Preparative synthesis of 3-cyano-4-difluoromethyl- and 3-cyano-4-trifluoromethyl-2(1*H*)-pyridones

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An efficient procedure for the synthesis of 3-cyano-4-difluoromethyl- and 3-cyano-4-trifluoromethyl-2(1*H*)-pyridones was developed. The structure of one of the resulting compounds was established by X-ray diffraction analysis.

Key words: 1,3-diketones, 2-polyfluoroacylcycloalkanones, 2-cyanoacetamide, 3-cyano-2(1*H*)-pyridones.

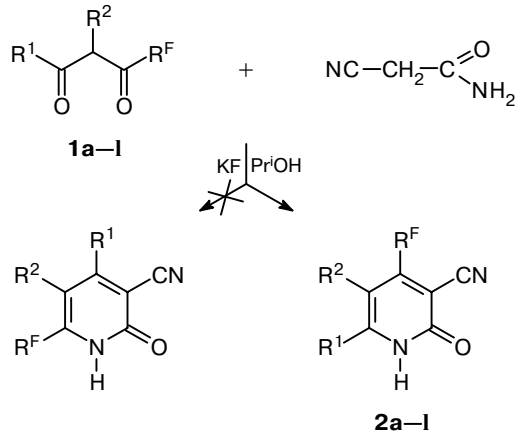
3-Cyano-2-pyridones are polyfunctional heterocycles, which are of interest in themselves because they exhibit a broad spectrum of biological activities[1] and can serve as a potential basis for the synthesis of more complex fused heterocyclic systems.[1—5] The best studied and preparatively the simplest procedure for the synthesis of 3-cyano-2-pyridones involves the reactions of malonodinitrile or 2-cyanoacetamide with 1,3-dicarbonyl compounds in the presence of bases.[6—8] Positional isomers, which differ by substituents at positions 4 and 6 of the heterocycle, can be formed if the substrate has a non-symmetrical structure. However, the data published previously[6,7] are indicative of a rather high degree of regioselectivity of these reactions. Thus, the reactions of a large number of 2-acylcycloalkanones with 2-cyanoacetamide afford only one isomer. The exception is 2-acetylcyclopentanone for which a mixture of isomeric pyridones was observed.

Reactions of non-symmetrical polyfluorinated 1,3-diketones with 2-cyanoacetamide are poorly studied. A series of β-dicarbonyl compounds involved in this reaction in the presence of sodium methoxide is limited by trifluoromethyl derivatives.[9—11] However, no evidence for the arrangement of the substituents in the pyridine ring was reported.

The present study was aimed at developing an efficient procedure for condensation of non-symmetrical polyfluorinated 1,3-diketones (**1**) with 2-cyanoacetamide.

In the search for the optimum reaction conditions, we used 2-trifluoroacetylcyclohexanone **1j** as a model substrate. The reactions in MeOH in the presence of MeONa or Et_3N as well as in water in the presence of K_2CO_3 afforded 3-cyanoquinolone (**2j**) in very low yields (10, 6, and 3%, respectively). We succeeded in increasing the yield to 71% by performing the reaction in propan-2-ol in the presence of freshly calcinted KF. Under these conditions, the reactions of 1,3-diketones **1a—i** with 2-cyanoacetamide gave rise to compounds **2a—i** in 64—92% yields (Scheme 1). The physicochemical characteristics and the spectral data for the resulting pyridones **2** are given in Tables 1 and 2, respectively.

Scheme 1



R^F = CF_2H (**a—d**), CF_3 (**e—j**), $(CF_2)_2H$ (**k**), $(CF_2)_4H$ (**l**);
R^1 = Ph (**a**), 4-FC_6H_4 (**b**), 4-BrC_6H_4 (**c, g**), 4-MeC_6H_4 (**d, f**), 2-thienyl (**e**), 4-ClC_6H_4 (**h**);
R^2 = H (**a—h**); $R^1 + R^2 = (CH_2)_3$ (**i**), $(CH_2)_4$ (**j—l**)

