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REACTIONS OF DIAZOALKANES WITH UNSATURATED CF_3-KETONES

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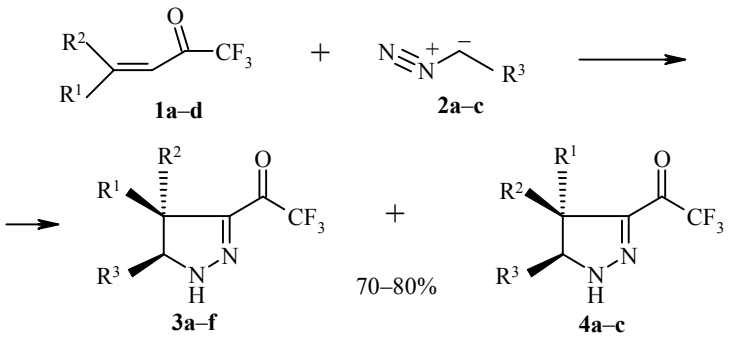
The cycloaddition reactions of various diazoalkanes with unsaturated trifluoromethyl-containing ketones have been investigated. The reactions proceed regiospecifically and stereoselectively to the formation of trifluoroacetyl derivatives of 1H-pyrazolines.

Keywords: CF_3-heterocycles, diazoalkanes, dipoles, dipolarophiles, cycloaddition.

1,3-Dipolar cycloaddition reactions play an important role in the chemistry of heterocycles, since they enable the preparation for organic synthesis of a large number of valuable compounds and intermediates difficult to obtain. Consequently the study of the rules for carrying out these reactions is an urgent problem.

The chemistry of diazo compounds has been well studied up to the present time and consequently a significant amount of work on this class of compound has been published. The most complete material on diazo compounds is published in [1].

During recent years we have published efficient methods of synthesis of α,β-unsaturated ketones containing trifluoromethyl groups [2-10], and their reactivity has also been investigated [11-20]. It turned out that the reactivity of similar compounds differs from that of their paraffin analogs due to the electron-withdrawing effect of the trifluoromethyl group. Analysis of the literature showed that α,β-unsaturated ketones containing a trifluoromethyl group have not been investigated in 1,3-dipolar cycloaddition reactions [2]. In the present work we have studied the behaviour of α,β-unsaturated trifluoromethyl-containing ketones in reactions with diazoalkanes using various aryldiazomethanes and ethyl diazoacetate as examples.



1a R^1 = Ph, R^2 = H; **b** R^1 = 2-thienyl, R^2 = H; **c** $R^1 = R^2 = -(CH_2)_3$; **d** R^1 = Ph, $R^2 = CH_3$;
2a R^3 = Ph; **b** R^3 = 4-O_2NPh; **c** R^3 = OCOEt; **3a** R^1 = Ph, R^2 = H, R^3 = Ph; **b** R^1 = Ph, R^2 = H, R^3 = 4-O_2NPh; **c** R^1 = 2-thienyl, R^2 = H, R^3 = Ph; **d** $R^1 = R^2 = -(CH_2)_3$, R^3 = Ph; **e** R^1 = Ph, R^2 = H, R^3 = OCOEt; **f** R^1 = 2-thienyl, R^2 = H, R^3 = OCOEt; **4a** R^1 = Ph, R^2 = H, R^3 = OCOEt; **b** R^1 = Ph, R^2 = H, 4-O_2NPh; **c** R^1 = 2-thienyl, R^2 = H, R^3 = OCOEt

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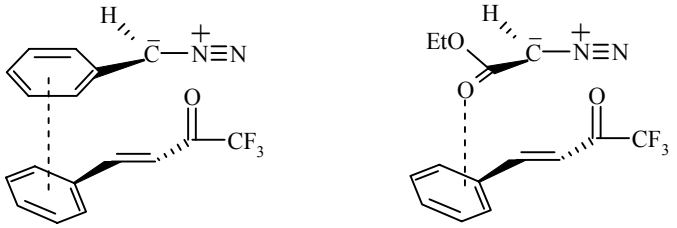
1H-Pyrazolines were obtained in all cases and are formed by an isomerization reaction of the 3H-pyrazolines formed initially. The ease of this isomerization is caused by the increased acidity of the α-proton on the trifluoroacetyl group.

