Haloacetylated Enol Ethers. 2 [1]. Synthesis of 5-Trifluoromethylpyrazoles

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1-Methyl-5-(trifluoromethyl)-1*H*-pyrazoles **2**, **3** and 4,5-dihydro-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol **4** were prepared by reaction of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1** and hydrazine, methylhydrazine, and phenylhydrazine, respectively, in good yields. Compound **1** proved to be a versatile building block for the regiospecific construction of pyrazole rings having an 5-trifluoromethyl substituent.

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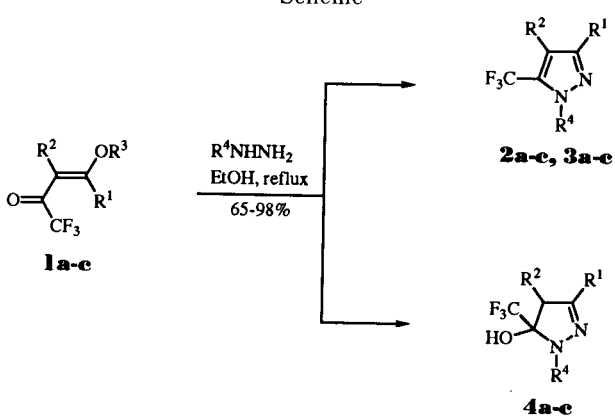
In previous work, we described the general procedure to synthesize β-acylated enol ethers [4-alkoxy-3-alken-2-ones] using functionalized acyl groups CX-CO [1]. These compounds are of general interest as precursors for a variety of halomethyl-substituted five- and six-membered heterocyclic compounds which can be synthesized by cyclocondensation with dinucleophiles [1,2]. Although the reaction of these compounds with hydrazines was mentioned elsewhere [3-4], the reactivity of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1** with hydrazines and its derivatives has not been studied systematically yet.

The synthetic access to pyrazoles is relatively well-explored using so-called [3+2] atom fragments [5]. Usually, β-diketones or derivatives thereof are used as 3-atom building blocks, and hydrazine is the 2-atom fragment. In this work, we explore the synthetic potential of 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **9** (3-atom fragment) for preparing 1-methyl-5-(trifluoromethyl)-1*H*-pyrazoles .,**3** and 4,5-dihydro-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol **4** by cyclocondensation with hydrazine, methylhydrazine and phenylhydrazine, respectively (Scheme). A systematic study using precursors with different structures was carried out to examine the scope of these cyclocondensation reactions.

Scheme



	R¹	R²	R³		R⁴
a	H	H	Et	**2**	H
b	H	Me	Et	**3**	Me
c	Me	H	Me	**4**	Ph

The cyclization of **1** with hydrazine (distilled from and stored over potassium hydroxide) and methylhydrazine in the molar relation 1:1.3 was carried out under reflux in ethanol for 2 hours to afford 1-methyl-5-(trifluoromethyl)-1*H*-pyrazoles **2,3a-c** in good yields (see Table). When phenylhydrazine was used as the nucleophile, the reaction requires 4 hours, and the 4,5-dihydro-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-5-oles **4a-c** were isolated. The sole formation of **4** from phenylhydrazine is probably due to the cross conjugation between the phenyl and imine groups which makes the aromatization of this system more difficult. The attempt to obtain 1-methyl-5-(trifluoromethyl)-1*H*-pyrazoles by dehydration of compound **4** with sulfuric acid was unsuccessful. The synthesis of 4-alkoxy-1,1,1-trifluor-3-alken-2-ones } by trihaloacetylation of enol ethers was reported in a previous paper [1]. The products were subjected to capillary gc (SE 54, 20 m glass column, on-column injection) and the pure material was characterized by nmr and microanalysis. Selected physical properties and spectral data of **2-4a-9** are presented in the Table.

EXPERIMENTAL

Synthesis of 1-Methyl-5-(trifluoromethyl)-1*H*-pyrazoles **2**, **3** and 4,5-Dihydro-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol **4**.

General Procedure.

Hydrazine (R^4NHNH_2, 20 mmoles) was added dropwise at room temperature to a stirred solution of the 4-alkoxy-1,1,1-trifluoro-3-alken-2-ones **1a-c** (15 mmoles) in absolute ethanol (10 ml). The mixture was stirred and heated under reflux for 2 hours (4 hours for R^4 = Ph), then the solvent was evaporated *in vacuo*. The products were purified by sublimation or recrystallization from diisopropyl ether to give 1-methyl-5-(trifluoromethyl)-1*H*-pyrazoles **2**, **3** and 4,5-dihydro-1-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-5-ol **4**.

