeOC_6H_4$); 7.25 (t, 1 H, H(5), 3-$MeOC_6H_4$, J = 8.2 Hz); 7.46 (br.s, 1 H, OH); 9.22 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.9 (C(3)); 47.3 (C(4)); 55.4 (OMe); 84.4 (q, C(5), J = 32.2 Hz); 112.9, 115.0, 121.3, 130.2, 141.8, 160.3 (3-$MeOC_6H_4$); 123.5 (q, CF_3, J = 285.5 Hz); 176.3 (C=O).

Diastereomer 2, 115 mg (19%), m.p. 154 °C, R_f = 0.28 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.13 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.4 Hz); 2.57 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 3.72 (s, 3 H, OMe); 3.90 (t, 1 H, CH, J = 9.6 Hz); 6.75 (m, 2 H, H(4), H(6), 3-$MeOC_6H_4$); 6.83 (m, 1 H, H(2), 3-$MeOC_6H_4$); 7.24 (t, 1 H, H(5), 3-$MeOC_6H_4$, J = 8.2 Hz); 7.38 (br.s, 1 H, OH); 9.27 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.6 (C(3)); 45.6 (C(4)); 55.3 (OMe); 84.4 (q, C(5), J = 32.2 Hz); 112.9, 114.8, 120.8, 130.5, 141.3, 160.3 (3-$MeOC_6H_4$); 125.4 (q, CF_3, J = 285.0 Hz); 177.5 (C=O).

5-Hydroxy-3-(2,5-dimethoxyphenyl)-5-trifluoromethylpyrrolidin-2-one (2e), the yield of a mixture of diastereomers was 430 mg (73%). IR, ν/cm^{-1}: 1700 (C=O), 3170 (O—H), 3280 (N—H). Found (%): C, 52.61; H, 5.02. $C_{13}H_{14}F_3NO_4$. Calculated (%): C, 51.15; H, 4.62.

Diastereomer 1, 180 mg (31%), m.p. 148 °C, R_f = 0.21 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.13 (dd, 1 H, CH_2, J = 13.0 Hz, J = 9.0 Hz); 2.79 (dd, 1 H, CH_2, J = 14.0 Hz, J = 10.2 Hz); 3.68 (s, 3 H, OMe); 3.70 (s, 3 H, OMe); 3.86 (t, 1 H, CH, J = 9.6 Hz); 6.75—6.85 (m, 2 H, H(2), H(5), 2,5-$(MeO)_2C_6H_3$); 6.91 (d, 1 H, H(4), 2,5-$(MeO)_2C_6H_3$, J = 8.55 Hz); 7.36 (br.s, 1 H, OH); 9.13 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.2 (C(3)); 42.3 (C(4)); 55.7 (OMe); 56.4 (OMe); 84.3 (q, C(5), J = 30.7 Hz); 112.9, 113.1, 116.5, 129.1, 152.2, 154.0 (2,5-$(MeO)_2C_6H_3$); 124.4 (CF_3, J = 285.4 Hz); 176.3 (C=O).

Diastereomer 2, 140 mg (24%), m.p. 195—196 °C, R_f = 0.12 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.36 (d, 2 H, CH_2, ^2J = 9.2 Hz); 3.65 (s, 3 H, OMe); 3.67 (s, 3 H, OMe); 3.95 (t, 1 H, CH, J = 8.9 Hz); 6.69 (s, 1 H, H(2), C_6H_3); 6.81 (dd, 1 H, H(4), 2,5-$(MeO)_2C_6H_3$, J = 8.2 Hz, J = 1.4 Hz); 6.90 (d, 1 H, H(6), C_6H_3, J = 8.55 Hz); 7.26 (br.s, 1 H, OH); 9.11 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 37.0 (C(3)); 42.4 (C(4)); 55.7 (OMe); 56.0 (OMe); 84.1 (q, C(5), J = 32.2 Hz); 112.9, 113.1, 117.2, 128.5, 152.2, 153.9 (C_6H_3); 123.8 (q, CF_3, J = 285.4 Hz); 177.6 (C=O).

5-Hydroxy-3-(2-thienyl)-5-trifluoromethylpyrrolidin-2-one (2f), the yield of a mixture of diastereomers was 585 mg (95%). IR, ν/cm^{-1}: 1700 (C=O), 3170 (O—H), 3280 (N—H). Found (%): C, 43.57; H, 3.25. $C_9H_8F_3NO_2S$. Calculated (%): C, 43.03; H, 3.21.

