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4-ACYL-5-HYDROXY-1-PHENYL-3-TRIFLUOROMETHYL-PYRAZOLES: SYNTHESIS AND NMR SPECTRAL INVESTIGATIONS

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Abstract – The title compounds were prepared by reaction of 1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol with trimethyl orthoacetate, triethyl orthopropionate and triethyl orthobenzoate, respectively, followed by hydrolytic cleavage of the primarily formed condensation products. Detailed NMR spectroscopic investigations with the obtained products are presented, revealing the title compounds to be present as 5-hydroxypyrazoles stabilized by an intramolecular hydrogen bond in $CDCl_3$ solution.

INTRODUCTION

The 1-aryl-3-trifluoromethyl-1*H*-pyrazole unit is a substructure of many biologically active compounds including, for instance, also the well-known cyclooxygenase-2 (COX-2) inhibitor Celecoxib (Celebrex™).[1] A large number of 1-aryl-3-trifluoromethyl-1*H*-pyrazoles thus have been synthesized in the last years, a current search in *Chemical Abstracts* reveals more than 6000 compounds containing this substructure. However, amongst these there can be found only a few examples containing a 4-acyl (or 4-aroyl) substituent on the pyrazole nucleus and, moreover, only a handful of 4-acyl-1-aryl-3-trifluoromethyl-1*H*-pyrazol-5-ols of type (**3**) hitherto have been described (Figure 1).[2-4] As compounds (**3**) are considered to be valuable building blocks for the construction of more complex 1-aryl-3-trifluoromethylpyrazoles including also corresponding condensed systems, we here present a short and simple synthesis of the title compounds (**3**).

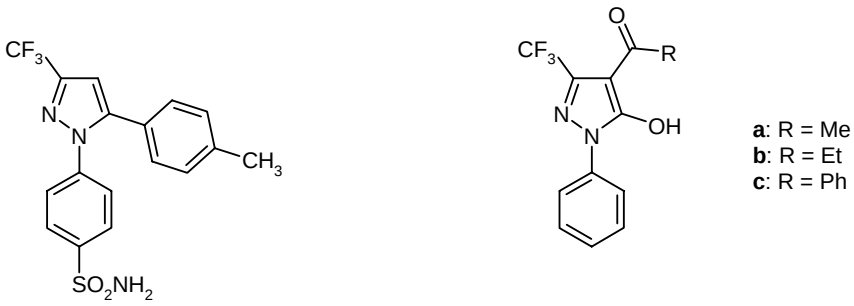
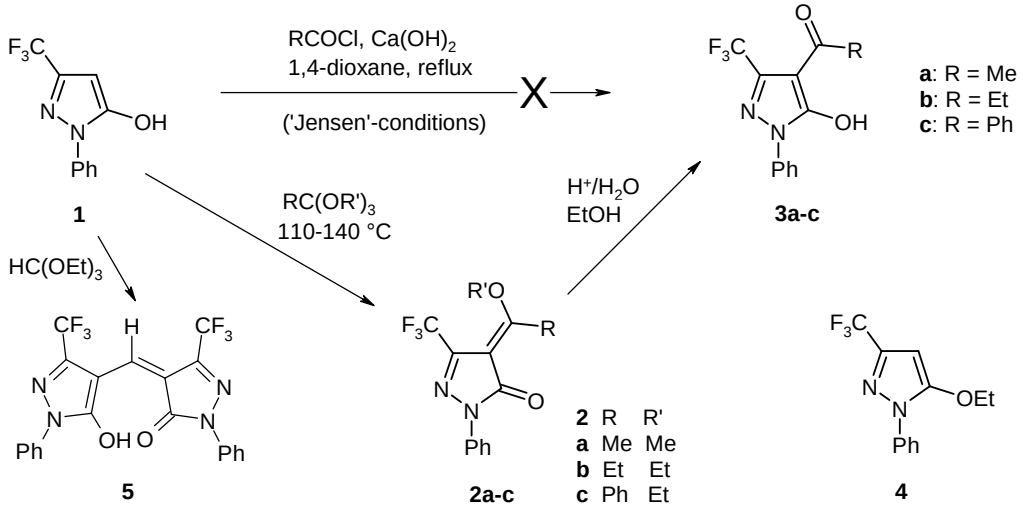


Figure 1

RESULTS AND DISCUSSION

The standard method for the synthesis of 1-substituted 4-acyl-1*H*-pyrazol-5-ols consists in the reaction of 1-substituted 2-pyrazolin-5-ones (1-substituted 1*H*-pyrazol-5-ols) with appropriate carboxylic acid chlorides in the presence of excess calcium hydroxide in boiling 1,4-dioxane ('Jensen'-method) (Scheme 1).[5] However, we found that this approach is not suitable when using 1-phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol (**1**) as the starting material: the desired 4-acyl products (**3**) here are only formed in traces and mainly unreacted **1** was isolated from the reaction mixture. An alternative way – described in a few examples – for the introduction of an acyl or aroyl substituent into position 4 of a 2-pyrazolin-5-one should be the condensation with appropriate orthoesters, primarily leading to correspondingly substituted 4-(1-alkoxyalkylidene)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-ones.[6,7] The latter 'enol ethers' can be smoothly transformed into the corresponding ketones by hydrolytic cleavage.[7]



