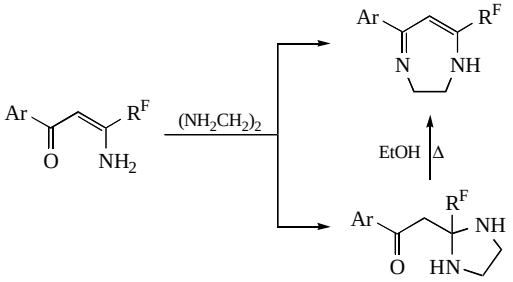
Reactions of 3-amino-1-aryl- and 3-amino-1-(2-thienyl)-4,4,4-trifluoro-2-buten-1-ones with 2-aminoethanol

Vyacheslav Ya. Sosnovskikh,* Valentin A. Kutsenko and Mikhail Yu. Morozov

Department of Chemistry, A. M. Gor'ky Urals State University, 620083 Ekaterinburg, Russian Federation. Fax: +7 3432 61 5978; e-mail: Vyacheslav.Sosnovskikh@usu.ru

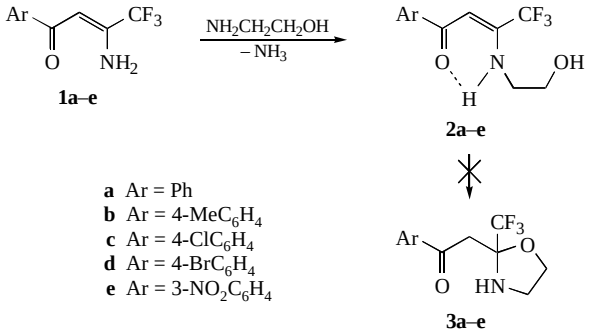
The reactions of 3-amino-1-aryl- and 3-amino-1-(2-thienyl)-4,4,4-trifluoro-2-buten-1-ones with 2-aminoethanol afford 1-aryl-3-(2-hydroxyethyl-amino)-4,4,4-trifluoro-2-buten-1-ones and 2-(2-thenoylmethyl)-2-trifluoromethyloxazolidine.

Transamination reactions at the double bond (N–N exchange) involving primary and secondary amines are described for the series of both nonfluorinated β-aminovinylketones[1] and their fluorinated analogues.[2,3] Ethylenediamine is known[4] to react with β-amino-β-polyfluoroalkylvinylketones simultaneously at two electrophilic centres to form 2,3-dihydro-1*H*-1,4-diazepines. We have recently repeatedly studied[5] this reaction and obtained 2,2-disubstituted imidazolidines in addition to the expected dihydrodiazepines. It turned out that under conditions of kinetic control (in the ethylenediamine medium at room temperature), the reaction proceeds *via* a double nucleophilic addition to the β-carbon atom with elimination of an ammonia molecule and formation of 2-aroylmethyl-2-polyfluoroalkylimidazolidines, which are transformed after 3–6 h refluxing in ethanol into thermodynamically more stable dihydrodiazepines, and the latter process is accompanied by water release.



Taking into account these results and in order to study further synthetic possibilities of aromatic β-amino-β-trifluoromethylvinylketones, we investigated the reactions of these compounds with 2-aminoethanol, especially as no data on similar reactions are available.

We found that 3-amino-1-aryl-4,4,4-trifluoro-2-buten-1-ones **1a**–**e**, obtained by the condensation of acetophenone and substituted acetophenones with trifluoroacetonitrile in the presence of *N*-ethylanilinomagnesium bromide,[6] react with 2-aminoethanol at room temperature in the absence of solvent during 2–3 days to give aminoenones **2a**–**e** containing the 2-hydroxyethyl substituent at the nitrogen atom in 46–75% yields. The same products were obtained when aminoenones **1a**–**e** were refluxed in ethanol for 6 h (40–54% yields).†



1a–e → **2a–e** ⇸ **3a–e**

a Ar = Ph
b Ar = 4-MeC_6H_4
c Ar = 4-ClC_6H_4
d Ar = 4-BrC_6H_4
e Ar = 3-$NO_2C_6H_4$

Unlike the reaction with ethylenediamine, which affords dihydrodiazepines or imidazolidines, the reaction of compounds **1a**–**e** with 2-aminoethanol ceases at the transamination stage and does not lead to the formation of oxazolidine derivatives **3a**–**e**. Moreover, despite various attempts (refluxing in ethanol or benzene, both with and without *p*-toluenesulfonic acid), we did not manage to perform the cyclization of aminoenones **2a**–**e** to the corresponding 2-aroylmethyl-2-trifluoromethyloxazolidines **3a**–**e**.

It is surprising that the thiophene analogue of aminoenones **1a**–**e**, 3-amino-1-(2-thienyl)-4,4,4-trifluoro-2-buten-1-one **1f**, reacts with 2-aminoethanol to form 2-(2-thenoylmethyl)-2-trifluoromethyloxazolidine **3f**‡ in 2-aminoethanol at room temperature, *i.e.*, under conditions where compounds **1a**–**e** give only transamination products **2a**–**e**.

