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Reaction of α,β-Unsaturated Trifluoromethyl Ketones with Ethyl Cyanoacetate

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Abstract—β-Aryl-substituted α,β-unsaturated trifluoromethyl ketones react with ethyl cyanoacetate to give the corresponding Michael addition products, ethyl 3-aryl-2-cyano-6,6,6-trifluoro-5-oxohexanoates, which are formed as mixtures of two diastereoisomers. The reaction time and product yield depend on electron-donating properties of the substituent in the initial ketone. The reaction is not accompanied by intramolecular cyclization of the Michael adducts.

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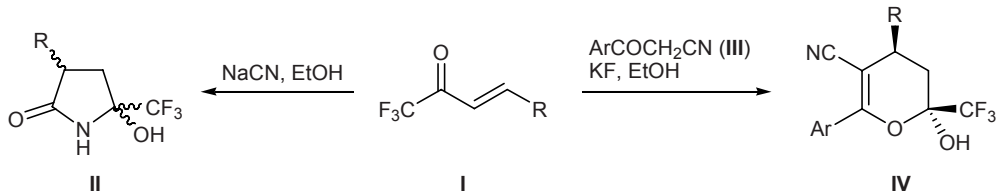
Trifluoromethyl group possesses unique stereoelectronic properties and is a very important substituent in organic chemistry due to its radically different physical, chemical, and physiological properties, as compared to methyl group [1]. α,β-Unsaturated trifluoromethyl ketones which are available via reactions of β-alkoxy and β-enamino α,β-unsaturated trifluoromethyl ketones with organomagnesium [2] and organolithium compounds [3] are promising building blocks for the synthesis of various carbo- and heterocyclic compounds containing a trifluoromethyl group [4]. The reaction of α,β-unsaturated carbonyl compounds with CH acids, which generally occurs as conjugate 1,4-addition (Michael reaction) underlies a classical method for building up carbon–carbon bonds [5].

α,β-Unsaturated trifluoromethyl ketones attract interest as substrates in the above reaction. For example, their reactions with nitriles do not stop at the stage of formation of the corresponding Michael adduct, but the subsequent cyclization (heterocyclization) leads to the corresponding functionalized carbo- and heterocyclic compounds, as was reported for the reactions with cyanoacetamide, malononitrile [6, 7], and lithiated imines [8].

We previously studied the reaction of α,β-unsaturated trifluoromethyl ketones **I** with sodium cyanide [9]. The reaction followed an analogous scheme and produced pyrrolidinone derivatives **II**. α,β-Unsaturated trifluoromethyl ketones **I** also reacted with aromatic α-cyano ketones **III** to give dihydropyran derivatives **IV** as a result of cyclization of intermediate Michael adducts [10] (Scheme 1).

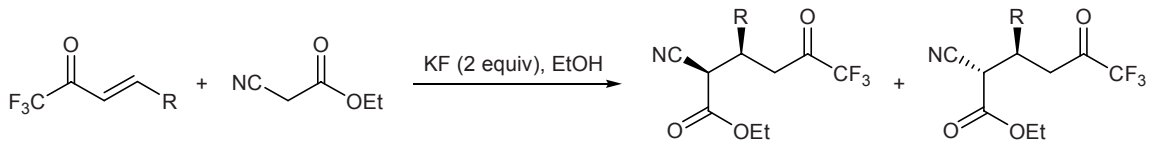
In the present work we examined addition reactions of ethyl cyanoacetate with a series of α,β-unsaturated trifluoromethyl ketones **I**. When the reaction was performed in ethanol or anhydrous propan-2-ol in the presence of 1 equiv of potassium fluoride, an inseparable mixture of unidentified products was obtained. However, the reaction in the presence of 2 equiv of anhydrous potassium fluoride led to the formation of the corresponding ethyl 3-aryl(2-thienyl)-2-cyano-6,6,6-trifluoro-5-oxohexanoates **VIa**–**VIf** as mixtures of diastereoisomers at a ratio of about 1:1 in a moderate overall yield. Presumably, the presence of 2 equiv

Scheme 1.



II **I** **IV**

Scheme 2.



Ia–Ie **V** **VIa–VIe**

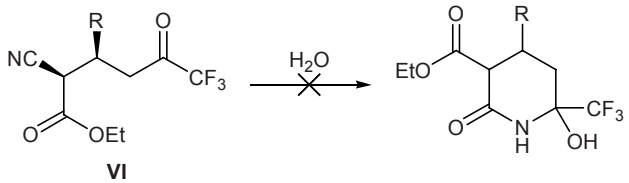
R = Ph (**a**), 4-MeC_6H_4 (**b**), 3-MeC_6H_4 (**c**), 3-$MeOC_6H_4$ (**d**), 2-thienyl (**e**).

of potassium fluoride as a base ensures intermediate formation of more stable dianion, as in the reaction of α,β-unsaturated trifluoromethyl ketones **I** with ethyl nitroacetate [11]. The reaction times and yields of compounds **VIa**–**VIf** are given below.

