

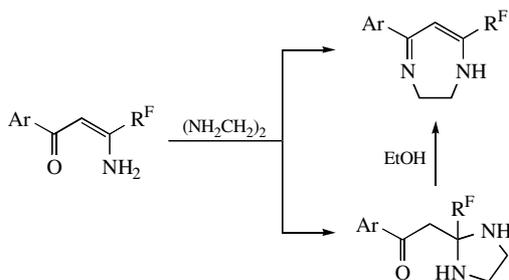
Reactions of 3-amino-1-aryl- and 3-amino-1-(2-thienyl)-4,4,4-trifluoro-2-buten-1-ones with 2-aminoethanol

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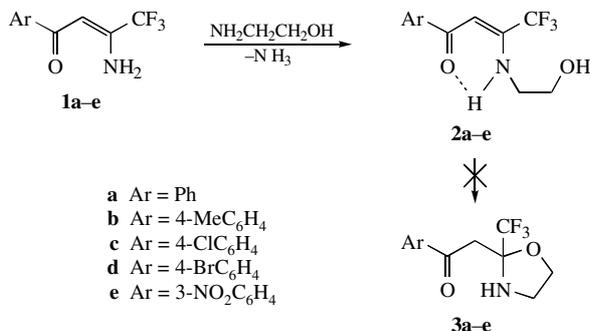
The reactions of 3-amino-1-aryl- and 3-amino-1-(2-thienyl)-4,4,4-trifluoro-2-buten-1-ones with 2-aminoethanol afford 1-aryl-3-(2-hydroxyethyl-amino)-4,4,4-trifluoro-2-buten-1-ones and 2-(2-thenoylmethyl)-2-trifluoromethyloxazolidine.

Transamination reactions at the double bond (N-N exchange) involving primary and secondary amines are described for the series of both nonfluorinated α -aminovinylketones¹ and their fluorinated analogues.^{2,3} Ethylenediamine is known⁴ to react with α -amino- β -polyfluoroalkylvinylketones simultaneously at two electrophilic centres to form 2,3-dihydro-1*H*-1,4-diazepines. We have recently repeatedly studied⁵ 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-arylmethyl-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 α -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 trifluoroacetone 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).[†]



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-arylmethyl-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.

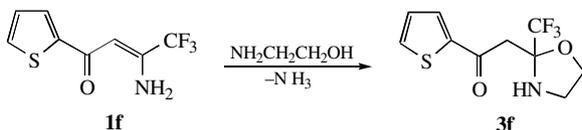
[†] 3-(2-Hydroxyethylamino)-1-phenyl-4,4,4-trifluoro-2-buten-1-one **2a**. Aminoenone **1a** (300 mg, 1.4 mmol) was dissolved in 260 ml (263 mg, 4.3 mmol) of 2-aminoethanol, and the reaction mixture was kept for three days at room temperature. The resulting crystals of aminoenone **2a** were recrystallised from hexane, yield 210 mg (58%), mp 63.6–4 °C. ¹H NMR (80 MHz, CDCl₃) δ : 2.46 (s, 1H, OH), 3.59 (t, 2H, CH₂N, *J* 5.0 Hz), 3.85 (t, 2H, CH₂O, *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 C₁₂H₁₂F₃NO₂ (%): 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. ¹H NMR (80 MHz, CDCl₃) δ : 2.40 (s, 3H, CH₃), 2.40 (br. s, 1H, OH), 3.60 (t, 2H, CH₂N, *J* 5.0 Hz), 3.86 (t, 2H, CH₂O, *J* 5.0 Hz), 6.23 (s, 1H, =CH), 7.51 (q, 4H, C₆H₄, *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 C₁₃H₁₄F₃NO₂ (%): C, 57.14; H, 5.16; N, 5.13.