Scheme 1

Thus, we heated starting material (**1**) with trimethyl orthoacetate, triethyl orthopropionate and triethyl orthobenzoate, respectively, to 110-140 °C to afford the deeply colored condensation products (**2**). Subsequent treatment of the latter with 96% EtOH containing some drops of HCl finally led to the target products (**3**) (Scheme 1). Although intermediates (**2**) can be easily isolated, they are labile compounds and show a high tendency to hydrolysis.[8] Thus, it is advantageous and more convenient to combine the two reaction steps into a one-pot procedure (40-70% overall yield). Performing the reaction in an inert solvent such as toluene or xylene gave lower yields and also the formation of by-products such as 5-ethoxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (**4**) was observed. The latter (**4**) was identical with a sample independently obtained from etherification of **1** with ethanol in a Mitsunobu-type reaction according to ref.[9] Reaction of **1** with triethyl orthoformate expectedly gave the dimeric product (**5**), resulting from addition of a second unit of **1** to the intermediate (**2**) (Scheme 1). Compound (**7**) (Figure 5), which was needed for comparison with related structures (**2**)**,** was prepared by reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one with triethyl orthopropionate.[6]

NMR SPECTROSCOPIC INVESTIGATIONS

Unambiguous assignment for all proton and carbon resonances was achieved by combined application of standard NMR spectral techniques, such as NOE-difference experiments, fully ^{1}H-coupled ^{13}C-NMR spectra, APT, HMQC and HMBC spectra as well as experiments with selective excitation such as 1D-TOCSY,[10] 1D-HETCOR[11] and selective long-range INEPT.[12,13] The ^{15}N-NMR spectra were mainly recorded using the gradient selected, sensitivity enhanced HMBC sequence.[14]

Compounds (**1**) and (**4**)

In principle, starting material (**1**) can be present in the CH- (**A**), OH- (**B**) or in the NH-form (**C**) (Figure 2).[15] As **1** has a very low solubility in $CDCl_3$, NMR spectroscopic investigations were performed in DMSO-d_6 solution. ^{1}H-NMR spectra and, particularly, ^{13}C-NMR spectra (δ pyrazole C-5 153.8 ppm) revealed **1** to exist exclusively as 5-hydroxypyrazole (form **B**) or as an equilibrium (with fast exchange) of OH- and NH-isomer with the former far predominating. The preference of the OH-form is also reflected by the ^{15}N-NMR chemical shifts showing two N-atoms of different type (N-1: δ −181.4 ppm; N-2: δ −103.1 ppm). Moreover, the close similarity of **1** and the 5-ethoxypyrazole (**4**) (δ pyrazole C-5 154.7 ppm), which can be seen as the ‘fixed’ OH-form of **1**, hints to the dominance of the OH-form (Figure 2). Comparison of key chemical shifts of **4** and the related 5-ethoxy-3-methyl-1-phenyl-1*H*-pyrazole (**6**) is also displayed in Figure 2.

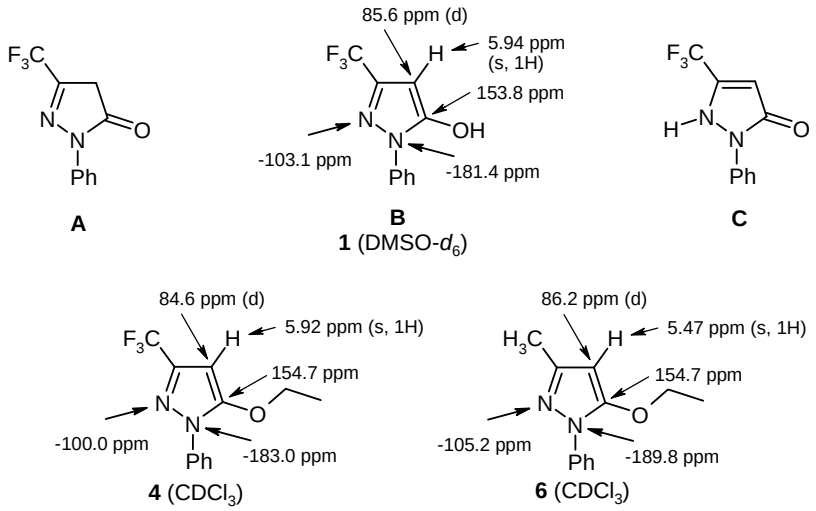


Figure 2

4-Acylpyrazol-5-ols (**3**)

For species of type (**3**) the number of possible tautomeric forms increases as now the 4-substituent can participate in tautomerism and also stabilization by intramolecular hydrogen bonds is possible (forms **B'** and **D'**) (Figure 3).[15,16]

