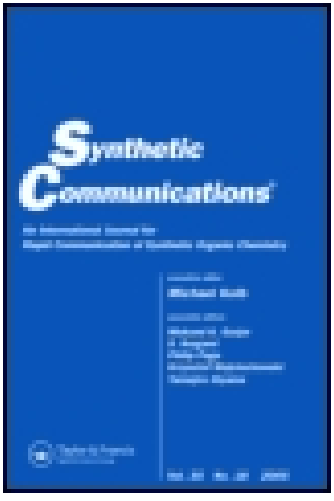

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A Convenient Method to Obtain 4,5-Dihydro-1H-Methylpyrazoles by A Ring Transformation Reaction

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A CONVENIENT METHOD TO OBTAIN 4,5-DIHYDRO-*1H*-1-METHYLPYRAZOLES BY A RING TRANSFORMATION REACTION.

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ABSTRACT: A convenient method for the synthesis of alkyl[aryl]-substituted 5-hydroxy-5-trifluoromethyl-4,5-dihydro-*1H*-1-methylpyrazole (**2**) from a new ring transformation reaction of alkyl[aryl]-substituted-5-hydroxy-5-trifluoromethyl-4,5-dihydro-*1H*-1-pyrazolethiocarboxyamide (**1**) with methylhydrazine in THF, and the thermal dehydration of **2**, are reported.

Although many methods[1, 2] have been published for the synthesis of *1H*-pyrazoles and derivatives, the synthesis of a very simple 4,5-dihydro-*1H*-1-methylpyrazoles, has not been described.

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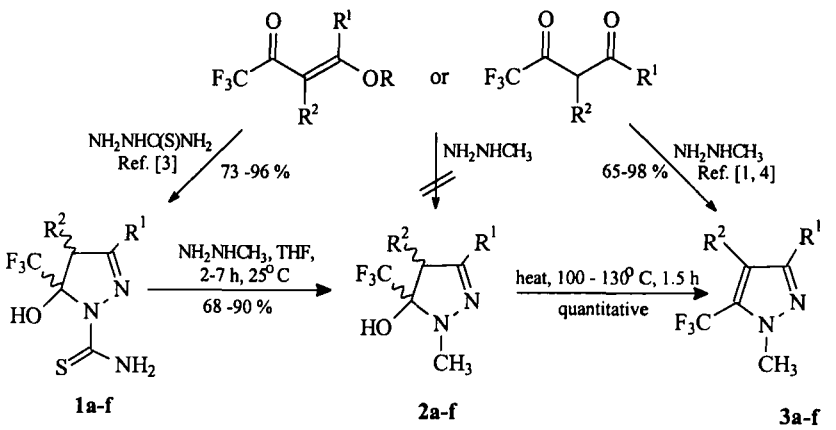
Conventionally, pyrazolines have been obtained by direct reaction of β-diketones and derivatives with hydrazines.[1,2] However, 4,5-dihydro-*1H*-pyrazoles have been obtained only when the ring substituent at C-4 acts as a protective group or when the N-1 and C-5 atoms are substituted by a strong electron-withdrawing group to hinder the elimination of water.[2] Some 5-trifluoromethylated- or 5-trichloro-methylated-5-hydroxy-*1H*-pyrazoline[2-5] and pyrazolidine [2] intermediates have been isolated, however the N-alkylated parent compounds have not been. The synthesis of pyrazoles by ring transformation reaction has been explored little and few pyrazoles have been obtained from other heterocycles. The reaction of 2-methylene-1,3-dithietanes with hydrazines affords 5-thiolpyrazoles. [6] Reaction with hydrazine has transformed substituted vinyl dioxolanes into 5-hydroxypyrazoles [7] Similarly, reaction of hydrazines with 3-unsubstituted isoxazolium salts, [8] 1,2,6-thiadizine-1,1-dioxides [9, 10] or an N-methyl-pyrimidinium carbinol salt [11] gives 3-aminopyrazoles, 3,5-dimethyl-pyrazole or N-carbinol-pyrazol, respectively. A wide variety of 3(5)-substituted pyrazoles were prepared in very good yields by ultrasonic desulfuration or deselenylation-ring contraction of 1,3,4-thiadiazines or 1,3,4-selenediazines. [12] However, pyrazoline-pyrazoline ring transformations have not been observed.