Diastereomer 1, 225 mg (37%), m.p. 154 °C, R_f = 0.48 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.27 (dd, 1 H, CH_2, J = 14.4 Hz, J = 9.2 Hz); 2.92 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 4.00 (t, 1 H, CH, J = 9.3 Hz); 6.90—7.30 (m, 2 H, H(3), H(4), 2-C_4H_3S); 7.41 (dd, 1 H, H(5), 2-C_4H_3S, J = 4.8 Hz, J = 1.4 Hz); 7.47 (br.s, 1 H, OH); 9.25 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.9 (C(3)); 42.3 (C(4)); 84.2 (q, C(5), J = 32.2 Hz); 124.6 (q, CF_3, J = 285.9 Hz); 125.9, 126.4, 127.2, 141.1 (2-C_4H_3S); 175.0 (C=O).

Diastereomer 2, 270 mg (44%), m.p. 143 °C, R_f = 0.25 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.41 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 2.66 (dd, 1 H, CH_2, J = 13.7 Hz, J = 9.6 Hz); 4.21 (t, 1 H, CH, J = 9.6 Hz); 6.97—7.00 (m, 2 H, H(3), H(4), 2-C_4H_3S); 7.39—7.43 (m, 2 H, H(5), 2-C_4H_3S, OH); 9.30 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 38.4 (C(3)); 40.9 (C(4)); 84.1 (q, C(5), J = 32.2 Hz); 125.9, 126.4, 127.4 141.6 (2-C_4H_3S); 126.2 (q, CF_3, J = 285.5 Hz); 176.1 (C=O).

5-Hydroxy-3-(indol-3-yl)-5-trifluoromethylpyrrolidin-2-one (2g), the yield of a mixture of diastereomers was 540 mg (90%). IR, ν/cm^{-1}: 1680 (C=O), 3280 (O—H), 3410 (N—H). Found (%): C, 54.58; H, 4.33. $C_{13}H_{11}F_3N_2O_2$. Calculated (%): C, 54.93; H, 3.90.

Diastereomer 1, 125 mg (21%), m.p. 219 °C, R_f = 0.2 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.33 (dd, 1 H, CH_2, J = 13.7 Hz, J = 9.2 Hz); 2.93 (dd, 1 H, CH_2, J = 14.0 Hz, J = 9.6 Hz); 3.92 (t, 1 H, CH, J = 9.6 Hz); 6.97 (t, 1 H, H(6), 3-C_8H_5N, J = 7.2 Hz); 7.08 (t, 1 H, H(2), 3-C_8H_5N, J = 7.5 Hz); 7.25 (d, 1 H, H(7), 3-C_8H_5N, J = 2.0 Hz); 7.36 (d, 1 H, H(4), 3-C_8H_5N, J = 8.2 Hz); 7.43 (br.s, 1 H, OH); 7.59 (d, 1 H, H(2), 3-C_8H_5N, J = 7.9 Hz); 9.15 (br.s, 1 H, NH); 10.92 (s, 1 H, C_8H_5N, NH). ^{13}C NMR (DMSO-d_6), δ: 38.1 (C(3)); 39.0 (C(4)); 84.2 (q, C(5), J = 32.2 Hz); 112.2, 112.5, 119.1, 119.7, 121.8, 124.5, 126.8, 137.3 (3-C_8H_5N); 124.1 (q, CF_3, J = 285.9 Hz); 176.8 (C=O).

Diastereomer 2, 100 mg (17%), m.p. 183 °C, R_f = 0.1 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.45—2.60 (m, 2 H, CH_2); 4.15 (t, 1 H, CH, J = 9.2 Hz); 6.97 (t, 1 H, H(6), 3-C_8H_5N, J = 7.2 Hz); 7.08 (t, 1 H, H(5), 3-C_8H_5N, J = 7.2 Hz); 7.25 (d, 1 H, H(7), 3-C_8H_5N, J = 2.0 Hz); 7.35—7.42 (m, 3 H, H(4), H(2), 3-C_8H_5N, OH); 9.22 (br.s, 1 H, NH); 10.95 (br.s, 1 H, 3-C_8H_5N, NH). ^{13}C NMR (DMSO-d_6), δ: 37.3 (C(3)); 46.6 (C(4)); 84.2 (q, C(5), J = 32.2 Hz); 111.7, 112.3, 119.0, 121.7, 124.3, 124.4, 126.7, 137.3 (3-C_8H_5N); 123.1 (q, CF_3, J = 285.9 Hz); 177.9 (C=O).