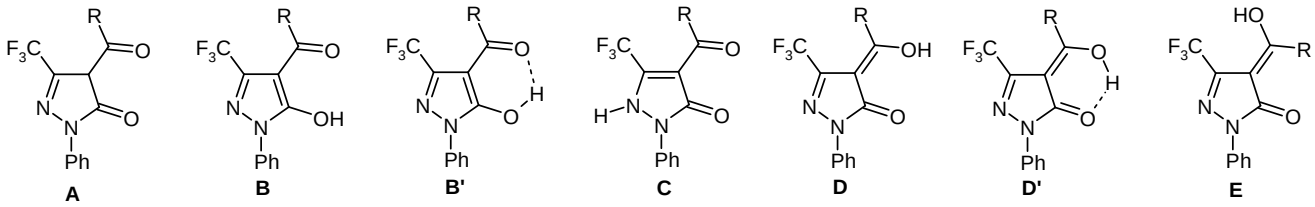


Figure 3

^{13}C-NMR and ^{15}N-NMR spectral data reveal compounds (**3a-c**) to exist exclusively as hydroxypyrazoles. However, there is an interesting phenomenon in the ^{13}C-NMR spectra. For instance, in the ^{1}H-broadband decoupled ^{13}C-NMR spectrum of **3a** in DMSO-d_6 solution the signal due to the methyl-C atom appears as a singlet (δ 27.5 ppm), whereas in $CDCl_3$ solution the corresponding signal is split into a quartet (δ 27.6 ppm, J = 3.3 Hz). This can be explained by the presence of **3a** (in $CDCl_3$) in form **B'**, where the strong intramolecular hydrogen bond fixes the acyl moiety and brings the methyl-C atom close to the trifluoromethyl group (Figure 4). In contrast, in DMSO-d_6 solution (a strong acceptor) the hydrogen bond is obviously broken (form **B**) and the average distance between methyl-C and CF_3 group is now much larger. Similar splittings due to ^{19}F,^{13}C through-space coupling[17] in $CDCl_3$ solution (and not in DMSO-d_6) were found with carbon atoms CO**C**H_2 in **3b** and CO-Ph **C**-2,6 in **3c**. Moreover, the intramolecular hydrogen bond of **3a** in $CDCl_3$ solution is evidenced by a significant downfield shift for the carbonyl

C-atom (δ 195.9 ppm) as well as for pyrazole C-5 (δ 160.2 ppm) compared to the corresponding values found in DMSO-d_6 (δ 189.1 ppm and δ 157.8 ppm) (Figure 4).

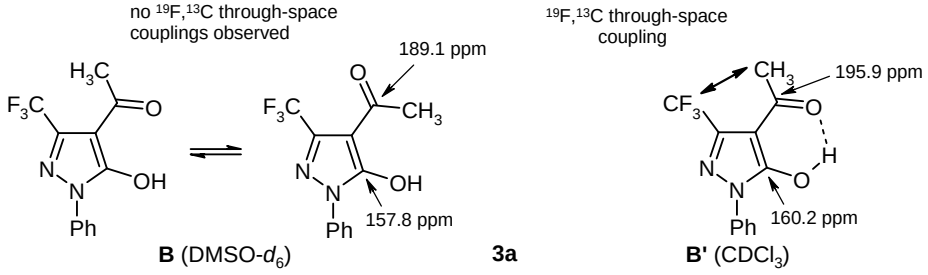


Figure 4

Compounds (**2**)

Assignment of (*E*)-configuration at the exocyclic C=C bond of compounds (**2**) is a difficult task and is based on comparison with closely related compound (**7**)[6] with known stereochemistry, the latter showing a clear NOE between the 5-Me protons and OCH_2, which is only possible in the (*E*)-configuration (Figure 5). Moreover, the absence of $^{19}F,^{13}C$ through-space couplings between the CF_3 flourine atoms and appropriate carbon atoms of the substituent R gives an additional hint for the stereochemistry displayed for compound (**2**) (Figure5).

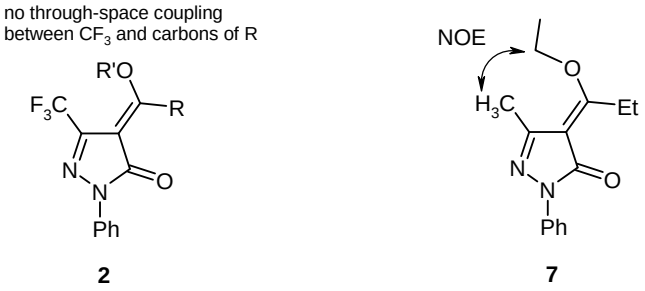


Figure 5

Compound (**5**)

Dimeric compound (**5**) exhibits complete equivalence of the two (substituted) pyrazole units in the NMR spectra. Also in low-temperature experiments down to 223 K no substantial changes in the ^{1}H-NMR spectra ($CDCl_3$) can be observed. This phenomenon can be explained by – either – the presence of a fast equilibrium (compared to the NMR-timescale) of tautomers (**A**) and (**B**) or by a situation displayed in formula **C** (Figure 6). Closely related compounds have been reported to be stabilized by a strong intramolecular hydrogen bond with double minimum potential under formation of a – formal – 8-membered ring system.[19] Moreover, the X-Ray crystal structure of a corresponding compound –

carrying CH_3 instead of CF_3 groups – clearly shows form **C** to be present in the solid state.[20] Thus, a similar situation is obviously also the case for compound (**5**), reflected by the extraordinary deshielding of the OH-proton (δ 17.4 ppm in $CDCl_3$).