This situation prompted us to investigate the possibility of the synthesis and isolation of a new series of 4,5-dihydro-*1H*-1-methyl pyrazoles, in the course of our research program in heterocyclic chemistry. [13-15] We now wish to present here a convenient and versatile synthetic method which allows the isolation of stable 4,5-dihydro-1H-1-methyl-pyrazoles (**2a-g**) using a new pyrazoline-

pyrazoline ring transformation reaction developed in our laboratory. All reactions are presented in the Scheme. Typical results of these reactions and selected physical and NMR spectral data are shown in Tables 1-3.

Scheme



1-3	a	b	c	d	e	f
R^1	H	Me	H	Ph	*p*-MePh	*p*-BrPh
R^2	H	H	Me	H	H	H

We reported recently that β-alkoxyvinyltrifluoromethyl ketones react with thiosemicarbazide to give alkyl[aryl]-substituted 5-hydroxy-5-trifluoromethyl-4,5-dihydro-*1H*-pyrazolethiocarboxyamides (**1a-f**) in excellent yields.[3] Compounds **1a-f** react with methylhydrazine in a small amount of tetrahydrofuran quite readily at 25°C for 2 to 7 hours to give very good yields of 4,5-dihydro-1H-1-methyl-pyrazoles (**2a-f**) and thiosemicarbazide, as by-product. The crystalline compounds

TABLE 1 – Selected Physical and Elemental Analysis Data of **2a-f** and **3a-f.**

No.	Yield (%) [a]	M.p. (°C) [b]	Molecular Formula (M. Wt.)	Elemental Analysis (%) Calcd./ Found C	H	N
2a	86	75 – 76	$C_5H_7N_2OF_3$	35.70	4.20	16.70
			168.11	35.60	4.20	16.47
2b	77	76– 78	$C_6H_9N_2OF_3$	39.60	5.00	15.40
			182.14	39.43	5.00	15.27
2c	68	71 – 73	$C_6H_9N_2OF_3$	39.60	5.00	15.40
			182.14	39.44	5.01	15.30
2d	90	110 – 112	$C_{11}H_{11}N_2OF_3$	54.10	4.50	11.50
			244.21	54.06	4.47	11.55
2e	80	119 – 120	$C_{12}H_{13}N_2OF_3$	55.81	5.07	10.85
			258.24	55.51	5.06	11.25
2f	89	85-86	$C_{11}H_{10}N_2OF_3Br$	40.90	3.10	8.70
			323.11	40.77	3.17	8.74
3a	97	oil	$C_5H_5F_3N_2$	[c]		
		68-70[c]	150.10			
3b	98	oil	$C_6H_7F_3N_2$	[c]		
		oil[c]	164.13			
3c	67	oil	$C_6H_7F_3N_2$	[c]		
		oil[c]	164.13			
3d	98	oil	$C_{11}H_9F_3N_2$	58.40	4.00	12.40
			226.20	58.13	3.66	12.48
3e	97	48 – 50	$C_{12}H_{11}F_3N_2$	60.00	4.60	11.70
			240.22	59.65	4.30	11.33
3f	96	70 -71	$C_{11}H_8BrF_3N_2$	43.30	2.60	9.20
			305.09	43.27	2.88	9.22

[a]Yields of isolated compounds. [b] Melting points are uncorrected.

[c] Known compounds, see references 1 and 4.