5-Hydroxy-3-(2-methylindol-3-yl)-5-trifluoromethylpyrrolidin-2-one (2h), the yield of a mixture of diastereomers was 270 mg (46%). IR, ν/cm^{-1}: 1680 (C=O), 3280 (O—H), 3410 (N—H). Found (%): C, 56.33; H, 4.45. $C_{14}H_{13}F_3N_2O_2$. Calculated (%): C, 56.38; H, 4.39.

Diastereomer 1, 65 mg (12%), m.p. 214 °C (decomp), R_f = 0.24 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.25 (m, 1 H, CH_2); 2.30 (s, 3 H, Me) 2.85 (dd, 1 H, CH_2, J = 13.7 Hz, J = 10.2 Hz); 3.81 (t, 1 H, CH, J = 9.9 Hz); 6.90 (t, 1 H, H(6), 2-MeC_8H_5N, J = 7.2 Hz); 6.99 (t, 1 H, H(5), 2-MeC_8H_5N, J = 7.4 Hz); 7.25 (d, 1 H, H(7), 2-MeC_8H_5N, J = 7.9 Hz); 7.42 (d, 1 H, H(4), 2-MeC_8H_5N, J = 7.9 Hz); 7.56 (br.s, 1 H, OH); 9.20 (br.s, 1 H, NH); 10.85 (br.s, 1 H, 2-MeC_8H_5N, NH). ^{13}C NMR (DMSO-d_6), δ: 11.4 (Me); 38.0 (C(3)); 38.6 (C(4)); 84.0 (q, C(5), J = 32.2 Hz); 108.0, 111.2, 118.6, 118.9, 120.8, 127.3, 134.1, 136.0 (2-MeC_8H_5N); 124.4 (q, $\underline{C}F_3$, J = 285.8 Hz); 176.8 (C=O).

Diastereomer 2, 180 mg (31%), m.p. 128 °C, R_f = 0.1 (hexane—ethyl acetate, 1 : 1). ^{1}H NMR (DMSO-d_6), δ: 2.30 (s, 3 H, Me); 2.99 (d, 2 H, CH_2, J = 9.8 Hz); 4.10 (t, 1 H, CH, J = 9.6 Hz); 6.87 (t, 1 H, H(6), 2-MeC_8H_5N, J = 7.5 Hz); 6.97 (t, 1 H, H(5), 2-MeC_8H_5N, J = 7.5 Hz); 7.15 (d, 1 H, H(7), 2-MeC_8H_5N, J = 7.9 Hz); 7.25 (d, 1 H, H(4), 2-MeC_8H_5N, J = 7.9 Hz); 7.35 (br.s, 1 H, OH); 9.25 (br.s, 1 H, NH); 10.87 (br.s, 1 H, 2-MeC_8H_5N, NH). ^{13}C NMR (DMSO-d_6), δ: 11.3 (Me); 36.7 (C(3)); 37.0 (C(4)); 83.9 (q, C(5), J = 32.2 Hz); 107.3, 111.4, 117.7, 119.0, 120.8, 127.3, 134.2, 136.1 (2-MeC_8H_5N); 124.1 (q, CF_3, J = 285.5 Hz); 177.3 (C=O).

X-ray diffraction study. Single crystals of compound **2a** were prepared by recrystallization from EtOH. The X-ray diffraction data were collected on an Enraf-Nonius CAD-4 diffractometer (β filter, Mo-Kα radiation, λ = 0.71073 Å) at 293 K using the θ/2θ scanning technique. The principal details of X-ray study and crystallographic data for compound **2a** are given in Table 1. The structure was solved by direct methods. The positions of the nonhydrogen atoms were refined by the full-matrix least-squares method with anisotropic thermal parameters. The hydrogen atoms were refined isotropically. Calculations were carried out using the SHELXTL PLUS program package.

In the crystal structure, the molecules are linked in chains by intermolecular O—H...O=C hydrogen bonds (d_{O-H} = 0.896 Å, $d_{H...O}$ = 1.95 Å, the O—H—O angle is 167.5°); the molecule whose carbonyl group is involved in the hydrogen bond is related to the molecule whose hydroxy group is involved in this bond by the transformation ($2 - x$, $y - 1/2$, $3/2 - z$).