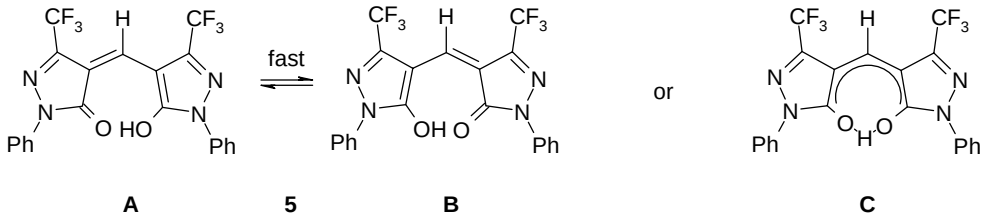


Figure 6

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. MS spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), HRMS spectra (EI) on a Finnigan MAT 8230 instrument. IR spectra were recorded on a Perkin-Elmer FTIR 1605 spectrophotometer. The NMR spectra were obtained on a Varian UnityPlus 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28 °C. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H in $CDCl_3$), δ 2.49 ppm (^{1}H in DMSO-d_6), δ 77.0 ppm (^{13}C in $CDCl_3$), δ 39.5 ppm (^{13}C in DMSO-d_6). ^{15}N-NMR spectra (50.69 MHz) were obtained on a Bruker Avance 500 spectrometer using a 'directly' detecting broadband observe probe and were referenced against neat, external nitromethane (coaxial capillary). Digital resolutions were 0.25 Hz/data point in the ^{1}H and 0.4 Hz/data point in the ^{1}H-coupled ^{13}C-NMR spectra (gated decoupling) and ≤ 59 Hz/data point in the ^{15}N,^{1}H HMBC spectra. Starting materials (**1**) and 3-methyl-1-phenyl-2-pyrazolin-5-one are commercially available (Aldrich).

1-Phenyl-3-trifluoromethyl-1*H*-pyrazol-5-ol (1)

^{1}H-NMR (DMSO-d_6): δ (ppm) 12.41 (br s, 1H, OH), 7.72 (m, 2H, Ph H-2,6), 7.49 (m, 2H, Ph H-3,5), 7.35 (m, 1H, Ph H-4), 5.94 (s, 1H, H-4); ^{13}C-NMR (DMSO-d_6): δ (ppm) 153.8 (C-5, ^2J(C5,H4) = 5.3 Hz), 140.5 (C-3, ^2J(C3,CF_3) = 37.4 Hz, ^2J(C3,H4) = 3.7 Hz), 137.8 (Ph C-1), 129.1 (Ph C-3,5), 127.2 (Ph C-4), 122.3 (Ph C-2,6), 121.4 (CF_3, ^1J = 268.6 Hz), 85.6 (C-4, ^1J = 181.9 Hz, ^3J(C4,CF_3) = 2.1 Hz); ^{15}N-NMR (DMSO-d_6): δ (ppm) −103.1 (N-2), −181.4 (N-1).

(4*E*)-4-(1-Methoxyethylidene)-2-phenyl-5-trifluoromethyl-2,4-dihydro-3*H*-pyrazol-3-one (2a)

The intermediate product described in the synthesis of **3a** was filtered off with suction, washed with some cold light petroleum and dried to afford 545 mg (96%) of **2a** as a dark red solid of mp 135−138 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.90 (m, 2H, Ph H-2,6), 7.41 (m, 2H, Ph H-3,5), 7.22 (m, 1H, Ph H-4), 4.10 (s, 3H, OMe), 2.84 (s, 3H, CMe); ^{13}C-NMR ($CDCl_3$): δ (ppm) 179.8 (=C-O, ^2J(=C-O,CMe) = 6.2 Hz, ^3J(=C-O,OMe) = 4.2 Hz), 164.6 (C-3), 138.0 (Ph C-1), 137.6 (C-5, ^2J(C5,CF_3) = 39.1 Hz), 128.8 (Ph C-3,5), 125.7 (Ph C-4), 120.0 (Ph C-2,6), 120.0 (CF_3, ^1J = 269.7 Hz), 103.8 (C-4), 56.9 (OCH_3, ^1J = 148.2 Hz), 14.0 (CH_3, ^1J = 130.6 Hz); MS (m/z, %): 285 (M^++1, 15), 284 (M^+, 92), 270 (21), 255 (25), 253 (61), 252 (70), 251 (54), 105 (20), 77 (100). HRMS: Calcd for $C_{13}H_{11}N_2O_2F_3$: 284.0773. Found: 284.0779.

