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Reactions of CF_3-enones with ethyl nitroacetate and nitromethane: synthesis of CF_3-γ-nitroketones

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Abstract—Reactions of α,β-unsaturated CF_3-ketones with nitromethane and ethyl nitroacetate have been investigated. We found that α,β-unsaturated trifluoromethylketones react with ethyl nitroacetate in the presence of calcinated potassium fluoride to form two classes of 1,4-conjugated addition products: CF_3-γ-nitroketones and 6,6,6-trifluoro-2-nitro-5-oxohexanoates in nearly quantitative yields. The products obtained are precursors for CF_3-pyrrolidine synthesis.

The trifluoromethyl moiety is an important functional group. Methyl and trifluoromethyl groups are similar in geometrical size but compounds containing a trifluoromethyl group strongly differ in their chemical and pharmacological behaviour from their non-fluorinated analogues. A pyrrolidine ring is a structural fragment of many natural and synthetic physiologically active substances.[1] Trifluoromethyl derivatives of pyrrolidines have not been widely studied.[2] For example, unsubstituted 2-trifluoromethylpyrolidine was prepared by treatment of proline with the very toxic and dangerous sulfur tetrafluoride.[3] Reductive cyclization of γ-nitroketones is a standard way for the preparation of pyrrolidine derivatives.[4,5] γ-Nitroketones containing a trifluoromethyl group could serve as precursors for the synthesis of trifluoromethyl derivatives of pyrroles[6] and pyrrolidines.[2] Therefore methods for the synthesis of CF_3-substituted γ-nitroketones are necessary. It should be noted that there are significant differences in the properties of non-substituted ketones making the synthesis of the fluorinated compounds non-trivial task.[7]

Usually γ-nitroketones can be prepared by reaction of α,β-unsaturated ketones with nitroalkanes in the presence of secondary amines,[8,9] sodium ethoxide[10] and other bases.[11] Unfortunately, our attempts to carry out the reaction of CF_3-enone **1a** with nitromethane showed that an inseparable mixture of products was formed. The γ-nitroketone **3a** was effectively inaccessible using this reaction.

However, very interesting results were obtained while investigating the reaction with ethyl nitroacetate. Generation of an anion from ethyl nitroacetate[12] is even easier than in the case of nitromethane. It was found that the reaction of α,β-unsaturated trifluoromethylketones with ethyl nitroacetate proceeded in the presence of calcinated potassium fluoride (2 equiv) as the base[13] in ethanol at room temperature to give the Michael adducts **2** in almost quantitative yields.[14] The reaction was non-stereoselective and a mixture of the diastereomers **2** was formed (Table 1). In the case of the α,β-unsaturated trifluoromethylketones **1** with 3-indolyl and 3-(2-methylindolyl) substituents, the reaction did not proceed to any noticeable extent, perhaps due to the strongly electron-donating properties of these substituents (Scheme 1).

Table 1. Reactions of α,β-unsaturated CF_3-ketones with ethyl nitroacetate

Ketone	Diastereomer ratio of **2**	Yield of **2** (%)	Yield of **3** (%)
1a, R = Ph	1:1	99	99
1b, R = 4-MeC_6H_4	1:1	92	98
1c, R = 3-MeC_6H_4	1:1.5	95	87
1d, 3-$MeOC_6H_4$	1:1.6	88	99
1e, R = 2-Thiophenyl	1:1.7	87	99
1f, R = 2,5-$(MeO)_2C_6H_3$	1:3	95	98

Keywords: CF_3-Enones; γ-Nitroketones; Michael addition; CF_3-Groups; Nitromethane; Nitroacetate.

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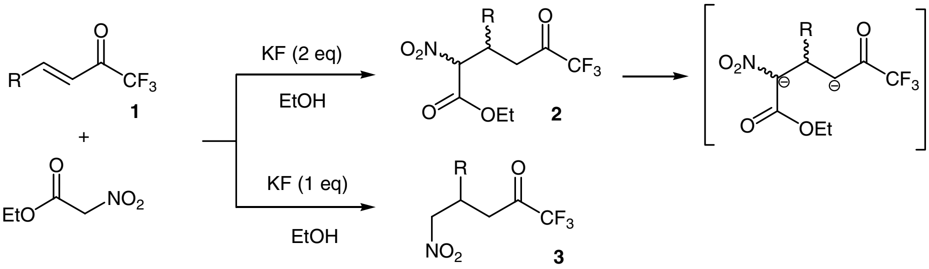

Scheme 1.

While carrying out the reaction in aqueous ethanol in the presence of 1 equiv of KF, unexpected results were obtained. Instead of the Michael adduct, the product of the reaction was the corresponding CF_3-γ-nitroketone **3**. Spontaneous hydrolysis and decarboxylation reactions had taken place. The reaction was carried out with several α,β-unsaturated trifluoromethylketones and excellent results were obtained (the yields of the nitroketones **3** were almost quantitative).[14] Therefore, we had succeeded in preparing the ester **2** and unsubstituted ketones **3** from the same reagents.