The substantial difference in the reactivities of compounds so similar in structure as aminoenones **1a**–**e** and **1f** is most likely related to the different electronic effects of the aryl and 2-thienyl substituents in the aminoenone systems, and this should be studied in more detail.

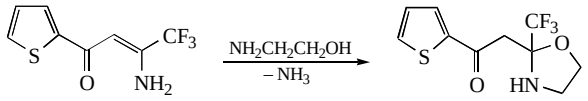
† 3-(2-*Hydroxyethylamino*)-1-*phenyl*-4,4,4-*trifluoro*-2-*buten*-1-*one* **2a**. Aminoenone **1a** (300 mg, 1.4 mmol) was dissolved in 260 μl (263 mg, 4.3 mmol) of 2-aminoethanol, and the reaction mixture was kept for three days at room temperature. The resulting crystals of aminoenone **2a** were recrystallised from hexane, yield 210 mg (58%), mp 63–64 °C. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 2.46 (s, 1H, OH), 3.59 (t, 2H, CH_2N, J 5.0 Hz), 3.85 (t, 2H, CH_2O, J 5.0 Hz), 6.23 (s, 1H, =CH), 7.32–7.61 (m, 3H, Ph), 7.78–8.02 (m, 2H, Ph), 10.9 (br. s, 1H, NH). IR (vaseline oil, ν/cm^{-1}): 3180 (OH, NH), 1635 (C=O), 1600, 1570 (C=C, NH). Found (%): C, 55.62; H, 4.58; N, 5.60. Calc. for $C_{12}H_{12}F_3NO_2$ (%): C, 55.60; H, 4.67; N, 5.40.

3-(2-*Hydroxyethylamino*)-1-*p-tolyl*-4,4,4-*trifluoro*-2-*buten*-1-*one* **2b**. Yield 46%, mp 72–73 °C. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 2.40 (s, 3H, CH_3), 2.40 (br. s, 1H, OH), 3.60 (t, 2H, CH_2N, J 5.0 Hz), 3.86 (t, 2H, CH_2O, J 5.0 Hz), 6.23 (s, 1H, =CH), 7.51 (q, 4H, C_6H_4, J 8.3 Hz), 10.9 (br. s, 1H, NH). IR (vaseline oil, ν/cm^{-1}): 3200 (OH, NH), 1635 (C=O), 1595, 1565 (C=C, NH). Found (%): C, 57.27; H, 5.24; N, 5.10. Calc. for $C_{13}H_{14}F_3NO_2$ (%): C, 57.14; H, 5.16; N, 5.13.

3-(2-*Hydroxyethylamino*)-1-*p-chlorophenyl*-4,4,4-*trifluoro*-2-*buten*-1-*one* **2c**. Yield 52%, mp 87–88 °C. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 2.19 (br. s, 1H, OH), 3.61 (t, 2H, CH_2N, J 5.0 Hz), 3.87 (t, 2H, CH_2O, J 5.0 Hz), 6.18 (s, 1H, =CH), 7.62 (q, 4H, C_6H_4, J 8.6 Hz), 11.0 (br. s, 1H, NH). IR (vaseline oil, ν/cm^{-1}): 3240 (OH, NH), 1630 (C=O), 1590, 1570 (C=C, NH). Found (%): C, 49.20; H, 3.83; N, 4.90. Calc. for $C_{12}H_{11}ClF_3NO_2$ (%): C, 49.08; H, 3.78; N, 4.77.

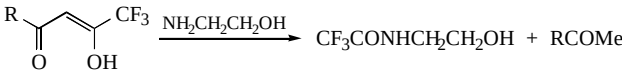
3-(2-*Hydroxyethylamino*)-1-*p-bromophenyl*-4,4,4-*trifluoro*-2-*buten*-1-*one* **2d**. Yield 54%, mp 93–94 °C. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 3.14 (s, 1H, OH), 3.60 (t, 2H, CH_2N, J 5.0 Hz), 3.86 (t, 2H, CH_2O, J 5.0 Hz), 6.15 (s, 1H, =CH), 7.64 (q, 4H, C_6H_4, J 8.8 Hz), 11.0 (br. s, 1H, NH). IR (vaseline oil, ν/cm^{-1}): 3380 (OH, NH), 1620 (C=O), 1585, 1545 (C=C, NH). Found (%): C, 42.78; H, 3.36; N, 4.10. Calc. for $C_{12}H_{11}BrF_3NO_2$ (%): C, 42.63; H, 3.28; N, 4.14.