(4*E*)-4-(1-Ethoxypropylidene)-2-phenyl-5-trifluoromethyl-2,4-dihydro-3*H*-pyrazol-3-one (2b)

The intermediate product described in the synthesis of **3b** was filtered off with suction and was then recrystallized from light petroleum to afford 437 mg (70%) of **2b** as a yellow solid of mp 125 °C (light petroleum). ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.92 (m, 2H, Ph H-2,6), 7.41 (m, 2H, Ph H-3,5), 7.21 (m, 1H, Ph H-4), 4.45 (q, J = 7.1 Hz, 2H, OCH_2), 3.27 (q, J = 7.6 Hz, 2H, CCH_2), 1.49 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.33 (t, J = 7.6 Hz, 3H, CCH_2CH_3); ^{13}C-NMR ($CDCl_3$): δ (ppm) 184.1 (=C-O), 164.2 (C-3), 138.1 (Ph C-1), 137.9 (C-5, ^2J(C5,CF_3) = 38.5 Hz), 128.7 (Ph C-3,5), 125.5 (Ph C-4), 120.1 (CF_3, ^1J = 269.7 Hz), 119.9 (Ph C-2,6), 102.8 (C-4), 65.9 (OCH_2, ^1J = 147.4 Hz, ^2J(OCH_2,CH_3) = 4.4 Hz), 21.0 (CCH_2, ^1J = 132.2 Hz, ^2J(CCH_2,CH_3) = 4.2 Hz), 14.3 (OCH_2CH_3, ^1J = 128.3 Hz, ^2J(CH_3,OCH_2) = 3.0 Hz), 11.2 (CCH_2CH_3, ^1J = 130.3 Hz, ^2J(CH_3,CH_2) = 5.8 Hz); IR (KBr): ν (cm^{-1}) 1684 (C=O); MS (m/z, %): 312 (M^+, 2), 284 (60), 255 (100), 235 (50), 77 (50), 51 (24). HRMS: Calcd for $C_{15}H_{15}N_2O_2F_3$: 312.1086. Found: 312.1076.

(4*E*)-4-[Ethoxy(phenyl)methylene]-2-phenyl-5-trifluoromethyl-2,4-dihydro-3*H*-pyrazol-3-one (2c)

The intermediate product described in the synthesis of **3c** was filtered off with suction, washed with some cold light petroleum and dried to afford 332 mg (46%) of **2c** as a yellow solid of mp 110−112 °C. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.83 (m, 2H, NPh H-2,6), 7.60 (m, 1H, CPh H-4), 7.58 (m, 2H, CPh H-3,5), 7.46 (m, 2H, CPh H-2,6), 7.34 (m, 2H, NPh H-3,5), 7.16 (m, 1H, NPh H-4), 4.11 (q, J = 7.1 Hz, 2H, OCH_2), 1.38 (t, J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C-NMR ($CDCl_3$): δ (ppm) 176.2 (=C-O), 163.3 (C-3), 138.0 (NPh C-1), 138.0 (C-5, ^2J(C5,CF_3) = 39.4 Hz), 131.8 (CPh C-4), 129.1 (CPh C-1), 129.0 (CPh C-3,5), 128.6 (NPh C-3,5), 128.3 (CPh C-2,6), 125.4 (NPh C-4), 120.1 (CF_3, ^1J = 269.8 Hz), 119.7 (NPh C-2,6), 104.5 (C-4), 68.9 (OCH_2), 14.5 (CH_3); IR (KBr): ν (cm^{-1}) 1693 (C=O); MS (m/z, %): 360 (M^+, 57), 254 (53), 105 (100), 77 (42), 51 (31). HRMS: Calcd for $C_{19}H_{15}N_2O_2F_3$: 360.1086. Found: 360.1078.

1-[5-Hydroxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-4-yl]ethanone (3a)

A mixture of **1** (456 mg, 2 mmol) and trimethyl orthoacetate (288 mg, 2.4 mmol) was heated to 110 °C for 15 min. The obtained solid (**2a**) was dissolved in boiling 96% EtOH (20 mL), the volume of the solution was reduced to 2 mL under reduced pressure, 2 drops of 6N HCl were added and the mixture was heated to reflux for 3 h. After cooling, red crystals were obtained which were filtered off, washed with some drops of cold EtOH, and dried. Yield: 276 mg (51%), mp 87 °C (EtOH). ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.50 (br s, 1H, OH), 7.82 (m, 2H, Ph H-2,6), 7.49 (m, 2H, Ph H-3,5), 7.38 (m, 1H, Ph H-4), 2.57 (q, $J(CH_3,CF_3)$ = 1.0 Hz, 3H, Me); ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.57 (br s, 1H, OH), 7.72 (m, 2H, Ph H-2,6), 7.50 (m, 2H, Ph H-3,5), 7.38 (m, 1H, Ph H-4), 2.45 (s, 3H, Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 195.9 (C=O, ^{2}J(C=O,CH_3) = 6.2 Hz), 160.2 (C-5), 138.8 (C-3, ^{2}J(C3,CF_3) = 38.5 Hz), 136.4 (Ph C-1), 129.3 (Ph C-3,5), 128.0 (Ph C-4), 121.5 (Ph C-2,6), 120.4 (CF_3, ^{1}J = 269.7 Hz), 101.0 (C-4), 27.6 (CH_3, ^{1}J = 128.9 Hz, $J(\underline{C}H_3,C\underline{F}_3)$ = 3.3 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 189.1 (C=O, ^{2}J(C=O,CH_3) = 6.1 Hz), 157.8 (C-5), 138.4 (C-3, ^{2}J(C3,CF_3) = 37.4 Hz), 137.3 (Ph C-1), 129.1 (Ph C-3,5), 127.4 (Ph C-4), 122.6 (Ph C-2,6), 120.8 (CF_3, ^{1}J = 269.2 Hz), 103.6 (C-4), 27.5 (CH_3, ^{1}J = 128.0 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) − (N-2), − (N-1); ^{15}N-NMR (DMSO-d_6): δ (ppm) −95.1 (N-2), −180.8 (N-1); IR (KBr): ν (cm^{-1}) 1630 (C=O); MS (m/z, %): 271 (M^++1, 21), 270 (M^+, 100), 255 (63), 250 (26), 235 (57), 105 (22), 77 (96), 65 (33), 51 (57), 43 (84). *Anal*. Calcd for $C_{12}H_9N_2O_2F_3$: C, 53.34; H, 3.36; N 10.37. Found: C, 53.33; H, 3.23; N, 10.32.