Synthesis of 3-substituted 5-trifluoromethyl-3-pyrrolin-2-ones (4a—f,h) (general procedure). *para*-Toluenesulfonic acid (2 mg) was added to a solution of the corresponding 5-hydroxy-5-trifluoromethylpyrrolidin-2-one (200 mg) in dry toluene (10 mL). The reaction mixture was refluxed until the starting compound disappeared (TLC control, 1 : 1 hexane—ethyl acetate). Then the solution was cooled to ~20 °C and chromatographed on silica gel; 3-pyrrolin-2-ones were eluted with a 5 : 1 hexane—ethyl acetate mixture.

Table 1. Details of X-ray diffraction study and crystallographic data for compound **2a**

Parameter	Characteristic
Molecular formula	$C_{11}H_{10}F_3NO_2$
Molecular weight	245.20
Crystal system	Monoclinic
Space group	$C2/c$
Unit cell parameters	
a/Å	20.735(4)
b/Å	9.821(2)
c/Å	11.153(2)
α/deg	90
β/deg	99.12(3)
γ/deg	90
V/Å^3	2242.5(7)
Z	8
d/g cm^{-3}	1.453
μ/mm^{-1}	0.133
Scan range	$1.99° \leq \theta \leq 24.97°$
Number of independent reflections	1533
Number of reflections with $I \geq 2\sigma(I)$	1533
Number of parameters in the refinement	195
R_1 ($I \geq 2\sigma(I)$)	0.0340
wR_2 (all reflections)	0.0888

3-Phenyl-5-trifluoromethyl-3-pyrrolin-2-one (4a), the yield was 0.185 g (96%); m.p. °C, R_f = 0.20. IR, ν/cm^{-1}: 1720 (C=O), 3240 (N—H). ^{1}H NMR (acetone-d_6), δ: 4.77 (m, 1 H, C$\underline{H}$—CF_3); 6.90—7.03 (m, 3 H, H(3), H(4), H(5), C_6H_5); 7.16 (d, 1 H, CH, J = 1.7 Hz); 7.51 (dd, 2 H, H(2), H(6), C_6H_5, J = 7.9 Hz, J = 1.7 Hz); 8.88 (br.s, 1 H, NH). ^{13}C NMR (acetone-d_6), δ: 47.2 (q, C(5), J = 32.2 Hz); 114.9 (q, CF_3, J = 281.0 Hz); 118.1, 119.4, 120.2, 124.9 (C_6H_5); 121.5 (C(3)); 129.5 (C(4)); 162.2 (C=O). Found (%): C, 58.50; H, 3.61. $C_{11}H_8F_3NO$. Calculated (%): C, 58.15; H, 3.55.

3-(4-Tolyl)-5-trifluoromethyl-3-pyrrolin-2-one (4b), the yield was 0.17 g (91%), m.p. 124—125 °C, R_f = 0.18. IR, ν/cm^{-1}: 1720 (C=O), 3230 (N—H). ^{1}H NMR (acetone-d_6), δ: 2.79 (s, 3 H, Me); 5.48 (m, 1 H, CH—CF_3); 7.68 (d, 2 H, H(3), H(5), 4-MeC_6H_4, J = 7.7 Hz); 7.87 (t, 1 H, CH, J = 1.7 Hz); 8.37 (d, 2 H, H(2), H(6), 4-MeC_6H_4, J = 8.2 Hz); 8.66 (br.s, 1 H, N$\underline{H}$). ^{13}C NMR (acetone-d_6), δ: 21.4 (Me); 58.1 (q, C(5), J = 32.5 Hz); 128.7, 130.6, 130.8, 142.8 (4-MeC_6H_4); 133.4 (C(3)); 140.8 (C(4)); 122.8 (q, CF_3, J = 278.5 Hz); 161.3 (C=O). Found (%): C, 60.17; H, 4.32. $C_{12}H_{10}F_3NO$. Calculated (%): C, 59.75; H, 4.18.