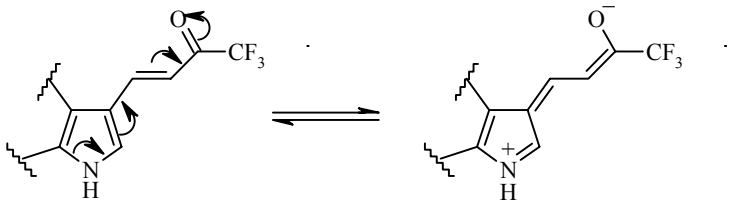
On interacting α,β-unsaturated ketones with previously isolated diazoalkanes in benzene a strong exothermy was observed and the yields of the compounds obtained did not exceed 10-15%. The method in which the diazoalkanes are generated *in situ* by heating the sodium salts of the appropriate tosylhydrazones in toluene in the presence of dipolarophiles proved to be more convenient. As a result the yields were 70-80%. The rate of cycloaddition of diazo compounds to α,β-unsaturated ketones and also the structure of the compounds obtained depends both on the structure of the initial diazo compound and on the structure of the α,β-unsaturated ketone. In all cases the reactions proceed regioselectively.

Reaction with phenyl diazomethane proceeds in the course of 1-2 min. Only the formation of *cis*-1H-pyrazolines was observed. An analogous predominance of *cis* isomers is observed on interacting α,β-unsaturated ketones with diazo compounds with a stabilized electron-withdrawing group. The interaction of *p*-nitrophenyl diazomethane and diazoacetic ester with a dipolarophile therefore occurs on refluxing for 5 h in toluene. Predominantly *cis*-1H-pyrazolines are formed as a result of the reaction, together with *trans* isomers in a *cis*-*trans* ratio of 3:1. Probably the preferential formation of *cis* isomers is linked in all cases with secondary orbital interactions in the transition state between the aryl substituents in the α,β-unsaturated ketones containing a trifluoromethyl group and the aryl substituents in the aryl diazomethanes or the carboxyl group in the case of ethyl diazoacetate.

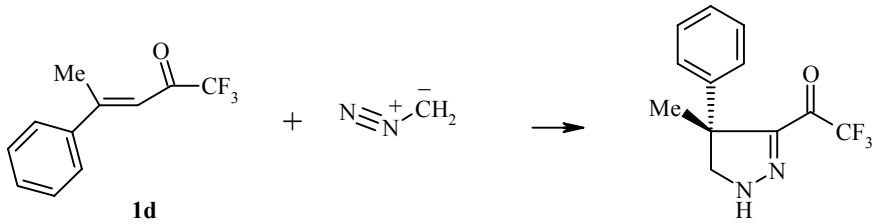


It may therefore be said that *cis*-(1H)-pyrazolines **3a-f** are products of kinetic control but the thermodynamically more stable *trans*-(1H)-pyrazolines **4a-c** are the products of thermodynamic control.

Attempts to carry out the reaction with 2-pyrrolyl-, 3-indolyl-, and dimethylamino-substituted α,β-unsaturated ketones containing a trifluoromethyl group proved to be unsuccessful even at increased temperatures and in the presence of Lewis acids (BF_3 and $ZnCl_2$). It should be noted that in these compounds it is possible to have vinylogous conjugation of the lone pair of the nitrogen atom and the trifluoroacetyl group, which probably is also a reason for the deactivation of these α,β-unsaturated ketones in 1,3-dipolar cycloaddition reactions with diazoalkanes.