Compound no.	**VIa**	**VIb**	**VIc**	**VId**	**VIe**
Reaction time, h	3	4	4	6	6
Overall yield, %	51	64	49	55	44

Trifluoromethyl ketones containing an electron-donating group (such as 2,5-dimethoxyphenyl, 1*H*-indol-3-yl, and 2-methyl-1*H*-indol-3-yl) in the β-position failed to react with ethyl cyanoacetate, presumably because of their reduced electrophilicity. By analogy with the reactions with sodium cyanide and aryl cyanomethyl ketones, intramolecular cyclization of compounds **VI** to the corresponding ethyl 2-oxopiperidine-3-carboxylates could be anticipated according to Scheme 3; however, no cyclization occurred under the given conditions. We tried to effect cyclization of adduct **VIa** by the action of such reagents as hydrochloric acid, a saturated solution of hydrogen chloride in methanol, trifluoromethanesulfonic acid in methylene chloride, and hydrogen sulfide in ethanol in the presence of triethylamine. In all cases, either inseparable mixtures of products were formed or the reaction mixture underwent complete tarring. A probable reason is the presence of two protons in the α-positions with respect to the cyano and trifluoromethyl groups in molecule **VIa**. High acidity of these protons favors generation of anions in basic medium or enol tautomer in acidic medium, while the presence of electrophilic cyano and carbonyl groups could favor intermolecular condensations.

Scheme 3.



VI

Thus the reaction of α,b-unsaturated trifluoromethyl ketones with ethyl cyanoacetate leads to the formation of the corresponding Michael adducts which fail to undergo cyclization into ethyl 6-hydroxy-6-trifluoromethyl-2-oxohexahydropyridine-3-carboxylates.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal reference; the chemical shifts were measured with an accuracy of 0.01 ppm. The IR spectra were obtained on a UR-20 spectrometer from thin films. Thin-layer chromatography was performed on Silufol UV-254 plates; the chromatograms were developed by treatment with an acidified aqueous solution of potassium permanganate or iodine vapor or under UV irradiation. Silica gel (63–200 mesh, Merck) was used for preparative column chromatography.

3-Substituted ethyl 2-cyano-6,6,6-trifluoro-5-oxohexanoates VIa–VIe (*general procedure*)**.** Ethyl cyanoacetate, 133 mg (1 mmol), was added to a mixture of 1 mmol of 4-substituted 1,1,1-trifluorobut-3-en-2-one **Ia**–**Ie** and 112 mg (2 mmol) of freshly calcined potassium fluoride in 5 ml of propan-2-ol or ethanol, and the mixture was kept until the initial ketone disappeared (TLC, hexan–ethyl acetate, 5:1). The mixture was diluted with 20 ml of water, and the alcohol was distilled off on a rotary evaporator. The aqueous solution was extracted with methylene chloride (3×20 ml), the extracts were combined, dried over anhydrous sodium sulfate, passed through a layer of silica gel, and evaporated. The light yellow oily residue was compound **VIa–VIe** as a mixture of two diastereoisomers.

Ethyl 2-cyano-6,6,6-trifluoro-5-oxo-3-phenylhexanoate (VIa). Yield 51%. IR spectrum, ν, cm^{-1}: 1750 br (C=O), 2260 (CN). ^1H NMR spectrum, δ, ppm: 1.17 t (3H, CH_2CH_3, J = 7.5 Hz), 1.26 t (3H, CH_2CH_3, J = 7.5 Hz), 3.38 d.d (2H, $COCH_2$, J = 7.0, 1.0 Hz), 3.45 d.d (2H, $COCH_2$, J = 7.0, 0.9 Hz), 3.84 d (2H, CHCN, J = 5.6 Hz), 3.89–3.95 m (2H, PhC**H**), 4.10 d