TABLE 2 – ^{1}H and ^{13}C NMR Data of N-methylpyrazolines **2a-f.**

No.	^{1}H-NMR, δ (ppm), J (Hz)[a] ^{13}C-NMR, δ (ppm), J (Hz)[a]
2a	7.22 (s, 1H, OH), 6.81 (s, 1H, H3), 3.10 (dd, 1H, $J_{H4a-H4b}$=18, H4a), 2.86 (dd, 1H, $J_{H4b-H4a}$=18, H4b), 2.79 (3H, NCH_3). 138.8 (C3), 124.3 (q, J_{C-F}=283, CF_3), 90.6 (q, J_{C-F}=30, C5), 44.0 (C4), 34.0 (NCH_3).
2b	7.13 (s, 1H, OH), 3.08 (d, 1H, $J_{H4a-H4b}$=18, H4a), 2.75 (d, 1H, $J_{H4b-H4a}$= 18, H4b), 2.70 (3H, NCH_3), 1.87 (s, 3H, CH_3). 147.4 (C3), 124.3 (q, J_{C-F}=283, CF_3), 92.0 (q, J_{C-F}=30, C5), 46.4 (C4), 34.5 (NCH_3), 15.2 (CH_3)
2c	7.02 (s, 1H, OH), 6.63 (s, 1H, H3), 3.20 (q, 1H, J_{H4-Me}=7, H4), 2.80 (s, 3H, NCH_3), 1.13 (d, 3H, J_{Me-H4}=7, CH_3). 144.0 (C3), 124.6 (q, J_{C-F}= 283, CF_3), 93.2 (q, J_{C-F}= 29, C5), 46.8 (C4), 34.5 (NCH_3), 9.1 (CH_3).
2d	7.65 – 7.63, 7.42 – 7.34 (m, 5H, Ph-H), 7.49 (s, 1H, OH), 3.48 (d, 1H, $J_{H4a-H4b}$=18, H4a), 3.34 (d, 1H, $J_{H4b-H4a}$=18, H4b), 2.93 (s, 3H, NCH_3). 146.6 (C3), 124.1 (q, J_{C-F}=283, CF_3), 131.8, 128.8, 128.6, 125.5 (Ph-C), 92.2 (q, J_{C-F}=30, C5), 42.6 (C4), 34.5 (NCH_3).
2e	7.54 – 7.50, 7.22 – 7.18 (m, 4H, Ph-H), 7.46 (s, 1H, OH), 3.45 (d, 1H, $J_{H4a-H4b}$=18, H4a), 3.29 (d, 1H, $J_{H4b-H4a}$=18, H4b), 2.90 (s, 3H, NCH_3), 2.31 (s, 3H, CH_3). 146.6 (C3), 138.3, 129.1, 129.0, 125.5 (Ph-C), 124.1 (q, J_{C-F}=283, CF_3), 92.1 (q, J_{C-F}=30, C5), 43.9 (C4), 34.5 (s, 3H, NCH_3), 21.0 (CH_3).
2f	7.63 – 7.54 (m, 4H, Ph-H), 3.50 (d, 1H, $J_{H4a-H4b}$=18, H4a), 3.47 (d, 1H, $J_{H4b-H4a}$=18, H4b), 2.92 (s, 3H, NCH_3). 145.5 (C3), 131.5, 131.0, 127.4, 121.9 (Ph-C), 123,9 (q, J_{C-F}= 284, CF_3), 92.3 (q, J_{C-F}=30, C5), 42.3 (C4), 34.4 (NCH_3).

[a] NMR spectra in DMSO-d_6/TMS.