These ketones do not react even with such a reactive dipole as diazomethane. Ketone **1d** also did not react with aryldiazomethanes. Probably in this case the methyl group creates steric hindrance in the transition state which prevents further approach of reacting particles and subsequent formation of C–C and C–N bonds. However the cycloadduct **5** of ketone **1d** with diazomethane was isolated and is a 1H-pyrazoline. This reaction also proceeds regiospecifically.



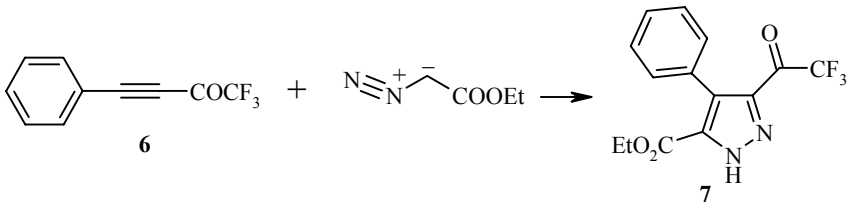
1d **5**

To explain the regiospecificity and stereoselectivity of the reactions we carried out a series of theoretical calculations using the PM3 method [21]. The cycloadition process is controlled by the interaction of the highest occupied molecular orbital (HOMO) of the dipole and the lowest unoccupied molecular orbital (LUMO) of the dipolarophile. It is known from the literature that a low energy level of the LUMO of the polarophile and a high energy level of the HOMO of the dipole aid the progress of the reaction [22]. We calculated the orbital coefficients and the orbital energy levels of the diazoalkanes (Table 1).

Analogous calculations were carried out for the LUMO energy levels and the orbital coefficients of atoms in various α,β-unsaturated ketones containing the trifluoromethyl group (Table 2).

It is known that in [4π+2π] cycloaddition reactions the formation of C–C bonds is observed between carbon atoms with large orbital coefficients. From the Tables given above it is seen that the $C_{(3)}$ atoms of the dipolarophiles and the $C_{(3)}$ atoms of the diazoalkanes possess the greatest orbital coefficients, which also explains the regiospecificity of the 1,3-dipolar cycloaddition reactions.

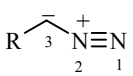
We also investigated the interaction of diazoacetic ester with trifluoroacetylated phenylacetylene **6** on refluxing in benzene for 1 day. The corresponding pyrazole **7** was obtained in 45% yield, and as in the previous cases the cycloaddition reaction proceeds regiospecifically.



6 **7**

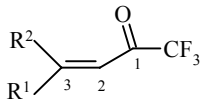
We have therefore investigated the reactivity of trifluoromethyl-containing α,β-unsaturated ketones in 1,3-dipolar cycloaddition reactions with diazoalkanes. It was shown that the reaction proceeds regiospecifically and stereoselectively. The 1H-pyrazolines obtained are promising compounds for further synthesis of pyrazoles and cyclopropanes containing the trifluoromethyl group.

TABLE 1. Energy Levels of the HOMO of Diazoalkanes and Orbital Coefficients of Atoms



R	HOMO	$N_{(1)}$	$N_{(2)}$	$C_{(3)}$
4-NO_2–Ph–	-9.21	0.446	0.155	0.617
Ph–	-8.49	0.445	0.174	0.578
EtOOC–	-9.75	0.527	0.112	0.781

TABLE 2. Energy Levels of the LUMO of Dipolarophiles and Orbital Coefficients of Atoms



R^1	R^2	LUMO	$C_{(3)}$	$C_{(2)}$	$C_{(1)}$	O
Ph	H	-1.36	0.498	0.386	0.380	0.356
2-Thienyl	H	-1.62	0.431	0.376	0.304	0.298
$-(CH_2)_3-$		-0.88	0.580	0.336	0.526	0.462
Ph	CH_3	-1.09	0.491	0.392	0.348	0.326

EXPERIMENTAL

The IR spectra were recorded on a UR 20 instrument as films. The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR 400 spectrometer (400 and 100 MHz respectively) in $CDCl_3$ at room temperature with TMS as internal standard. All solvents used were purified by standard procedures.