(1H, CHCN, J = 6.0 Hz), 4.10 q.d (2H, OC**H**$_2$, J = 7.5, 0.8 Hz), 4.19 q.d (2H, OC**H**$_2$, J = 7.5, 0.8 Hz), 7.07–7.20 m (10H, C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 13.5 (CH_3), 13.6 (CH_3), 38.6 CO**C**H$_2$), 39.0 (CO**C**H$_2$), 39.4 (Ph**C**H), 39.7 (Ph**C**H), 43.1 (**C**HCN), 43.7 (**C**HCN), 63.0 (OCH_2), 63.3 (OCH_2), 114.7 (CN), 114.9 (CN), 115.2 q (CF_3, J = 291.5 Hz), 127.2, 128.5, 128.9, 129.3, 129.6, 129.8, 134.5, 139.0 (C_{arom}), 164.3 (**C**OOEt), 164.6 (**C**OOEt), 188.1 q (CF_3**C**=O, J = 36.6 Hz), 189.1 q (CF_3**C**=O, J = 36.6 Hz). Found, %: C 57.31; H 4.28. $C_{15}H_{14}F_3NO_3$. Calculated, %: C 57.51; H 4.50.

Ethyl 2-cyano-6,6,6-trifluoro-3-(4-methylphenyl)-5-oxohexanoate (VIb). Yield 64%. IR spectrum, ν, cm^{-1}: 1780 br (C=O), 2260 (CN). ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, CH_2C**H**$_3$, J = 7.5 Hz), 1.23 t (3H, CH_2C**H**$_3$, J = 7.5 Hz), 2.31 br.s (6H, C**H**$_3C_6H_4$), 3.37 d.d (2H, $COCH_2$, J = 7.0, 0.8 Hz), 3.42 d.d (2H, $COCH_2$, J = 7.0, 0.8 Hz), 3.80 d (1H, CHCN, J = 5.3 Hz), 3.93–3.95 m (2H, C_6H_4C**H**), 4.10 d (1H, CHCN, J = 5.9 Hz), 4.10 q.d (2H, OCH_2, J = 7.5, 0.9 Hz), 4.19 q.d (2H, OCH_2, J = 7.5, 0.9 Hz), 7.12–7.22 m (8H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 13.7 (CH_2**C**H$_3$), 13.9 (CH_2**C**H$_3$), 21.4 (CH_3), 38.6 (CO**C**H$_2$), 39.1 (CO**C**H$_2$), 39.1 (C_6H_4**C**H), 39.7 (C_6H_4**C**H), 43.2 (**C**HCN), 43.7 (**C**HCN), 63.0 (OCH_2), 63.2 (OCH_2), 114.8 (CN), 115.0 (CN), 115.2 q (CF_3, J = 291.5 Hz), 127.2, 127.6, 129.6, 129.8, 133.5, 134.3, 138.4, 138.5 (C_{arom}), 164.3 (**C**OOEt), 164.5 (**C**OOEt), 188.4 q (CF_3**C**=O, J = 36.6 Hz), 188.9 q (CF_3**C**=O, J = 36.6 Hz). Found, %: C 58.55; H 4.78. $C_{16}H_{16}F_3NO_3$. Calculated, %: C 58.71; H 4.93.

Ethyl 2-cyano-6,6,6-trifluoro-3-(3-methylphenyl)-5-oxohexanoate (VIc). Yield 49%. IR spectrum, ν, cm^{-1}: 1760 br (C=O), 2270 (CN). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, CH_2C**H**$_3$, J = 7.5 Hz), 1.23 t (3H, CH_2C**H**$_3$, J = 7.5 Hz), 2.33 br.s (6H, C**H**$_3C_6H_4$), 3.35 d.d (2H, $COCH_2$, J = 7.3, 0.9 Hz), 3.40 d.d (2H, $COCH_2$, J = 7.9, 0.9 Hz), 3.78 d (1H, CHCN, J = 5.3 Hz), 3.93–3.95 m (2H, MeC_6H_4C**H**), 4.01 d (1H, CHCN, J = 6.2 Hz), 4.10 q.d (2H, OCH_2, J = 7.5, 2.0 Hz), 4.20 q.d (2H, OCH_2, J = 7.5, 2.0 Hz), 7.05–7.13 m (6H, C_6H_4), 7.19–7.26 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 13.7 (CH_2**C**H$_3$), 13.8 (CH_2**C**H$_3$), 21.2 (C_6H_4**C**H$_3$), 38.6 (CO**C**H$_2$), 39.0 (CO**C**H$_2$), 39.4 (C_6H_4**C**H), 39.7 (C_6H_4**C**H), 43.1 (**C**HCN), 43.7 (**C**HCN), 63.0 (OCH_2), 63.3 (OCH_2), 114.8 (CN), 114.9 (CN), 115.2 q (CF_3, J = 291.5 Hz), 128.2, 128.5, 128.9, 129.1, 129.4, 129.5, 137.4, 139.0 (C_6H_4), 164.3 (**C**OOEt), 164.6 (**C**OOEt), 188.1 q (CF_3**C**=O, J = 36.6 Hz), 189.1 q (CF_3**C**=O, J = 36.6 Hz). Found, %: C 58.47; H 4.81. $C_{16}H_{16}F_3NO_3$. Calculated, %: C 58.71; H 4.93.