It appeared that the above-described procedure is applicable to the preparative synthesis of only 3-cyano-2-pyridones containing short polyfluoroalkyl substituents (CF_2H or CF_3). Tetrafluoroethyl- and octafluorobutyl-containing pyridones **2k** and **2l** were obtained in 20 and 4% yields, respectively. In the reactions of linear 1,3-diketones, the target heterocycles are formed only if $R^F = CF_2H$ or CF_3 and R^1 = Ar. For $R^F = (CF_2)_2H$ and

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Table 1. Data from elemental analysis and yields of 3-cyano-4-polyfluoroalkyl-2(1*H*)-pyridones **2a—l** synthesized

Compound	R^F	R^1	R^2	Molecular formula	Found / Calculated (%)				Yield (%)
					C	H	F	N	
3-Cyano-4-difluoromethyl-6-phenyl-2(1*H*)-pyridone (**2a**)	HCF_2	Ph	H	$C_{13}H_8F_2N_2O$	62.66 63.42	3.16 3.27	15.48 15.43	11.21 11.38	83
3-Cyano-4-difluoromethyl-6-(4-fluorophenyl)-2(1*H*)-pyridone (**2b**)	HCF_2	4-FC_6H_4	H	$C_{13}H_7F_3N_2O$	58.80 59.09	2.59 2.67	21.91 21.57	10.56 10.60	89
6-(4-Bromophenyl)-3-cyano-4-difluoromethyl-2(1*H*)-pyridone (**2c**)	HCF_2	4-BrC_6H_4	H	$C_{13}H_7BrF_2N_2O$	48.17 48.03	2.09 2.17	11.35 11.69	8.68 8.62	92
3-Cyano-4-difluoromethyl-6-(4-tolyl)-2(1*H*)-pyridone (**2d**)	HCF_2	4-MeC_6H_4	H	$C_{14}H_{10}F_2N_2O$	64.65 64.61	3.88 3.87	14.92 14.60	10.76 10.76	87
3-Cyano-4-difluoromethyl-6-(2-thienyl)-2(1*H*)-pyridone (**2e**)	CF_3	2-Thienyl	H	$C_{11}H_5F_3N_2OS$	48.72 48.89	1.93 1.86	21.26 21.09	10.12 10.37	81
3-Cyano-6-(4-tolyl)-4-trifluoromethyl-2(1*H*)-pyridone (**2f**)	CF_3	4-MeC_6H_4	H	$C_{14}H_9F_3N_2O$	60.56 60.45	3.27 3.26	20.78 20.49	10.05 10.07	85
6-(4-Bromophenyl)-3-cyano-4-trifluoromethyl-2(1*H*)-pyridone (**2g**)	CF_3	4-BrC_6H_4	H	$C_{13}H_6BrF_3N_2O$	45.82 45.51	1.73 1.76	16.48 16.61	8.23 8.16	79
6-(4-Chlorophenyl)-3-cyano-4-trifluoromethyl-2(1*H*)-pyridone (**2h**)	CF_3	4-ClC_6H_4	H	$C_{13}H_6ClF_3N_2O$	52.36 52.28	2.14 2.02	19.27 19.08	9.16 9.38	85
3-Cyano-4-trifluoromethyl-6,7-dihydro-2(1,5*H*)-cyclopenta[*e*]pyridone (**2i**)	CF_3	$(CH_2)_3$		$C_{10}H_7F_3N_2O$	52.68 52.64	2.95 3.09	25.12 24.98	12.02 12.28	64
3-Cyano-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**2j**)	CF_3	$(CH_2)_4$		$C_{11}H_9F_3N_2O$	54.31 54.55	3.84 3.75	23.41 23.53	11.70 11.57	71
3-Cyano-4-(1,1,2,2-tetrafluoroethyl)-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**2k**)	$H(CF_2)_2$	$(CH_2)_4$		$C_{12}H_{10}F_4N_2O$	52.77 52.56	3.76 3.68	27.72 27.71	10.25 10.22	20
3-Cyano-4-(1,1,2,2,3,3,4,4-octafluorobutyl)-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**2l**)	$H(CF_2)_4$	$(CH_2)_4$		$C_{14}H_{10}F_8N_2O$	44.81 44.93	2.74 2.69	40.42 40.61	7.53 7.49	4

Table 2. Spectral characteristics of 3-cyano-4-fluoroalkyl-2(1*H*)-pyridones **2a—l**