General Reaction Procedure with Phenyldiazomethane. Sodium methylate solution (1 M : 1 ml) was added to the tosylhydrazone (0.001 mol) of the appropriate aldehyde, the mixture was stirred for 1 h, and then evaporated. The tosylhydrazone sodium salt obtained in this way was treated with the appropriate α,β-unsaturated CF_3-ketone (0.001 mol), toluene (10 ml), and heated to 110°C with stirring, and maintained for 30 min. The reaction mixture was then filtered, evaporated, and chromatographed on a column of silica gel (hexane–ether, 10:1).

General Reaction Procedure for Ketone 1a with Diazo Compounds 2b and 2c. Diazo compounds **2b** and **2c** were synthesized by the standard procedure. Dipolarophile **1a** (0.001 mol) and **2b** or **2c** (0.001 mol) were refluxed in toluene for 2 days. The reaction mixture was evaporated. In the case of reaction with ethyl diazoacetate the reaction products were isolated chromatographically (hexane–ether, 10:1). For reaction with *p*-nitrophenyldiazomethane the reaction mixture was filtered, and a mixture of compounds **3b** and **4b** was obtained as a brown powder.

***cis*-4,5-Diphenyl-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (3a).** Yield 61%. IR spectrum, ν, cm^{-1}: 3430 (NH), 1700 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 7.59 (1H, s, NH); 7.24-7.39 (6H, m, H arom.); 7.10-7.17 (4H, m, H arom.); 4.95 (1H, d, *J* = 6.47, CH-N); 4.35 (1H, d, *J* = 6.47, CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 174.5 (q, *J* = 35.4, C=O); 143.0, 140.0, 139.8, 129.4, 129.2, 128.8, 127.7, 127.0, 125.6, 116.5 (q, *J* = 290.43, CF_3); 74.5, 57.0. Found, %: C 64.23; H 3.83. $C_{17}H_{13}F_3N_2O$. Calculated, %: C 64.15; H 4.12.

***cis*- and *trans*-4,5-Bis(4-nitrophenyl)-3-trifluoracetyl-4,5-dihydro-1H-pyrazole (3b and 4b)** 3:1 mixture. Yield 34%. IR spectrum, ν, cm^{-1}: 3380 (NH), 1660 (CO). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.25 (1H, s, NH-*cis*); 7.90 (1H, s, NH-*trans*); 6.90-7.80 (m, H arom.); 5.53 (1H, d, *J* = 12.0, *trans* isomer); 5.08 (1H, d, *J* = 4.7, *cis* isomer); 4.80 (1H, d, *J* = 12.0, *trans* isomer); 4.30 (1H, d, *J* = 4.7, *cis* isomer). ^{13}C NMR spectrum, (*cis* isomer), δ, ppm (*J*, Hz): 174.0 (q, *J* = 36.0, C=O); 148.0, 146.7, 143.2, 138.8, 129.4, 128.3, 127.0, 126.8, 124.6, 116.0 (q, *J* = 291.1, CF_3); 73.9, 57.9. Found, %: C 55.78; H 3.06. $C_{17}H_{11}F_3N_4O_5$. Calculated, %: C 56.20; H 3.33.

***cis*-5-Phenyl-4-(2-thienyl)-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (3c).** Yield 56%. IR spectrum, ν, cm^{-1}: 3430 (NH), 1700 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.43 (1H, s, NH); 7.05-7.35 (6H, m, H arom.); 6.88 (1H, m, thiophene); 6.78 (1H, d, *J* = 2.2, thiophene); 4.96 (1H, d, *J* = 6.44, CH–N); 4.62 (1H, d, *J* = 6.44, CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 174.90 (q, *J* = 35.1, C=O); 142.8, 142.5, 140.0, 130.2, 129.7,

128.1, 126.4, 125.9, 125.8, 116.0 (q, J = 290.1, CF_3); 75.5, 52.4. Found, %: C 55.20; H 3.68. $C_{15}H_{11}F_3N_2OS$. Calculated, %: C 55.55; H 3.42.