Ethyl 2-cyano-6,6,6-trifluoro-3-(3-methoxyphenyl)-5-oxohexanoate (VId). Yield 55%. IR spectrum, ν, cm^{-1}: 1750 br (C=O), 2270 (CN). ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, CH_2C**H**$_3$, J = 7.0 Hz), 1.23 t (3H, CH_2C**H**$_3$, J = 7.0 Hz), 3.36 d.d (2H, $COCH_2$, J = 7.0, 2.3 Hz), 3.40 d.d (2H, $COCH_2$, J = 7.6, 2.3 Hz), 3.78 br.s (6H, OCH_3), 3.80 d (1H, CHCN, J = 5.3 Hz), 3.91–3.99 m (2H, C_6H_4C**H**), 4.02 d (1H, CHCN, J = 6.2 Hz), 4.10 q.d (2H, OCH_2, J = 7.0, 2.6 Hz), 4.20 q.d (2H, OCH_2, J = 7.0, 2.3 Hz), 6.81–6.91 m (6H, C_6H_4), 7.22–7.29 m (2H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 13.7 (CH_2**C**H$_3$), 13.9 (CH_2**C**H$_3$), 38.6 (CO**C**H$_2$), 39.1 (CO**C**H$_2$), 39.4 (C_6H_4**C**H), 39.6 (C_6H_4**C**H), 43.0 (**C**HCN), 43.5 (**C**HCN), 55.2 (OCH_3) 63.0 (OCH_2), 63.3 (OCH_2), 113.4, 113.7, 113.8, 114.0, 138.0, 139.0, 159.9, 160.0 (C_6H_4), 114.7 (CN), 114.9 (CN), 115.2 q (CF_3, J = 291.5 Hz), 164.2 (**C**OOEt), 164.5 (**C**OOEt), 188.0 q (CF_3**C**=O, J = 36.6 Hz), 188.7 q (CF_3**C**=O, J = 36.6 Hz). Found, %: C 55.67; H 4.53. $C_{16}H_{16}F_3NO_4$. Calculated, %: C 55.98; H 4.70.

Ethyl 2-cyano-6,6,6-trifluoro-5-oxo-3-(2-thienyl)-hexanoate (VIe). Yield 44%. IR spectrum, ν, cm^{-1}: 1750 br (C=O), 2270 (CN). ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH_3, J = 7.0 Hz), 1.26 t (3H, CH_3, J = 7.0 Hz,), 3.40 d.d (2H, $COCH_2$, J = 8.5, 2.9 Hz), 3.43 d.d (2H, $COCH_2$, J = 7.9, 2.9 Hz), 3.90 d (1H, CHCN, J = 5.0 Hz), 4.04 d (1H, CHCN, J = 5.3 Hz), 4.17 q.d (2H, OCH_2, J = 7.0, 2.6 Hz), 4.23 q.d (2H, OCH_2, J = 7.0, 2.3 Hz), 4.26–4.36 m (2H, C_4H_3SCH), 6.95 t (1H, C_4H_3S, J = 3.5 Hz), 6.97 t (1H, C_4H_3S, J = 3.5 Hz), 7.04 d (1H, C_4H_3S, J = 3.5 Hz), 7.07 d (1H, C_4H_3S, J = 3.5 Hz), 7.24 d.d (2H, C_4H_3S, J = 5.3, 1.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.8 (CH_3), 34.8 (CO**C**H$_2$), 35.0 (CO**C**H$_2$), 39.9 (C_4H_3S**C**H), 40.7 (C_4H_3S**C**H), 43.8 (**C**HCN), 44.0 (**C**HCN), 63.2 (OCH_2), 63.5 (OCH_2), 114.4 (CN), 114.6 (CN), 115.2 q (CF_3, J = 291.5 Hz), 125.5, 125.6, 126.2, 126.6, 127.2, 127.3, 138.3, 139.7 (C_4H_3S), 164.0 (**C**OOEt), 164.2 (**C**OOEt), 188.1 q (CF_3**C**=O, J = 36.6 Hz), 188.8 q (CF_3**C**=O, J = 36.6 Hz). Found, %: C 48.61; H 3.83. $C_{13}H_{12}F_3NO_3S$. Calculated, %: C 48.90; H 3.79.

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