In the case of compounds **2b** and **4c**, the purification was carried out by sublimation of the residue (Table).

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Table

Selected Physical and Spectral [a] Data of 5-Trifluoromethylpyrazoles **2-4a-c**

No.	Yield (%)	Mp [b] (C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N	^{1}H-NMR δ, J (Hz)	^{13}C-NMR δ, J $_{C-F}$ (Hz)
2a	98	86-87	$C_4H_3F_3N_2$ 136.08	35.30 35.47	2.22 2.29	20.59 20.70	6.68 (d, 1H, J = 1.9, H-4), 7.94 (d, 1H, J = 1.9, H-3), 13.60 (*s*, 1H, NH) [c]	103.2 (C-4), 130.5 (C-3), 140.8 (J = 36.7, C-5), [c]
2b	75	48	$C_5H_5F_3N_2$ 150.11	40.01 40.17	3.36 3.51	18.67 18.16	2.21 (d, 3H, J = 0.7, CH_3), 7.45 (q, 1H, J = 0.7, H-3), 9.63 (*s*, 1H, NH)	114.9 (C-4), 129.8 (C-3), 140.3 (J = 39.2, C-3)
2c	98	102-104	$C_5H_5F_3N_2$ 150.11	40.01 39.99	3.36 3.45	18.67 18.81	2.35 (d, 3H, J = 0.7, CH_3), 6.31 (q, 1H, J = 0.7, H-4), 8.71 (*s*, 1H, NH)	102.8 (C-4), 141.5 (C-3), 142.9 (J = 40.6, C-5)
3a	78	68-70	$C_5H_5F_3N_2$ 150.11	40.01 40.26	3.36 3.53	18.67 18.54	3.99 (*s*, 3H, NCH_3), 6.58 (d, 1H, J = 0.7, H-3), 7.45 (d, 1H, J = 0.7, H-4)	107.5 (C-4), 133.8 (J = 40.3, C-5), 138.1 (C-4)
3b	98	oil	$C_6H_7F_3N_2$ 164.08	43.92 44.15	4.30 4.41	17.07 17.29	2.13 (d, 3H, J = 0.6, CH_3), 3.87 (*s*, 3H, NCH_3), 7.18 (q, 1H, J = 0.6, H-3)	115.6 (C-4), 130.9 (C-3), 139.3 (J = 35.6, C-5)
3c	65	oil	$C_6H_7F_3N_2$ 164.08	43.92 43.98	4.30 4.32	17.07 17.15	2.29 (d, 3H, J = 0.5, CH_3), 3.81 (*s*, 3H, NCH_3), 6.26 (q, 1H, J = 0.5, H-4)	103.5 (C-4), 140.1 (C-3), 140.8 (J = 37.8, C-5)
4a	73	134-135	$C_{10}H_9F_3N_2O$ 230.19	52.18 52.40	3.74 4.13	12.17 12.00	3.08 (d, 1H, J = 18.8, H-4a), 3.44 (d, 1H, J = 18.8, H-4b), 6.93 (*s*, 1H, H-3), 7.34 (m, 5H, arom)	47.8 (C-4), 92.5 (J = 31.6, C-5), 148.2 (C-3)
4b	82	91-92	$C_{11}H_{11}F_3N_2O$ 244.22	54.10 54.24	4.54 4.57	11.47 11.54	1.29 (d, 3H, J = 7.5, CH_3), 3.51 (q, 1H, J = 7.5, H-4), 6.76 (*s*, 1H, H-3), 7.32 (m, 5H, arom)	48.2 (C-4), 93.2 (J = 30.4, C-5), 145.7 (C-3)
4c	70	50-51	$C_{11}H_{11}F_3N_2O$ 244.22	54.10 54.30	4.54 4.59	11.47 11.56	1.98 (*s*, 3H, CH_3), 3.06 (d, 1H, J = 19.0, H-4a), 3.43 (d, 1H, J = 19.0, H-4b), 7.34 (m, 5H, arom)	45.7 (C-4), 92.1 (J = 31.4, C-5), 140.7 (C-3)

[a] NMR-Spectra were recorded on a Bruker AC 80 (^{1}H and 80 MHz an d ^{13}C at 20 MHz) in DMSO-d_6/TMS. [b] Melting points determined with a Reichert Thermovar apparatus. [c] In deuteriochloroform/TMS.

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