Compound	IR, ν/cm^{-1}		^{1}H NMR (DMSO-d$_6$, δ, *J*/Hz)			
	N—H	C=O	HCF_2 (1 H)	R^1	R^2	NH (br.s, 1 H)
2a	2310	1650	7.16 (t, $^2J_{H,F}$ = 53.5)	7.51—7.96 (m, 5 H, Ph)	7.03	13.0
2b	2215	1660	7.13 (t, $^2J_{H,F}$ = 53.5)	7.25—8.06 (m, 4 H, C_6H_4)	7.06	13.2
2c	2220	1655	6.78 (t, $^2J_{H,F}$ = 53.9)	7.55—7.61 (m, 4 H, C_6H_4)	6.76	13.2
2d	2220	1640	7.14 (t, $^2J_{H,F}$ = 53.5)	2.38 (s, 3 H, Me); 7.29—7.85 (m, 4 H, C_6H_4)	6.99	13.2
2e	—	—	—	7.21—8.22 (m, 3 H, C_4H_3S)	7.64	13.3
2f	2220	1650	—	2.38 (s, 3 H, Me); 7.30—7.93 (m, 4 H, C_6H_4)	7.19	13.4
2g	2260	1680	—	7.22—8.01 (m, 4 H, C_6H_4)	7.08	13.2
2h	2220	1645	—	7.57—8.09 (m, 4 H, C_6H_4)	7.39	13.2
2i	2220	1655	—	1.98—2.17 (m, 2 H, CH_2); 2.75—3.00 (m, 4 H, 2 CH_2)		Not detected
2j	2220	1650	—	1.68 (m, 4 H, 2 CH_2); 2.50, 2.67 (both m, 4 H, 2 CH_2)		13.1
2k	2220	1645	7.16 (tt, $^2J_{H,F}$ = 51.4, $^3J_{H,F}$ = 4.7)	1.66—1.70 (m, 4 H, 2 CH_2); 2.15—2.69 (m, 4 H, 2 CH_2)		9.2
2l	2220	1640	7.15 (tt, $^2J_{H,F}$ = 50.3, $^3J_{H,F}$ = 5.5)	1.98—2.17 (m, 2 H, CH_2); 2.75—3.00 (m, 4 H, 2 CH_2)		13.2

R^1 = Ph, R^F = $(CF_2)_2H$ and R^1 = Bu^t, R^F = C_3H_7 and R^1 = Ph, or R^F = CF_2H and R^1 = Me, no 2-pyridones were obtained even in trace amounts.

The ^{19}F NMR spectrum of compound **2i** has two signals, which apparently correspond to the tautomeric keto and hydroxy forms existing in the equilibrium (or to two regioisomers). However, the ratio between the integral intensities of these signals (49 : 1) as well as the presence of only one set of signals in the ^{1}H and ^{13}C NMR spectra of all the synthesized compounds is indicative of the substantial predominance of one tautomeric form. The IR spectra have a band at 1640—1680 cm^{-1} assigned[9] to absorption of the C=O group along with the band at 2215—2310 cm^{-1} attrib-

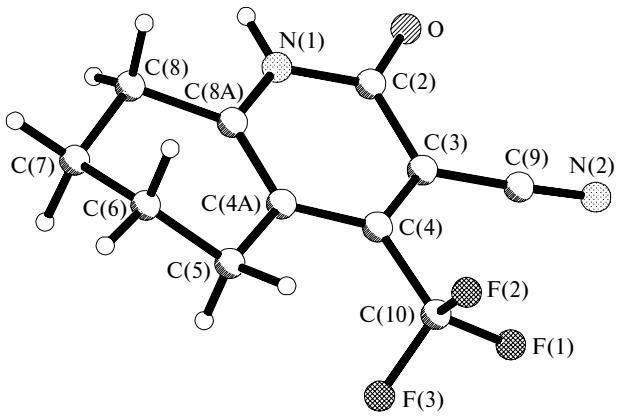

Fig. 1. Overall view of molecule **2j**.

uted to vibration of the nitrile fragment. This fact provides clear evidence that compound **2** has the 2-pyridone structure rather than the 2-hydroxypyridine structure.