3-(3-Tolyl)-5-trifluoromethyl-3-pyrrolin-2-one (4c), the yield was 0.160 g (81%), m.p. 99—100 °C, R_f = 0.21. IR, ν/cm^{-1}: 1730 (C=O), 3200 (N—H). ^{1}H NMR (acetone-d_6), δ: 2.35 (s, 3 H, Me); 5.05 (m, 1 H, CH—CF_3); 7.21 (d, 1 H, H(2), 3-MeC_6H_4, J = 7.5 Hz); 7.29 (t, 1 H, H(4), 3-MeC_6H_4, J = 7.9 Hz); 7.46 (t, 1 H, CH, J = 2.0 Hz); 7.83 (m, 2 H, H(5), 3-MeC_6H_4, H(6)); 8.23 (br.s, 1 H, NH). ^{13}C NMR (acetone-d_6), δ: 21.5 (Me); 58.2 (q, C(5), J = 32.2 Hz); 117.5 (q, CF_3, J = 284.0 Hz); 126.0, 129.4, 129.9, 131.5, 139.8, 141.1 (3-MeC_6H_4);

134.4 (C(3)); 139.5 (C(4)); 173.6 (C=O). Found (%): C, 60.22; H, 4.41. $C_{12}H_{10}F_3NO$. Calculated (%): C, 59.75; H, 4.18.

3-(3-Methoxyphenyl)-5-trifluoromethyl-3-pyrrolin-2-one (4d), the yield was 0.155 g (85.5%), m.p. 122 °C (decomp.), R_f = 0.14. IR, ν/cm^{-1}: 1700 (C=O), 3220 (N—H). ^{1}H NMR (acetone-d_6), δ: 3.82 (s, 3 H, OMe); 5.05 (m, 1 H, CH—CF_3); 6.97 (dd, 1 H, H(2), 3-$MeOC_6H_4$, J = 8.2 Hz, J = 2.3 Hz); 7.32 (t, 1 H, H(6), 3-$MeOC_6H_4$, J = 7.9 Hz); 7.51 (t, 1 H, CH, J = 1.7 Hz); 7.59 (d, 1 H, H(5), 3-$MeOC_6H_4$, J = 7.9 Hz); 7.65 (t, 1 H, H(4), 3-$MeOC_6H_4$, J = 2.1 Hz); 8.23 (br.s, 1 H, NH). ^{13}C NMR (acetone-d_6), δ: 55.8 (OMe); 57.6 (q, C(5), J = 33.5 Hz); 114.1, 116.4, 121.0, 131.0, 134.8, 153.1 (3-$MeOC_6H_4$); 122.0 (q, CF_3, J = 279.5 Hz); 134.4 (C(3)); 140.7 (C(4)); 161.6 (C=O). Found (%): C, 56.54; H, 4.11. $C_{12}H_{10}F_3NO_2$. Calculated (%): C, 56.04; H, 3.92.

3-(2,5-Dimethoxyphenyl)-5-trifluoromethyl-3-pyrrolin-2-one (4e), the yield was 0.077 g (37%), m.p. 138 °C, R_f = 0.1. IR, ν/cm^{-1}: 1710 (C=O), 3220 (N—H). ^{1}H NMR (DMSO-d_6), δ: 3.70 and 3.78 (both s, 3 H each, OMe); 5.21 (m, 1 H, CH—CF_3); 6.90 (m, 1 H, H(3), 2,5-$(MeO)_2C_6H_3$); 7.00 (t, 1 H, H(4), 2,5-$(MeO)_2C_6H_3$, J = 7.9 Hz); 7.80 (d, 1 H, CH, J = 3.0 Hz); 7.95 (d, 1 H, H(6), 2,5-$(MeO)_2C_6H_3$, J = 6.5 Hz); 9.30 (br.s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 55.8 (OMe); 56.3 (OMe); 57.0 (q, C(5), J = 33.7 Hz); 113.0, 115.4, 115.7, 127.8, 152.8, 153.4 (2,5-$(MeO)_2C_6H_3$); 124.5 (q, CF_3, J = 275.2 Hz); 134.6 (C(3)); 137.4 (C(4)); 173.0 (C=O). Found (%): C, 54.08; H, 4.21. $C_{13}H_{12}F_3NO_3$. Calculated (%): C, 54.36; H, 4.21.

