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Diastereoselective synthesis of α-hydroxydihydropyrans containing the CF_3 group

Valentine G. Nenajdenko,* Sergey V. Druzhinin and Elizabeth S. Balenkova

Department of Chemistry, M. V. Lomonosov Moscow State University, 119992 Moscow, Russian Federation. Fax: +7 495 932 8846; e-mail: nen@acylium.chem.msu.ru

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A new method for the stereoselective synthesis of 2-trifluoromethyl-2-hydroxy-4,6-diaryl-5-cyano-2,3-dihydropyrans using reactions of α,β-unsaturated trifluoromethyl ketones with substituted α-cyanoacetophenones is proposed.

The stereoelectronic properties of the trifluoromethyl group attract considerable attention because of principal differences between methyl and trifluoromethyl groups.[1] Heterocyclic compounds containing a trifluoromethyl group are of intense interest. α,β-Unsaturated trifluoromethyl ketones, which can be readily obtained from organolithium[2] or organomagnesium[3] reagents and β-enamino- and β-alkoxy α,β-unsaturated trifluoromethyl ketones or by the direct trifluoroacetylation of alkenes[4] are promising building blocks for the synthesis of both alicyclic and heterocyclic compounds containing the trifluoromethyl group.[5] Note that reactions of these compounds proceed differently from their non-fluorinated analogues.[5]

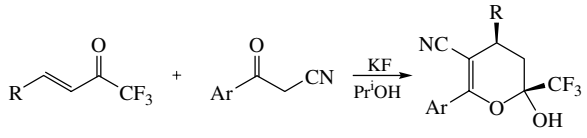
The reaction of α,β-unsaturated carbonyl compounds with CH acids, which usually proceed as 1,4-conjugated addition, is a classic method for the creation of a C–C bond.[6] This reaction for α,β-unsaturated trifluoromethyl ketones is not well investigated.

Only reactions for CF_3 ketones containing eliminating groups in the β-position, such as β-alkoxy-substituents, with C-nucleophiles are described: reaction with α-lithiated imines, leading to substituted pyridines;[7] reaction with 1,3-diketones, leading to various products depending on reaction conditions[8] and reaction with cyanothioacetamide.[9] Only several reactions with CH acids are known for ketones having no eliminating group in the β-position. For example, reactions with azoenolates,[10] malonodinitrile[11] and cyanoacetamide[11] were described.

Here we report a method for obtaining new compounds – α-hydroxydihydropyrans containing the CF_3 group. The dihydropyran ring is the structural fragment of many natural compounds, especially, antibiotics and flavonoids.[12] There are no convenient methods for the synthesis of simple dihydropyran derivatives containing the CF_3 group.

We studied the reactions of aromatic and heteroaromatic α,β-unsaturated trifluoromethyl ketones **1a–g** with α-cyanoketones **2a–c**. The appropriate deprotonation agent KF in isopropanol was used.[11,13] The reaction proceeded during a reasonable time under mild conditions (at ~20 °C). The reaction time varied from approximately 15 min for **2b** with a 4-methoxyphenyl substituent to several hours for 4-nitrophenyl ketone **2c**. All of the α,β-unsaturated trifluoromethyl ketones, except for **1f** and **1g** smoothly react with all of the three α-cyanoketones resulting in products **3** in good to nearly quantitative yields. In the case of α,β-unsaturated trifluoromethyl ketones **1f** and **1g** containing 3-indolyl and 3-(2-methylindolyl) substituents, no products were isolated, the reaction proceeded extremely slow and with noticeable resinification† (Table 1).

As expected, the reaction is 1,4-conjugated addition, but unexpected products were obtained. The structures of the products were determinined from spectral data. Note that the reaction proceeds stereoselectively and a single diastereomer is formed (Scheme 1). The structure of compound **3g** was confirmed by X-ray analysis.‡ The crystal of **3g** was obtained by crystallization from hexane–ethyl acetate (3:1). It is clear from Figure 1 that more bulky trifluoromethyl and 4-methylphenyl groups are arranged in more energy favourable equatorial positions while the hydroxy group is arranged in an axial position. The spectral data obtained for all compounds are similar to those of compound **3g**. This allows us to consider that all compounds have the same stereo configuration as dihydropyran **3g**.



1a R = Ph
1b R = 4-MeC_6H_4
1c R = 3-MeC_6H_4
1d R = 3-$MeOC_6H_4$
1e R = 2-thienyl
1f R = 3-indolyl
1g R = 3-(2-methylindolyl)

2a Ar = Ph
2b Ar = 4-$MeOC_6H_4$
2c Ar = 4-$NO_2C_6H_4$

3

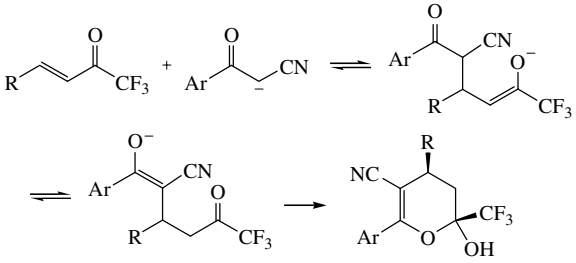
Scheme 1

Table 1 Reaction products of α,β-unsaturated trifluoromethyl ketones with α-cyanoketones.