8-Phenyl-5-trifluoracetyl-6,7-diazaspiro[3,4]oct-5-ene (3d). Yield 77%. IR spectrum, ν, cm^{-1}: 3460 (NH), 1710 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.35-7.45 (3H, m, H arom.); 7.34 (1H, s, NH); 7.21-7.26 (2H, m, H arom.); 4.91 (1H, s, CH); 2.70-2.90 (1H, m, CH_2); 2.15-2.30 (1H, m, CH_2); 1.97-2.15 (2H, m, CH_2); 1.43-1.70 (2H, m, CH_2). ^{13}C NMR spectrum, δ, ppm (J, Hz): 175.50 (q, J = 34.68, C = O), 145.98, 136.22, 128.99, 128.81, 128.30, 127.18, 117.00 (q, J = 291.13, CF_3); 77.35, 52.80, 33.64, 26.59, 15.60. Found, %: C 59.88; H 4.46. $C_{14}H_{13}F_3N_2O$. Calculated, %: C 59.57; H 4.64.

***cis*-5-Ethoxycarbonyl-4-phenyl-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (3e).** Yield 55%. IR spectrum, ν, cm^{-1}: 3320 (NH), 1740 (C=O), 1680 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 8.15 (1H, s, NH); 7.54-7.68 (3H, m, H arom.); 7.47-7.52 (2H, m, H arom.); 5.03 (1H, d, J = 4.88, CH-N); 4.79 (1H, d, J = 4.88, CH); 4.57 (2H, dq, J = 1.44, J = 7.14, CH_2CH_3); 1.61 (3H, t, J = 7.14, CH_3CH_2). ^{13}C NMR spectrum, δ, ppm (J, Hz): 174.50 (q, J = 47.93, C=O); 169.60, 144.57, 138.48, 129.19, 128.01, 126.80, 116.26 (q, J = 288.43, CF_3); 70.40, 62.60, 51.34, 13.90. Found, %: C 54.00; H 4.22. $C_{14}H_{13}F_3N_2O_3$. Calculated, %: C 53.51; H 4.17.

***trans*-5-Ethoxycarbonyl-4-phenyl-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (4a).** Yield 18%. IR spectrum, ν, cm^{-1}: 3320 (NH), 1740 (C=O), 1680 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz): 7.47 (1H, s, NH); 7.20-7.40 (3H, m, H arom.); 7.05-7.15 (2H, m, H arom.); 5.01 (1H, d, J = 13.27, CH-N); 4.76 (1H, d, J = 13.27, CH); 3.74-3.82 (1H, m, CH_2); 3.63-3.72 (1H, m, CH_2); 0.80 (3H, t, J = 7.15, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 174.00 (q, J = 36.39, C=O); 167.80, 144.16, 134.54, 128.55, 128.09, 127.96, 116.00 (q, J = 290.30, CF_3); 67.92, 61.69, 50.59, 13.23. Found, %: C 53.77; H 4.09. $C_{14}H_{13}F_3N_2O_3$. Calculated, %: C 53.51; H 4.17.

***cis*-5-Ethoxycarbonyl-4-(2-thienyl)-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (3f).** Yield 47%. IR spectrum, ν, cm^{-1}: 3300 (NH), 1740 (C=O), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.69 (1H, s, NH); 7.20 (1H, dd, J = 2.6, J = 3.6, thiophene); 6.92 (1H, s, thiophene); 6.91 (1H, s, thiophene); 5.03 (1H, d, J = 4.64, CH–N); 4.56 (1H, d, J = 4.64, CH); 4.27 (1H, q, J = 7.15, OCH_2); 1.30 (3H, t, J = 7.15, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 174.01 (q, J = 36.4, C=O); 168.95, 143.58, 140.05, 127.21, 125.31, 125.16, 115.98 (q, J = 290.40, CF_3); 70.43, 62.71, 46.04, 13.87. Found, %: C 45.38; H 3.18. $C_{12}H_{11}F_3N_2O_3S$. Calculated, %: C 45.00; H 3.46.