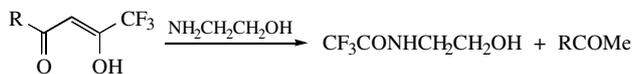
3-(2-Hydroxyethylamino)-1-*p*-chlorophenyl-4,4,4-trifluoro-2-buten-1-one **2c**. Yield 52%, mp 87–88 °C. ¹H NMR (80 MHz, CDCl₃) δ : 2.19 (br. s, 1H, OH), 3.61 (t, 2H, CH₂N, *J* 5.0 Hz), 3.87 (t, 2H, CH₂O, *J* 5.0 Hz), 6.18 (s, 1H, =CH), 7.62 (q, 4H, C₆H₄, *J* 8.6 Hz), 11.0 (br. s, 1H, NH). IR (vaseline 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 C₁₂H₁₁ClF₃NO₂ (%): 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. ¹H NMR (80 MHz, CDCl₃) δ : 3.14 (s, 1H, OH), 3.60 (t, 2H, CH₂N, *J* 5.0 Hz), 3.86 (t, 2H, CH₂O, *J* 5.0 Hz), 6.15 (s, 1H, =CH), 7.64 (q, 4H, C₆H₄, *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 C₁₂H₁₁BrF₃NO₂ (%): 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. ¹H NMR (250 MHz, CDCl₃, *J*/Hz) δ : 1.97 (t, 1H, OH, *J* 4.5), 3.64 (dt, 2H, CH₂NH, *J*_{CH₂-NH} 5.5, *J*_{CH₂-CH₂} 5.2), 3.90 (dt, 2H, CH₂OH, *J*_{CH₂-OH} 4.5, *J*_{CH₂-CH₂} 5.2), 6.23 (s, 1H, =CH), 7.63 (dd, 1H, H⁵, *J*_{H⁵-H⁴} 8.1, *J*_{H⁵-H⁶} 7.8), 8.21 (ddd, 1H, H⁶, *J*_{H⁶-H⁵} 7.8, *J*_{H⁶-H²} 1.4, *J*_{H⁶-H⁴} 1.1), 8.34 (ddd, 1H, H⁴, *J*_{H⁴-H⁵} 8.1, *J*_{H⁴-H²} 2.0, *J*_{H⁴-H⁶} 1.1), 8.71 (dd, 1H, H², *J*_{H²-H⁴} 4.0, *J*_{H²-H⁶} 1.4), 11.1 (br. s, 1H, NH). After addition of CD₃COOD the ND-CH₂-C H₂-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 (NO₂). Found (%): C, 47.50; H, 3.72; N, 9.12. Calc. for C₁₂H₁₁F₃N₂O₄ (%): C, 47.38; H, 3.64; N, 9.21.



It is noteworthy that compounds **1** with Ar = 2-CH₃OC₆H₄ and 2-C₄H₃O 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 ¹H 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 CDCl₃, 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 ¹H NMR spectrum of aminoenone **2a** exhibits protons

‡ *N*-(2-Thienylmethyl)-2,2,2-trifluoromethyloxazolidine **3f**. Yield 77%, mp 110–111 °C. ¹H NMR (80 MHz, CDCl₃, *J*/Hz) δ: 3.36 (AB system, 2H, CH₂, δ = 0.82, *J* 14.6 Hz), 3.14–4.05 (m, 5H, CH₂CH₂, NH), 7.17 (dd, 1H, H⁴, *J*_{H⁴-H⁵} 5.0, *J*_{H⁴-H³} 4.0), 7.73 (dd, 1H, H⁵, *J*_{H⁵-H⁴} 5.0, *J*_{H⁵-H³} 1.2), 7.80 (dd, 1H, H³, *J*_{H³-H⁴} 4.0, *J*_{H³-H⁵} 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 C₁₀H₁₀F₃N₂S (%): C, 45.28; H, 3.80; N, 5.28.

§ *N*-(2-Hydroxyethyl)-2,2,2-trifluoroacetamide, mp 34–36 °C. ¹H NMR (80 MHz, CDCl₃) δ: 2.06 (s, 1H, OH), 3.57 (t, 2H, CH₂N, *J* 5.0 Hz), 3.82 (t, 2H, CH₂O, *J* 5.0 Hz), 6.8 (br. s, 1H, NH). IR (ν/cm⁻¹): 3300, 3110 (OH, NH), 1710 (C=O), 1570 (NH).

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 *trans*-arrangement of CF₃ and NH₂ groups, which was observed previously⁸ 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 CF₃ group. They can be used for preparing fluorine-containing heterocycles with different types of biological activity.

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