1-[5-Hydroxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-4-yl]propan-1-one (3b)

A mixture of **1** (456 mg, 2 mmol) and triethyl orthopropionate (423 mg, 2.4 mmol) was heated to 140 °C for 1 h. Then the obtained solid (**2b**) was taken up in 96% EtOH (1 mL) containing 1 drop of 6N HCl and the mixture was heated to reflux for 3 h. After cooling, orange crystals were obtained which were filtered off, washed with some drops of cold EtOH, and dried. Yield: 392 mg (69%), mp 95−96 °C (EtOH). ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.70 (br s, 1H, OH), 7.82 (m, 2H, Ph H-2,6), 7.50 (m, 2H, Ph H-3,5), 7.38 (m, 1H, Ph H-4), 2.93 (q, J = 7.2 Hz, 2H, CH_2), 1.24 (t, J = 7.2 Hz, 3H, CH_3); ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.64 (br s, 1H, OH), 7.69 (m, 2H, Ph H-2,6), 7.51 (m, 2H, Ph H-3,5), 7.40 (m, 1H, Ph H-4), 2.84 (q, J = 7.2 Hz, 2H, CH_2), 1.04 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C-NMR ($CDCl_3$): δ (ppm) 199.4 (C=O), 160.0 (C-5), 138.5 (C-3, ^{2}J(C3,CF_3) = 38.5 Hz), 136.4 (Ph C-1), 129.3 (Ph C-3,5), 128.0 (Ph C-4), 121.5 (Ph C-2,6), 120.5 (CF_3, ^{1}J = 269.7 Hz), 100.4 (C-4), 33.0 (CH_2, ^{1}J = 126.9 Hz, $^{2}J(\underline{C}H_2,C\underline{H}_3)$ = 4.4 Hz, $J(\underline{C}H_2,C\underline{F}_3)$ = 3.2 Hz), 7.6 (CH_3, ^{1}J = 128.6 Hz, $^{2}J(\underline{C}H_3,C\underline{H}_2)$ = 4.6 Hz); ^{13}C-NMR (DMSO-d_6): δ (ppm) 193.0 (C=O), 156.5 (C-5), 138.7 (C-3, ^{2}J(C3,CF_3) = 37.4 Hz), 137.1 (Ph C-1), 129.2 (Ph C-3,5), 127.8 (Ph C-4), 123.1 (Ph C-2,6), 120.9 (CF_3, ^{1}J = 269.3 Hz), 103.7 (C-4), 33.1 (CH_2, ^{1}J = 126.4 Hz,

$^2J(\underline{C}H_2,C\underline{H}_3)$ = 3.7 Hz), 8.0 (CH_3, ^1J = 127.5 Hz, $^2J(\underline{C}H_3,C\underline{H}_2)$ = 4.4 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) − (N-2), − (N-1); ^{15}N-NMR (DMSO-d_6): δ (ppm) −95.7 (N-2), −180.1 (N-1); IR (KBr): ν (cm^{-1}) 1639 (C=O); MS (m/z, %): 285 (M^++1, 20), 284 (M^+, 100), 255 (97), 235 (87), 93 (21), 91 (21), 77 (87), 57 (36), 51 (49). *Anal*. Calcd for $C_{13}H_{11}N_2O_2F_3$: C, 54.93; H, 3.90; N 9.86. Found: C, 55.22; H, 3.71; N, 9.77.

1-[5-Hydroxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-4-yl](phenyl)methanone (3c)