The position of the trifluoromethyl substituent in the pyridone ring of compound **2j** was established by X-ray diffraction analysis. The overall view of the molecule is shown in Fig. 1. The six-membered heterocycle is virtually planar (the mean deviation of the atoms from the plane of the ring is 0.007(2) Å). The six-membered carbocycle adopts a half-chair conformation. The C(6) and C(7) atoms deviate from the plane passing through the C(5), C(4a), C(8a), and C(8) atoms (planar to within 0.003(1) Å) by +0.443(5) and −0.294(5) Å, respectively. The atoms of the six-membered heterocycle and the planar portion of the carbocycle are coplanar (the mean deviation of the atoms from the plane is 0.009(2) Å).

In the crystal, the molecules are linked in centrosymmetrical dimers, which are packed in stacks along the axis *a* through the intermolecular N(1)—H(1N)...O hydrogen bonds (N(1)—H(1N), 0.85(3) Å; N(1)...O, 2.770(2) Å; H(1N)...O, 1.92(3) Å; the N1—H(1N)...O angle is 176(3)°).

The ^{13}C NMR spectra of compound **2j** whose structure was established by X-ray diffraction analysis and of compounds **2f,i** have the same characteristic features. The chemical shifts of the C atom bound to the CF_3 group are 144.0, 144.9, and 142.6 in **2j** and **2f,i**, respectively, which indicates that this C atom is in the same environment in all three compounds. In other words, pyridones **2f,i,j** are the products of the attachment of the active methylene group of the binucleophile at the carbonyl group bound to the trifluoromethyl substituent. Taking into account that the IR and ^1H NMR spectra of pyridones **2a—h** which do not contain the carbocycle are similar with those of bicyclic compounds **2i—l**, it can be said with assurance that both series of compounds have the 4-R^F structure.

To summarize, we developed an efficient procedure for the preparation of 4-R^F-3-cyano-2-pyridones containing short fluoroalkyl substituents by the reactions of 1,3-diketones with 2-cyanoacetamide in the presence of KF.

Experimental

The IR spectra were recorded on a Specord 75 IR spectrophotometer in Nujol mulls. The ^1H, ^{13}C, and ^{19}F NMR spectra were measured on a Tesla BS-587A spectrometer (80, 20.1, and 75.3 MHz, respectively) with Me_4Si and C_6F_6 as the internal standards. The starting 1,3-diketones **1** were synthesized by condensation of ketones with esters of polyfluoroalkanoic acids in benzene in the presence of LiH.[12]

3-Cyano-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone (2j). ***A.*** 2-Cyanoacetamide (1.65 g, 0.02 mol) was added portionwise to a solution of NaOMe, which was prepared from Na (0.51 g, 0.022 g-at.) in anhydrous MeOH (40 mL), for 10 min. The reaction solution was refluxed with stirring for 1 h. Then a solution of diketone **1j** (3.8 g, 0.02 mol) in anhydrous MeOH (15 mL) was added dropwise for 30 min. The reaction mixture was refluxed for 20 h, poured into water (200 mL), neutralized with 15% HCl (~12 mL), and extracted with $CHCl_3$. The solvent was distilled off from the combined extracts and the residue was recrystallized from Bu^nOH. Quinolone **2j** was obtained as colorless crystals in a yield of 0.5 g (10%).

B. 2-Cyanoacetamide (0.6 g, 7 mmol) was added to a solution of K_2CO_3 (0.98 g, 7 mmol) in water (30 mL). The reaction mixture was heated at 70 °C for 30 min, a solution of diketone **1j** (1.39 g, 0.007 mmol) in EtOH (10 mL) was added dropwise for 30 min, and the mixture was refluxed for 20 h. Compound **2j** was obtained in a yield of 0.05 g (3%).

C. Triethylamine (0.81 g, 8 mmol) was added to a solution of 2-cyanoacetamide (0.6 g, 7 mmol) in MeOH (30 mL) and the mixture was heated to boiling. Then a solution of compound **1j** (1.39 g, 7 mmol) in MeOH (15 mL) was added dropwise for 30 min and the reaction mixture was refluxed for 20 h. Compound **2j** was obtained in a yield of 0.1 g (6%).