TABLE 3- ^{1}H and ^{13}C NMR Data of N-methylpyrazoles **5a-f.**

No.	^{1}H-NMR, δ (ppm), J (Hz)[a] ^{13}C-NMR, δ (ppm), J (Hz)[a]
3a[b]	7.46 (d, 1H, $J_{H4a-H4b}$=2, H4), 6.60 (d, 1H, $J_{H4b-H4a}$=2, H3), 3.99 (s, 3H, NCH_3). 138.1 (C3), 131.9 (q, J_{C-F}=39, C5), 120.2 (q, J_{C-F}=268, CF_3), 107.5 (C4), 37.9 (NCH_3).
3b	6.60 (s, 1H, H4), 3.87 (s, 3H, NCH_3), 2.20 (s, 3H, CH_3). 140.8 (C3), 138.9 (q, J_{C-F}=37, C5), 121.6 (q, J_{C-F}=268, CF_3), 103.2 (C4), 30.4 (NCH_3), 10.4 (CH_3).
3c	7.65 (s, 1H, H3), 3.87 (s, 3H, NCH_3), 2.01 (s, 3H, CH_3). 137.8 (q, J_{C-F}=35, C5), 131.5 (C3), 121.7 (q, J_{C-F}=268, CF_3), 114,0 (C4), 38,2 (NCH_3), 6,8 (CH_3).
3d	7.95 – 7.86, 7.52 – 7.40 (m, 5H, Ph-H), 7.37 (s, 1H, H4), 4.02 (s, 3H, NCH_3). 149.5 (C3), 131.9 (q, J_{C-F}=39, C5), 131.6, 128.7, 128.2, 125.2 (Ph-C), 119.9 (q, J_{C-F}=269, CF_3) 104.9 (C4), 38.0 (NCH_3).
3e	7.77 – 7.73, 7.26 – 7.22 (m, 4H, Ph-H), 7.31 (s, 1H, H4), 4.00 (s, 3H, NCH_3), 2.33 (s, 3H, CH_3). 149.5 (C3), 131.7 (q, J_{C-F}=39, C5), 137.6, 129.3, 128.9, 125.1 (Ph-C), 119.9 (q, J_{C-F}=269, CF_3), 104.6 (C4), 37.9 (NCH_3), 20.7 (CH_3).
3f	7.82 – 7.78, 7.63 – 7.60 (m, 4H, Ph-H), 7.39 (s, 1H, H4), 4.02 (s, 3H, NCH_3). 148.3 (C3), 132.0 (q, J_{C-F}=39, C5), 131.6, 130.8, 127.1, 122.4 (Ph-C), 119.8 (q, J_{C-F}=269, CF_3), 105.2 (C4), 38.1 (NCH_3).

[a] NMR spectra in DMSO-d_6/TMS. [b] NMR spectra in $CDCl_3$/TMS

2a-f are stable in air at room temperature for a week and stored in freezer for more than a month. The pyrazolines **2a-f** were quantitative dehydrated on heating at 25 °C above the melting point for 1.5 hours, giving the corresponding aromatic *1H*-1-methylpyrazoles **3a-f.** The transformation reaction was tested with hydrazine, which worked using mild conditions and phenylhydrazine, which gave no product under various conditions.

Experimental

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purification. The compounds **1a-f** were synthesized according with the literature.[3] The melting points were taken on a melting point microscope Reichert-Thermovar and are uncorrected. The elemental analysis were performed on an Elementar Analysensysteme CHNS - Vario EL equipment. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6/TMS.

Preparation of Alkyl[aryl]-substituted 5-hydroxy-5-trifluoromethyl-4,5-dihydro-*1H*-1-methylpyrazoles (**2a-f**).

General Procedure: To a stirred solution of 5-hydroxy-5-trifluoromethyl-4,5-dihydro-*1H*-pyrazole-1-thiocarboxyamides **1a-f** (10 mmoles) in 10 ml of tetrahydrofuran, methylhydrazine (12 mmoles) was added at 20 - 25 ^{o}C. The mixture was stirred for 4 hours for **2a**, 2 hours for **2b** or 7 hours for **2c-f**. After the reaction time, 50 ml of tetrahydrofuran was added to the mixture. Most of thiosemicarbazide precipitated and was filtered off and the solvent evaporated under reduced pressure. The solid residue was dissolved in a small amount of hot chloroform and the remaining thiosemicarbazide was filtered off. The chloroform was evaporated under reduced pressure and the solid product was recrystallized from hexane.

Preparation of Alkyl[aryl]-substituted 5-trifluoromethyl-*1H*-1-methylpyrazoles (**3a-f**).

General Procedure: The pure 5-hydroxy-5-trifluoromethyl-4,5-dihydro-*1H*-pyrazole-1-thiocarboxyamides **1a-f** (4 mmoles) were stirred and heated for 1.5 hours at 100°C to 130 °C . After cooling to room temperature 20 ml of dichloromethane were added to the reaction. The organic solution was dried with magnesium sulfate and filtered. The solvent was evaporated under reduced pressure and liquid (**3a-d**) or solid product (**3e-f**) were obtained in high purity.

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