R	Ar	Dihydropyran	Yield[a] (%)
Ph	Ph	**3a**	95
4-MeC_6H_4	Ph	**3b**	87
3-MeC_6H_4	Ph	**3c**	83
3-$MeOC_6H_4$	Ph	**3d**	95
2-thienyl	Ph	**3e**	80
Ph	4-$MeOC_6H_4$	**3f**	73
4-MeC_6H_4	4-$MeOC_6H_4$	**3g**	96
3-MeC_6H_4	4-$MeOC_6H_4$	**3h**	85
3-$MeOC_6H_4$	4-$MeOC_6H_4$	**3i**	94
2-thienyl	4-$MeOC_6H_4$	**3j**	91
Ph	4-$NO_2C_6H_4$	**3k**	88
4-MeC_6H_4	4-$NO_2C_6H_4$	**3l**	96
3-MeC_6H_4	4-$NO_2C_6H_4$	**3m**	97
3-$MeOC_6H_4$	4-$NO_2C_6H_4$	**3n**	98
2-thienyl	4-$NO_2C_6H_4$	**3o**	88

[a] Yields for isolated compounds are given.

The results obtained could be explained looking through the supposed reaction mechanism. The first stage of this reaction is anion generation from α-cyanoketone affected by KF. The second is standard Michael addition of this anion to α,β-unsaturated trifluoromethyl ketone forming cyano-substituted 1,5-diketone enolised on the carbonyl group neighbouring to the trifluoromethyl group, which is probably transformed into a more stable enolate form. The further cyclization takes place to generate semiketal centre, which is very typical of trifluoromethyl ketones.[14]



Scheme 2

The proposed mechanism explains the reaction observed. Note that all but the last stage of probable reaction scheme are reversible and it also proves the stability of dihydropyran formed. The comparative reaction times can also be explained.

† *Typical procedure for preparation of α-hydroxydihydropyrans with CF_3 group*. The mixture of 1 mmol of 4-substituted 1,1,1-trifluorobut-3-en-2-one **1**, 116 mg (2 mmol) of freshly calcinated potassium fluoride and 1 mmol of α-cyanoketone **2** was taken up in 3 ml of anhydrous isopropanol and stirred at room temperature until completion of reaction (TLC monitoring, hexane–ethyl acetate, 3:1). After solvent evaporation the residue was dissolved in a mixture of water (10 ml) and methylene chloride (10 ml) and acidified with aqueous hydrochloric acid to pH ~ 5. The organic layer was separated and the water layer was extracted with methylene chloride (2×10 ml). Combined organic fractions were dried over sodium sulfate and passed through silica gel. The solvent was evaporated to result in the target α-hydroxydihydropyran.

*2-Hydroxy-4,6-diphenyl-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-carbonitrile* **3a**: yield 656 mg (95%), white solid, mp 120 °C, R_f = 0.50 (hexane–ethyl acetate, 3:1). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.00 (br. dd, 1H, CH_2, ^2J –13.3 Hz, ^3J 13.0 Hz), 2.38 (dd, 1H, CH_2, ^2J –13.3 Hz, ^3J 6.3 Hz), 3.96–4.05 (dd, 1H, CH, ^3J 13.0 Hz, ^3J 6.3 Hz), 7.30–7.58 (m, 8H, Ph), 7.74–7.80 (m, 2H, Ph), 8.93 (br. s, 1H, OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 32.7 (CH), 35.9 (CH_2), 89.8 (*C*–CN), 95.1 (q, C–OH, ^2J 35.1 Hz), 118.2 (CN), 122.3 (q, CF_3, ^1J –285.4 Hz), 127.7, 128.1, 128.2, 128.3, 128.5, 128.6, 128.9, 140.0 (2Ph), 161.3 (C=*C*–O). IR (ν/cm^{-1}): 1605 (C=C–O), 2240 (CN), 3230 (OH). Found (%): C, 66.11; H, 4.18. Calc. for $C_{19}H_{14}F_3NO_2$ (%): C, 66.09; H, 4.09.