In summary, we have investigated the preparation of CF_3-γ-nitroketones starting from α,β-unsaturated trifluoromethylketones and ethyl nitroacetate. The yields of the reaction are excellent and much higher than the results obtained in the direct addition of nitromethane. The CF_3-γ-nitroketones obtained are precursors for the preparation of pyrrolidines and pyrroles, containing a trifluoromethyl group.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.095.

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14. General procedure for ethyl 3-aryl-6,6-trifluoro-2-nitro-5-oxohexanoates **2** and 4-aryl-1,1,1-trifluoro-5-nitropentan-2-ones **3**: A mixture of 1 mmol of 4-aryl-1,1,1-trifluorobut-3-en-2-one and calcinated potassium fluoride (2 mmol in the case of **2** and 1 mmol in the case of **3**) was dissolved in 3 ml of ethanol and 1 mmol of ethyl nitroacetate was added. The suspension was stirred for approximately 2 h until the absence of ketone (TLC monitoring, hexane/ethyl acetate 3:1) and then the solvent was evaporated. The residue was taken up in water and methylene chloride mixture, the organic layer was separated and the water layer was extracted with methylene chloride. The combined organic fractions were passed through a thin layer of silica gel. After solvent evaporation analytically pure product was obtained. Some spectral data are given. For full data see the Supporting information.
Ethyl 6,6,6-trifluoro-2-nitro-5-oxo-3-phenylhexanoate **2a** (mixture of diastereomers 1/1), viscous light-yellow oil:

IR (diastereomeric mixture, ν, cm^{-1}): 1770 (C═O, COOEt), 1380, 1580 (NO_2). ^1H NMR (diastereomeric mixture, chloroform-*d*, 400 MHz, δ ppm): 1.07 (t, 3H, OCH_2CH_3, $J = 7.0$ Hz); 1.27 (t, 3H, OCH_2CH_3, $J = 7.0$ Hz); 3.21 and 3.23 (each dd, 1H, CF_3COCH_2, $J = 18.8$ Hz, $J = 3.8$ Hz); 3.42 (m, 2H, CF_3COCH_2); 4.09 (m, 2H, OCH_2CH_3); 4.27 (m, 2H); 4.27–4.36 (m, 2H, C_6H_5–C*H*); 5.37 (d, 1H, $J = 8.2$ Hz, –C*H*–NH_2); 5.39 (d, 1H, $J = 8.5$ Hz, –C*H*–NO_2); 7.19–7.38 (m, 10H, C_6H_5). ^{13}C NMR (diastereomeric mixture, chloroform-*d*, δ ppm): 13.5 (CH_2CH_3); 13.6 (CH_2CH_3); 38.4 (CF_3COCH_2); 38.7 (CF_3COCH_2); 40.2 (C_6H_5–*C*H); 40.4 (C_6H_5–*C*H); 63.3 (CH_2CH_3); 63.6 (CH_2CH_3); 90.5 (*C*H–NO_2); 90.8 (*C*H–NH_2); 115.2 (q, CF_3, $J_{C-F} = 291.5$ Hz); 127.3, 127.8, 128.1, 128.6, 128.7, 129.2, 135.4, 136.3 (C_6H_5); 162.7 (*C*OOEt); 163.2 (*C*OOEt); 188.0 (q, $J_{C-F} = 36.6$ Hz, *C*═O); 188.3 (q, $J_{C-F} = 36.6$ Hz, *C*═O). Anal. calcd. for $C_{14}H_{14}F_3NO_5$ C, 50.46; H, 4.23. Found: C, 50.11; H,4.18.

1,1,1-Trifluoro-4-(4-methylphenyl)-5-nitropentan-2-one **3b**, viscous light-yellow oil: IR (ν, cm^{-1}): 1775 (C═O), 1385, 1570 (NO_2). ^1H NMR (chloroform-*d*, δ ppm): 2.32 (s, 3H, CH_3); 3.21 (dd, 1H, CF_3COCH_2, $J = 19.0$ Hz, $J = 7.0$ Hz); 3.28 (dd, 1H, CF_3COCH_2, $J = 19.0$ Hz, $J = 7.0$ Hz); 4.03 (quin, 1H, 4-MeC_6H_4–C*H*, $J = 7.0$ Hz); 4.62 (dd, 1H, CH_2NO_2, $J = 12.6$ Hz, $J = 7.0$ Hz); 4.67 (dd, 1H, CH_2NO_2, $J = 12.6$ Hz, $J = 7.0$ Hz); 7.07 (d, 2H, 4-MeC_6H_4, H-3, H-5, $J = 7.9$ Hz); 7.12 (d, 2H, 4-MeC_6H_4, H-2, H-6, $J = 7.9$ Hz). ^{13}C NMR (chloroform-*d*, δ ppm): 21.0 (CH_3); 37.7 (CF_3COCH_2); 39.4 (4-MeC_6H_4–*C*H); 78.9 (CH_2NO_2); 115.2 (q, CF_3, $J_{C-F} = 291.5$ Hz); 127.8, 130.7, 135.0, 139.0 (4-MeC_6H_4); 188.7 (q, $J_{C-F} = 36.6$ Hz, *C*═O). Anal. calcd. for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39. Found: C, 52.05; H, 4.45.