Following the procedure given for the preparation of **3b**, from **1** (456 mg, 2 mmol) and triethyl orthobenzoate (538 mg, 2.4 mmol) were obtained 273 mg (41%) of **3c** as orange crystals of mp 61−65 °C (EtOH). ^{1}H-NMR ($CDCl_3$): δ (ppm) 12.50 (br s, 1H, OH), 7.87 (m, 2H, NPh H-2,6), 7.67 (m, 2H, CPh H-2,6), 7.61 (m, 1H, CPh H-4), 7.53 (m, 2H, NPh H-3,5), 7.50 (m, 2H, CPh H-3,5), 7.41 (m, 1H, NPh H-4); ^{1}H-NMR (DMSO-d_6): δ (ppm); 7.85 (m, 2H, CPh H-2,6), 7.75 (m, 2H, NPh H-2,6), 7.63 (m, 1H, CPh H-4), 7.54 (m, 2H, NPh H-3,5), 7.51 (m, 2H, CPh H-3,5), 7.42 (m, 1H, NPh H-4), 6.91 (br s, 1H, OH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 193.7 (C=O), 160.4 (C-5), 139.4 (C-3, ^2J(C3,CF_3) = 38.4 Hz), 137.9 (CPh C-1), 136.4 (NPh C-1), 132.4 (CPh C-4), 129.4 (NPh C-3,5), 128.2 (CPh C-3,5), 128.1 (NPh C-4), 127.6 (CPh C-2,6, $J(\underline{C}2/6,C\underline{F}_3)$ = 1.5 Hz), 121.7 (NPh C-2,6), 120.0 (CF_3, ^1J = 270.8 Hz), 100.6 (C-4); ^{13}C-NMR (DMSO-d_6): δ (ppm) = 187.3 (C=O), 153.7 (C-5), 139.4 (C-3, ^2J(C3,CF_3) = 37.2 Hz), 137.7 (CPh C-1), 137.2 (NPh C-1), 132.9 (CPh C-4), 129.3 (CPh C-2,6), 129.1 (NPh C-3,5), 128.4 (CPh C-3,5), 127.7 (NPh C-4), 123.1 (NPh C-2,6), 120.8 (CF_3, ^1J = 269.6 Hz), 102.6 (C-4); ^{15}N-NMR (DMSO-d_6): δ (ppm) −97.7 (N-2), −180.2 (N-1); IR (KBr): ν (cm^{-1}) 1628 (C=O); MS (m/z, %): 333 (M^++1, 8), 332 (M^+, 47), 312 (13), 254 (30), 105 (100), 77 (74), 51 (24). *Anal*. Calcd for $C_{17}H_{11}N_2O_2F_3$: C, 61.45; H, 3.34; N 8.43. Found: C, 61.54; H, 3.37; N, 8.36.

5-Ethoxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazole (4)

To a mixture of **1** (228 mg, 1 mmol), PPh_3 (393 mg, 1.5 mmol), and abs EtOH (63 mg, 1.3 mmol) in anhyd THF (20 mL) was added dropwise diethyl azodicarboxylate (261 mg, 1.5 mmol). After the addition was complete the mixture was refluxed for 20 h and then poured onto H_2O (20 mL). After extraction with CH_2Cl_2 (5 × 10 mL) the combined organic phases were washed with 2N NaOH (10 mL) and then H_2O (5 × 15 mL) and brine (10 mL). After drying (Na_2SO_4), the solvents were evaporated and the residue was subjected to column chromatography (silica gel, CH_2Cl_2) to afford 97 mg (38 %) of a colorless oil.

^{1}H-NMR ($CDCl_3$): δ (ppm) 7.71 (m, 2H, Ph H-2,6), 7.45 (m, 2H, Ph H-3,5), 7.33 (m, 1H, Ph H-4), 5.92 (s, 1H, H-4), 4.21 (q, J = 7.1 Hz, 2H, OCH_2), 1.47 (t, J = 7.1 Hz, 3H, Me); ^{13}C-NMR ($CDCl_3$): δ (ppm) 154.7 (C-5, ^2J(C5,H4) = 5.3 Hz, ^3J(C5, OCH_2) = 3.1 Hz), 141.8 (C-3, ^2J(C3,CF_3) = 38.3 Hz, ^2J(C3,H4) = 2.9 Hz), 137.9 (Ph C-1), 128.9 (Ph C-3,5), 127.3 (Ph C-4), 122.7 (Ph C-2,6), 121.1 (CF_3, ^1J = 269.0 Hz),

84.6 (C-4, ^1J = 181.4 Hz, ^3J(C4,CF_3) = 2.1 Hz), 68.6 (OCH_2, ^1J = 146.2 Hz, ^2J(O<u>C</u>H_2,C<u>H</u>$_3$) = 4.5 Hz), 14.5 (CH_3, ^1J = 127.5 Hz, ^2J(<u>C</u>H_3,OC<u>H</u>$_2$) = 2.8 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −100.0 (N-2), −183.0 (N-1); MS (m/z, %): 257 (M^++1, 21), 256 (M^+, 76), 228 (96), 159 (25), 131 (21), 105 (23), 77 (100), 51 (77). *Anal*. Calcd for $C_{12}H_{11}N_2OF_3$: C, 56.25; H, 4.33; N 10.93. Found: C, 56.49; H, 4.63; N, 10.88.

(4*Z*)-4-{[5-Hydroxy-1-phenyl-3-trifluoromethyl-1*H*-pyrazol-4-yl]methylene}-2-phenyl-5-trifluoromethyl-2,4-dihydro-3*H*-pyrazol-3-one (5)