3-(2-Thienyl)-5-trifluoromethyl-3-pyrrolin-2-one (4f), the yield of the product was 0.155 g (86%), m.p. 129 °C, R_f = 0.27. IR, ν/cm^{-1}: 1730 (C=O), 3200 (N—H). ^{1}H NMR (acetone-d_6), δ: 5.10 (m, 1 H, CH—CF_3); 7.13 (dd, 1 H, 2-C_4H_3S, H(4), J = 5.1 Hz, J = 3.8 Hz); 7.33 (t, 1 H, CH, J = 1.8 Hz); 7.59 (dd, 1 H, C_4H_3S, H(5), J = 5.0 Hz, J = 1.1 Hz); 7.87 (dd, 1 H, H(3), 2-C_4H_3S, J = 3.8 Hz, J = 0.8 Hz); 8.33 (br.s, 1 H, NH). ^{13}C NMR (acetone-d_6), δ: 58.2 (q, C(5), J = 33.5 Hz); 125.5 (q, CF_3, J = 279.6 Hz); 128.9, 129.1, 129.8, 130.3 (C_4H_3S); 133.6 (C(3)); 135.9 (C(4)); 172.6 (C=O). Found (%): C, 46.25; H, 2.82. $C_9H_7F_3NOS$. Calculated (%): C, 46.35; H, 2.59.

3-(2-Methylindol-3-yl)-5-trifluoromethyl-3-pyrrolin-2-one (4h), the yield of the product was 0.120 g (63.8%), m.p. 182 °C (decomp.), R_f = 0.2. IR, ν/cm^{-1}: 1710 (C=O), 3350 (N—H). ^{1}H NMR (DMSO-d_6), δ: 2.44 (s, 3 H, Me); 5.20 (m, 1 H, CH—CF_3); 6.97 (t, 1 H, H(6), 2-MeC_8H_4, J = 7.5 Hz); 7.05 (m, 2 H, H(5), 2-MeC_8H_4, CH); 7.30 (d, 1 H, H(7), 2-MeC_8H_4, J = 7.9 Hz); 7.47 (d, 1 H, H(4), 2-MeC_8H_4, J = 7.9 Hz); 9.17 (br.s, 1 H, NH); 11.31 (br.s, 1 H, 2-MeC_8H_4, NH). ^{13}C NMR (DMSO-d_6), δ: 13.1 (Me); 57.4 (q, C(5), J = 32.2 Hz); 103.4, 111.3, 119.6, 119.9, 121.5, 127.9, 136.0, 136.5 (2-MeC_8H_4); 124.1 (q, CF_3, J = 281.1 Hz); 132.9 (C(3)); 137.3 (C(4)); 172.7 (C=O). Found (%): C, 60.17; H, 4.09. $C_{13}H_{12}F_3NO_3$. Calculated (%): C, 60.00; H, 3.96.

This study was financially supported by the Russian Foundation for Basic Research (Project No. 04-03-32285-a

References

1. V. G. Nenajdenko, A. V. Sanin, and E. S. Balenkova, *Usp. Khim.*, 1999, **6**, 483 [*Russ. Chem. Rev.*, 1999, **6** (Engl. Transl.)].
2. V. G. Nenajdenko, A. V. Sanin, and E. S. Balenkova, *Molecules*, 1997, **2,** 186.
3. W. Nagata, M. Yoshioka, and M. Murakami, *J. Am. Chem. Soc.*, 1972, **94**, 4644.
4. A. Hann and A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 1335.
5. W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, 1961, **26**, 2413.
6. P. Kurtz, *Liebigs Ann. Chem.*, 1951, **572**, 23.
7. W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Lett.*, 1962, 461.
8. I. Kruchok, I. Gerus, and V. Kukhar, *Tetrahedron*, 2000, **56**, 6533.
9. I. Kruchok, I. Gerus, and V. Kukhar, *Synthesis*, 2002, 71.
10. N. Zannata, L. Da Rossa, H. Loro, E. Bonacorso, and M. Martins, *J. Fluorine Chem.*, 2001, **107**, 149.
11. L. Qiao, L. Zhao, S. Rong, X. Wu Wu, S. Wang, T. Fujii, M. Kazanietz, L. Rauser, J. Savage, B. Roth, J. Flippen-Andersond, and A. Kozikowski, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 955.
12. H. Plieninger, H. Bauer, and A. Katritzky, *Liebigs Ann.*, 1962, **654**, 165.
13. H. Plieninger, H. Bauer, W. Buhler, J. Kurze, and U. Lerch, *Liebigs Ann.*, 1964, **680**, 69.
14. V. G. Nenajdenko, S. V. Druzhinin, and E. S. Balenkova, *Izv. Akad. Nauk, Ser. Khim.*, 2004, № 2 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, No. 2].

Received July 15, 2003;
in revised form October 21, 2003