D. A mixture of compound **1j** (1.44 g, 7 mmol), 2-cyanoacetamide (1.0 g, 11.9 mmol), and freshly calcined and finely dispersed KF (0.2 g, 3.4 mmol) in propan-2-ol (30 mL) was refluxed for 15 h. Then the reaction mixture was poured into water (150 mL) and the precipitate that formed was filtered off and recrystallized from Bu^nOH. Compound **2j** was obtained in a yield of 1.3 g (71%).

^{13}C NMR of compound **2j** (DMSO-d_6), δ: 19.8 and 21.2 (both s, CH_2); 23.1 (q, CH_2, $^4J_{C-F}$ = 3.6 Hz); 27.8 (s, CH_2); 98.1—99.0 (m, C(3)); 110.6 (s, CN); 113.4 (s, C(5)); 121.6 (q, CF_3, $^1J_{C-F}$ = 278.8 Hz); 144.0 (q, C(4), $^2J_{C-F}$ = 29.8 Hz); 154.0 (s, C(6)); 159.1 (s, C(2)).

Crystals of compound **2j** belong to the monoclinic system. At 20 °C, a = 7.392(2) Å, b = 9.906(2) Å, c = 14.560(3) Å, β = 91.54(2)°, V = 1065.8(4) Å^3, d_{calc} = 1.509 g cm^{-3}, the absorption coefficient μ = 0.134 mm^{-1}, space group $P2_1/n$, Z = 4. The intensities of 2831 independent reflections (R_{int} = 0.06) were measured on a four-circle automated Siemens P3/PC diffractometer (Mo-Kα radiation, λ = 0.7107 Å, graphite monochromator, θ/2θ scanning technique, $2\theta_{max}$ = 58°).

The structure was solved by the direct method using the SHELXTL PLUS 4.2 and SHELXTL PLUS 5.0 program packages.[13,14] The nonhydrogen atoms were refined by the full-matrix least-squares method (based on F_0^2) with anisotropic thermal parameters to R_1 = 0.067 using 2079 reflections with $F_0 > 2\sigma(F_0)$; wR_2 = 0.18, GOOF = 1.035. The positions of the H atoms were revealed from the difference electron density synthesis and refined isotropically. The atomic coordinates,

bond lengths, and bond angles were deposited with the Cambridge Structural Database.

Synthesis of compounds 2a—l (general procedure). A mixture of 1,3-diketone (10 mmol), 2-cyanoacetamide (15 mmol), and freshly calcined and finely dispersed KF (20 mg) in propan-2-ol (30 mL) was refluxed for 10 h. Then the reaction mixture was poured into water (100 mL). The precipitate that formed was filtered off and recrystallized from Bu^nOH. Compounds **2a—h** were obtained as yellow-green needle-like crystals.

^{13}C NMR of compound **2f** (DMSO-d_6), δ: 20.8 (s, Me); 98.0—102.7 (m, C(3)); 113.2 (s, CN); 113.7 (s, C(5)); 121.1 (q, CF_3, $^1J_{C-F}$ = 275.9 Hz); 127.7 (s, *m*-C_6H_4); 129.4 (s, *o*-C_6H_4 + *p*-C_6H_4); 142.1 (s, *i*-C_6H_4); 144.9 (q, C(4), $^2J_{C-F}$ = 32.2 Hz); 155.9 (s, C(6)); 162.0 (s, C(2)).

^{13}C NMR of compound **2i** (DMSO-d_6), δ: 22.7 (s, CH_2); 29.8 (q, CH_2, $^4J_{C-F}$ = 2.4 Hz); 32.3 (s, CH_2); 96.2 (br.s, C(3)); 114.9 (s, CN); 116.8 (br.s, C(5)); 122.5 (q, CF_3, $^1J_{C-F}$ = 277.2 Hz); 142.6 (q, C(4), $^2J_{C-F}$ = 32.5 Hz); 162.1 (s, C(6)); 163.9 (s, C(2)).

^{19}F NMR of compound **2i** (DMSO-d_6), δ: 96.4 and 100.2 (both s, CF_3).

All the synthesized compounds **2** exhibit blue fluorescence under UV light. M.p.s of compounds **2i,j,k,l** are > 190 °C (sublim.), 247—248, 261—262, and 249—251 °C, respectively. The remaining compounds **2** sublime without melting above 250 °C.

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