***trans*-5-Ethoxycarbonyl-4-(2-thienyl)-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (4c).** Yield 17%. IR spectrum, ν, cm^{-1}: 3300 (NH), 1740 (C=O), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 9.59 (1H, s, NH); 7.30 (1H, d, J = 4.1, thiophene); 6.92 (1H, dd, J = 4.1, J = 3.6, thiophene); 6.91 (1H, d, J = 3.6, thiophene); 5.21 (1H, d, J = 13.1, CH–N); 5.20 (1H, d, J = 13.1, CH); 3.83 (1H, m, J = 7.3, OCH_2); 0.90 (3H, t, J = 7.3, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 174.7 (q, J = 35.1, C=O), 167.75, 142.99, 138.44, 127.62, 127.53, 126.04, 117.98 (q, J = 290.0, CF_3); 69.48, 61.83, 45.24, 13.95. Found, %: C 45.33; H 3.13. $C_{12}H_{11}F_3N_2O_3S$. Calculated, %: C 45.00; H 3.46.

Reaction of Ketone 1d with Diazomethane. An excess of diazomethane in ether at -80°C was added to a solution of ketone **1d** (0.001 mol) in ether (10 ml) cooled to -80°C. After adding all the diazomethane solution the temperature was brought up to room temperature, the reaction mixture was evaporated, and hexane added. Pyrazoline **5** was isolated as yellow crystals.

4-Methyl-4-phenyl-3-trifluoroacetyl-4,5-dihydro-1H-pyrazole (5). Yield 73%. IR spectrum, ν, cm^{-1}: 3300 (NH), 1740 (C=O). ^{1}H NMR spectrum, δ, ppm (J, Hz): 7.32-7.40 (2H, m, H arom.); 7.25-7.30 (3H, m, H arom.); 3.89, (1H, d, J = 11.54, CH_2); 3.80 (1H, d, J = 11.54, CH_2); 1.78 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm (J, Hz): 174.00 (q, J = 34.85, C=O); 143.52, 128.74, 128.61, 127.14, 125.53, 116.60 (q, J = 291.28, CF_3); 66.57, 50.07, 22.34. Found, %: C 56.43; H 4.56. $C_{12}H_{11}F_3N_2O$. Calculated, %: C 56.25; H 4.33.

Reaction of Acetylenic Ketone 6 with Ethyl Diazoacetate. Ketone **6** (0.01 mol) and ethyl diazoacetate (0.001 mol) were refluxed in benzene for 1 day. The reaction mixture was evaporated, and the reaction product isolated chromatographically (hexane–ether, 10:1).

5-Ethoxycarbonyl-4-phenyl-3-(trifluoroacetyl)-1H-pyrazole (7). Yield 45%. IR spectrum, ν, cm^{-1}: 1730 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.30 (1H, s, NH); 7.31-7.44 (5H, m, H arom.); 4.29 (2H, q, *J* = 7.14, $CH_3C\underline{H}_2$); 1.15 (3H, t, *J* = 7.14, $C\underline{H}_3CH_2$);. ^{13}C NMR spectrum ($CHCl_3$), δ, ppm (*J*, Hz): 175.00 (q, *J* = 36.92, C=O); 158.70 (C=O); 142.70, 132.81, 130.05, 129.92, 128.78, 128.53, 127.64, 116.00 (q, *J* = 291.07, CF_3); 62.00, 13.50. Found, %: C 53.77; H 3.39. $C_{14}H_{11}F_3N_2O$. Calculated, %: C 53.85; H 3.55.

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