3-(2-*Hydroxyethylamino*)-1-*m-nitrophenyl*-4,4,4-*trifluoro*-2-*buten*-1-*one* **2e**. Yield 75%, mp 89–90 °C. ^{1}H NMR (250 MHz, $CDCl_3$, J/Hz) δ: 1.97 (t, 1H, OH, J 4.5), 3.64 (dt, 2H, CH_2NH, $J_{CH_2–NH}$ 5.5, $J_{CH_2–CH_2}$ 5.2), 3.90 (dt, 2H, CH_2OH, $J_{CH_2–OH}$ 4.5, $J_{CH_2–CH_2}$ 5.2), 6.23 (s, 1H, =CH), 7.63 (dd, 1H, H^5, $J_{H^5–H^4}$ 8.1, $J_{H^5–H^6}$ 7.8), 8.21 (ddd, 1H, H^6, $J_{H^6–H^5}$ 7.8, $J_{H^6–H^2}$ 1.4, $J_{H^6–H^4}$ 1.1), 8.34 (ddd, 1H, H^4, $J_{H^4–H^5}$ 8.1, $J_{H^4–H^2}$ 2.0, $J_{H^4–H^6}$ 1.1), 8.71 (dd, 1H, H^2, $J_{H^2–H^4}$ 4.0, $J_{H^2–H^6}$ 1.4), 11.1 (br. s, 1H, NH). After addition of CD_3COOD the ND–CH_2–CH_2–OD group signal simplifies to dt with J 5.2 Hz. IR (vaseline oil, ν/cm^{-1}): 3530 (OH, NH), 1635 (C=O), 1615, 1600, 1570 (C=C, NH), 1530 (NO_2). Found (%): C, 47.50; H, 3.72; N, 9.12. Calc. for $C_{12}H_{11}F_3N_2O_4$ (%): C, 47.38; H, 3.64; N, 9.21.



1f **3f**

It is noteworthy that compounds **1** with Ar = 2-$CH_3OC_6H_4$ and 2-C_4H_3O do not react with 2-aminoethanol under the conditions studied, whereas the isoelectronic analogues of aminoenones **1a**,**f**, enols of 1-phenyl- and 1-(2-thienyl)-4,4,4-trifluoro-1,3-butanediones, are cleaved under the action of this reagent to give *N*-(2-hydroxyethyl)-2,2,2-trifluoroacetamide,§ acetophenone and 2-acetothienone.



R = Ph, 2-thienyl

The ^{1}H NMR spectra of aminoenones **2a**–**e** contain, along with the signals of the 2-hydroxyethyl substituent and aromatic ring, singlets of the hydroxyl group in the region of 1.97–3.14 ppm and of the vinyl proton at 6.15–6.23 ppm and a broadened singlet of the NH proton at 10.9–11.1 ppm, which participates in the formation of an intramolecular hydrogen bond stabilizing the *Z*-configuration of aminoenones **2a**–**e**.[7] When deuterioacetic acid is added to solutions of compounds **2a**–**e** in $CDCl_3$, the signals of the OH and NH protons disappear, but the singlet of the vinyl proton remains, which indicates the absence of prototropic tautomerism on the NMR time scale in the aminoenone system of these compounds. The ^{1}H NMR spectrum of aminoenone **2a** exhibits protons of the phenyl group as two multiplets at 7.32–7.61 and 7.78–8.02 ppm, the latter belonging to two *ortho*-hydrogen atoms affected by the carbonyl group. This fact, and the equal values of the chemical shifts of the vinyl proton in compounds **1a** and **2a** (6.23 ppm), proves that the Ph–C=O fragment is retained in product **2a** and rules out the possibility of formation of an isomeric aminoenone with a γ-arrangement of CF_3 and NH_2 groups, which was observed previously[8] for compound **1a** after prolonged storage at room temperature.

The aminoenones **2a**–**e** described containing the 2-hydroxyethyl substituent at the nitrogen atom are of interest as new polyfunctional organic compounds with a CF_3 group. They can be used for preparing fluorine-containing heterocycles with different types of biological activity.

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‡ 2-(2-*Thienylmethyl*)-2-*trifluoromethyloxazolidine* **3f**. Yield 77%, mp 110–111 °C. ^{1}H NMR (80 MHz, $CDCl_3$, *J*/Hz) δ: 3.36 (AB system, 2H, CH_2, Δδ = 0.82, *J* 14.6 Hz), 3.14–4.05 (m, 5H, CH_2CH_2, NH), 7.17 (dd, 1H, H^4, $J_{H^4–H^5}$ 5.0, $J_{H^4–H^3}$ 4.0), 7.73 (dd, 1H, H^5, $J_{H^5–H^4}$ 5.0, $J_{H^5–H^3}$ 1.2), 7.80 (dd, 1H, H^3, $J_{H^3–H^4}$ 4.0, $J_{H^3–H^5}$ 1.2). IR (vaseline oil, ν/cm^{-1}): 3355, 3290 (NH), 3120, 3100 (=CH), 1640 (C=O), 1520 (thiophene ring). Found (%): C, 45.30; H, 3.76; N, 5.18. Calc. for $C_{10}H_{10}F_3NO_2S$ (%): C, 45.28; H, 3.80; N, 5.28.

§ *N*-(2-*Hydroxyethyl*)-2,2,2-*trifluoroacetamide*, mp 34–36 °C. ^{1}H NMR (80 MHz, $CDCl_3$) δ: 2.06 (s, 1H, OH), 3.57 (t, 2H, CH_2N, *J* 5.0 Hz), 3.82 (t, 2H, CH_2O, *J* 5.0 Hz), 6.8 (br. s, 1H, NH). IR (ν/cm^{-1}): 3300, 3110 (OH, NH), 1710 (C=O), 1570 (NH).

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