A mixture of **1** (456 mg, 2 mmol) and triethyl orthoformate (356 mg, 2.4 mmol) was heated to 140 °C for 1 h. Then the crude solid reaction product was recrystallized from diisopropyl ether to afford 378 mg (81% regarding **1**) of yellow needles, mp 222 °C (diisopropyl ether). ^{1}H-NMR ($CDCl_3$): δ (ppm) 17.42 (s, sharp, 1H, OH), 7.91 (s, 1H, =CH-C), 7.87 (m, 4H, Ph H-2,6), 7.50 (m, 4H, Ph H-3,5), 7.38 (m, 2H, Ph H-4); ^{13}C-NMR ($CDCl_3$): δ (ppm) 161.4 (C-5, ^3J(C5,=CH-C) = 10.0 Hz), 143.6 (C-3, ^2J(C3,CF_3) = 37.5 Hz, ^3J(C3,=CH-C) = 5.5 Hz), 139.3 (=CH-C, ^1J = 154.9 Hz, J(=CH-C,CF_3) = 1.9 Hz, septet-splitting), 136.6 (Ph C-1), 129.2 (Ph C-3,5), 128.0 (Ph C-4), 121.7 (Ph C-2,6), 119.9 (CF_3, ^1J = 271.6 Hz), 107.1 (C-4, ^2J(C4,=CH-C) = 2.3 Hz); IR (KBr): ν (cm^{-1}) 1616; MS (m/z, %): 467 (M^++1, 9), 466 (M^+, 37), 228 (100), 105 (45), 91 (23), 77 (78), 51 (19). *Anal*. Calcd for $C_{21}H_{12}N_4O_2F_6$: C, 54.09; H, 2.59; N 12.01. Found: C, 54.15; H, 2.73; N, 12.04.

5-Ethoxy-3-methyl-1-phenyl-1*H*-pyrazole (6)[21]

^{1}H-NMR ($CDCl_3$): δ (ppm) 7.72 (m, 2H, Ph H-2,6), 7.39 (m, 2H, Ph H-3,5), 7.21 (m, 1H, Ph H-4), 5.47 (s, 1H, H-4), 4.11 (q, J = 7.0 Hz, 2H, OCH_2), 2.28 (s, 3H, 3-Me), 1.42 (t, J = 7.0 Hz, 3H, CH_2<u>Me</u>); ^{13}C-NMR ($CDCl_3$): δ (ppm) 154.7 (C-5, ^2J(C5,H4) = 6.0 Hz, ^3J(C5, OCH_2) = 2.8 Hz), 148.6 (C-3, ^2J(C3,CH_3) = 6.7 Hz, ^2J(C3,H4) = 3.7 Hz), 138.8 (Ph C-1), 128.6 (Ph C-3,5), 125.5 (Ph C-4), 121.6 (Ph C-2,6), 86.2 (C-4, ^1J = 175.8 Hz, ^3J(C4,3-CH_3) = 3.4 Hz), 67.7 (OCH_2, ^1J = 145.7 Hz, ^2J(O<u>C</u>H_2,C<u>H</u>$_3$) = 4.5 Hz), 14.5 (CH_3, ^1J = 127.2 Hz, ^2J(<u>C</u>H_3,OC<u>H</u>$_2$) = 2.8 Hz), 14.4 (3-CH_3, ^1J = 127.3 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −105.2 (N-2), −189.8 (N-1).

(4*E*)-4-(1-Ethoxypropylidene)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (7)

A mixture of 3-methyl-1-phenyl-2-pyrazolin-5-one (1.742 g, 10 mmol) and triethyl orthopropionate (1.763 g, 10 mmol) was heated to 140 °C for 30 min. After cooling to rt, a solid was obtained which was recrystallized from cyclohexane (addition of charcoal) to afford 1.990 g (77%) of orange-yellow crystals, mp 115−117 °C (lit.,[6] mp 120 °C); ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.95 (m, 2H, Ph H-2,6), 7.35 (m, 2H, Ph H-3,5), 7.11 (m, 1H, Ph H-4), 4.31 (q, J = 7.1 Hz, 2H, OCH_2), 3.19 (q, J = 7.5 Hz, 2H, CC<u>H</u>$_2$Me), 2.33 (s, 3H, 5-Me), 1.43 (t, J = 7.1 Hz, 3H, OCH_2<u>Me</u>), 1.26 (t, J = 7.5 Hz, CCH_2<u>Me</u>); ^{13}C-NMR ($CDCl_3$): δ (ppm)

181.8 (=C-OCH_2), 165.1 (C-3), 148.6 (C-5, ^2J(C5,5-Me) = 7.5 Hz), 139.0 (Ph C-1), 128.5 (Ph C-3,5), 124.1 (Ph C-4), 119.0 (Ph C-2,6), 107.6 (C-4, ^3J(C4,5-Me) = 2.5 Hz, ^3J(C4,CH_2) = 2.5 Hz), 64.6 (OCH_2, ^1J = 146.8 Hz, ^2J(OCH_2,CH_3) = 4.4 Hz), 20.5 (CCH_2, ^1J = 131.5 Hz, ^2J(CCH_2,CH_3) = 4.2 Hz), 17.8 (5-Me, ^1J = 129.0 Hz), 14.8 (OCH_2CH_3, ^1J = 127.7 Hz, ^2J(CH_3,OCH_2) = 2.9 Hz), 11.6 (CCH_2CH_3, ^1J = 126.7 Hz, ^2J(CH_3,CH_2) = 5.7 Hz); ^{15}N-NMR ($CDCl_3$): δ (ppm) −87.8 (N-1), −189.8 (N-2); IR (KBr): ν (cm^{-1}) 1672 (C=O); MS (m/z, %): 258 (M^+, 3), 230 (29), 201 (100), 77 (22), 51 (12). *Anal*. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.47; H, 7.02; N, 10.89.

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