*2-Hydroxy-6-(4-methoxyphenyl)-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-carbonitrile* **3f**: yield 550 mg (73%), white solid, mp 159 °C, R_f = 0.50 (hexane–ethyl acetate, 3:1). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.96 (br. dd, 1H, CH_2, ^2J –13.3 Hz, ^3J 12.8 Hz), 2.36 (dd, 1H, CH_2, ^2J –13.3 Hz, ^3J 6.2 Hz), 3.82 (s, 3H, 4-*Me*OC_6H_4), 3.98 (dd, 1H, CH, ^3J 12.8 Hz, ^3J 6.2 Hz), 7.07 (d, 2H, 4-$MeOC_6$*H*$_4$, ^3J 8.8 Hz), 7.30–7.47 (m, 5H, Ph), 7.73 (d, 2H, 4-$MeOC_6$*H*$_4$, ^3J 8.8 Hz), 8.84 (br. s, 1H, OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 32.8 (CH), 36.0 (CH_2), 55.4 (4-*Me*OC_6H_4), 88.2 (*C*–CN), 94.9 (q, C–OH, ^2J 32.9 Hz), 113.2 (4-Me*O*C_6H_4), 118.6 (CN), 122.3 (q, CF_3, ^1J –286.2 Hz), 124.2 (4-Me*O*C_6H_4), 128.1, 128.8, 129.9, 140.3 (Ph), 160.0 (4-Me*O*C_6H_4), 161.4 (C=*C*–O). IR (ν/cm^{-1}): 1615 (C=C–O), 2235 (CN), 3240 (OH). Found (%): C, 63.80; H, 4.23. Calc. for $C_{20}H_{16}F_3NO_3$ (%): C, 64.00; H, 4.30.

*2-Hydroxy-6-(4-nitrophenyl)-4-phenyl-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-carbonitrile* **3k**: yield 690 mg (88%), light-yellow solid, mp 122 °C, R_f = 0.38 (hexane–ethyl acetate, 3:1). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.06 (br. dd, 1H, CH_2, ^2J –12.5 Hz, ^3J 12.3 Hz), 2.41 (dd, 1H, CH_2, ^2J –12.5 Hz, ^3J 5.6 Hz), 4.04 (dd, 1H, CH, ^3J 12.3 Hz, ^3J 5.2 Hz), 7.26–7.56 (m, 5H, Ph), 8.04 (d, 2H, 4-$NO_2C_6H_4$, *J* 8.4 Hz), 7.73 (d, 2H, 4-$NO_2C_6H_4$, *J* 8.4 Hz), 9.09 (br. s, 1H, OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 32.4 (CH), 36.0 (CH_2), 92.3 (*C*–CN), 95.5 (q, C–OH, ^2J 34.4 Hz), 117.5 (CN), 125.2 (q, CF_3, ^1J –285.2 Hz), 123.8, 128.3 (4-$NO_2C_6H_4$), 127.8, 128.9, 129.9 (Ph), 138.0 (4-$NO_2C_6H_4$), 139.6 (Ph), 148.8 (4-$NO_2C_6H_4$), 159.3 (C=*C*–O). IR (ν/cm^{-1}): 1600 (C=C–O), 2210 (CN), 3250 (OH). Found (%): C, 58.65; H, 3.32. Calc. for $C_{19}H_{13}F_3N_2O_4$ (%): C, 58.47; H, 3.36.

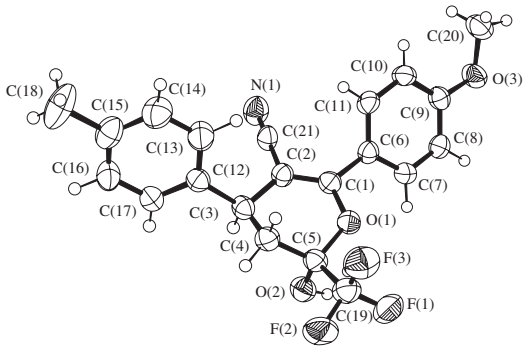


Figure 1 X-ray structure of compound **3g**.

In the case of a more donor Ar-group the carbanions formed from cyano ketone are more nucleophilic and the addition reaction proceeds with a higher rate and so the overall reaction rate is higher.

In summary, we elaborated the stereoselective synthesis of CF_3-substituted dihydropyrans. The reaction proceeds in good yields under mild conditions. The obtained dihydropyrans are attractive objects for further transformations. They present the hidden cyclic form of 1,5-diketone and can be used in Hantzsch pyridine synthesis and some other reactions.

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‡ *Crystallographic data for* **3g**: at 293 K crystals of $C_{21}H_{18}F_3NO_3$ are monoclinic, space group $P2_1/c$, $a = 10.844(2)$, $b = 8.969(2)$, $c = 19.748(4)$ Å, $\beta = 97.81(3)°$, $V = 1902.9(7)$ Å^3, $Z = 4$, $M = 389.36$, $d_{calc} = 1.359$ g cm^{-3}, u(MoKα), $F(000) = 808$. Intensities were measured with CAD4 diffractometer. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 299928. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2006.