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Haloacetylated enol ethers 10. Condensation of β-alkoxyvinyl trifluoromethyl ketones with thiosemicarbazide. Synthesis of new trifluoromethyl 4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides

H.G. Bonacorso*, A.D. Wastowski, N. Zanatta, M.A.P. Martins, J.A. Naue

Departamento de Química, Universidade Federal de Santa Maria 97105-900, Santa Maria, RS, Brazil

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Abstract

The synthesis of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides (**2a–g**) from the direct cyclo-condensation reaction of β-alkoxyvinyl trifluoromethyl ketones (**1a–g**) with thiosemicarbazide in methanol, under mild conditions, is reported. Similarly, the 1*H*-1-pyrazolethiocarboxyamide derivatives (**2a–g**) were easily dehydrated and the thiocarboxyamide group hydrolyzed in a one-step reaction by stirring with concentrated sulfuric acid to give the 3-aryl[alkyl]-5-trifluoromethyl-1*H*-pyrazoles (**3a–g**) in good yields. Specific syntheses and physical properties of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides are reported here for the first time.

Keywords: β-alkoxyvinyl trifluoromethyl ketones; 4,5-dihydro-1*H*-pyrazoles; Trifluoromethyl-1*H*-pyrazoles

1. Introduction

Many trifluoromethylated 1*H*-pyrazoles and derivatives are known to exhibit important biological activities in medicinal and agricultural scientific fields [1–6]. Therefore, much attention has been paid to the development of new methods for the synthesis of fluorine containing heterocycles. The synthesis of pyrazoles is relatively well explored by the so-called [3+2] atom fragments, where β-diketones or derivatives thereof as the 3-atom fragment is condensed with hydrazine or its derivatives (2-atom fragment) to close the five-membered ring [7]. In previous papers the versatility of the β-alkoxyvinyl-β-aryl [alkyl] trifluoromethyl ketones as readily available CCC building block for the regiospecific construction of isoxazoles [8,9], pyrimidines [10,11], pyrazoles and pyrazolines [12], was reported.

With a continuing interest in heterocyclic structures that may have biological activities, the aim of this work is to report the results of the regiospecific synthesis of a series of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides (**2a–g**) and 3-aryl[alkyl]-5-trifluoromethyl-1*H*-pyrazoles (**3a–g**) from the reactions of the 4-alkoxy-4-aryl[alkyl]-1,1,1-trifluoro-3-buten-2-ones (**1a–g**) and thiosemicarbazide (Scheme 1).

*Corresponding author. E-mail: heliogb@base.ufsm.br

2. Results and discussion

The β-alkoxyvinyl trifluoromethyl ketones (**1a–c**) were prepared according to Ref. [8] and the β-aryl-β-methoxy-vinyl trifluoromethyl ketones (**1d–g**) were synthesized from the reaction of the respective acetophenone dimethyl acetals with trifluoroacetic anhydride [13,14]. The cyclocondensation reactions of compounds (**1a–g**) with thiosemicarbazide were carried out in a molar ratio of 1:1, using pure methanol as solvent. The reactions were monitored by TLC and the most satisfactory reaction time and reaction temperature were found to be 24 h at 20–25°C for **2a–b** and 20 h at 40–45°C for **2c–g**. It was observed that the compounds (**1a**) and (**1b**) derived from vinyl ethers could be readily converted into 4,5-dihydro-1*H*-pirazoles (**2a–b**) at only ambient temperature. The same reaction carried out for compounds (**1a–b**) at temperature above 35°C, led to the polymerization product. The cyclo-condensation reactions for the propenyl enol ether and *p*-substituted acetophenone acetals derivatives (**2c–g**) with thiosemicarbazide were carried out at temperature above 40°C. This study afforded a methodology to obtain a series of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides (**2a–g**) in good to excellent yield (see Table 1). A series of 3-aryl[alkyl]-5-trifluoromethyl-1*H*-pyrazoles (**3a–g**) was obtained by dehydratation and simultaneous removal of the

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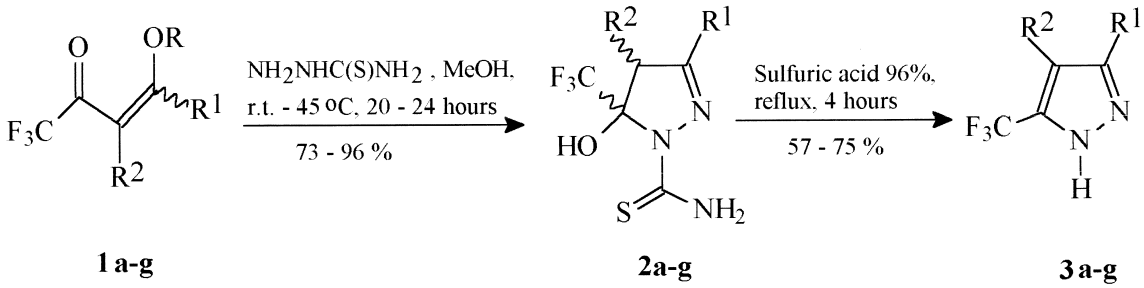

1 a-g 2a-g 3 a-g

1-3	a	b	c	d	e	f	g
R	Et	Me	Me	Me	Me	Me	Me
R^1	H	Me	H	Ph	*p*-MePh	*p*-BrPh	*p*-NO_2Ph
R^2	H	H	Me	H	H	H	H

Scheme 1.

thiocarboxyamide group of compound **2** with sulfuric acid under reflex for 4 h. The crude products were purified by recrystallization. The crystalline compounds (**2a–g**) and (**3d–g**) are stable in air and may be stored at 20–30°C for months without deterioration. The compounds (**3a–c**) darkens after 30 days at 0–5°C.

All reactions are presented in Scheme 1. The most satisfactory results of these reactions and the selected physical data are shown in Tables 1 and 3. Selected NMR spectral data are presented in Tables 2 and 4.

3. Conclusion

Our experiments show that the thiocarboxyamide group on position 1 of the pyrazolines (**2**) acts as a protective group with an electron withdrawing effect, hindering the elimination of water and the subsequent aromatization of the five-membered ring. The presence of a trifluoromethyl group on the vinyl ketone (**1**) and the thiocarboxyamide group on the dinucleophile (thiosemicarbazide) was the determining factor of the regiochemistry of the reaction. The α-alkyl- and β-alkyl[aryl]-substituent on the vinyl ketone (**1**) and the adopted procedures produced no observable effects on the regiochemistry of the reaction.

In summary, the use of this methodology developed in this work allowed the isolation of a new series of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamides (**2**) and 3-aryl[alkyl]-5-trifluoromethyl-1*H*-pyrazoles (**3**), which have been prepared in analytically pure form and in high yield.

Table 1
Selected physical data of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazolethiocarboxyamides (**2a–g**)

Compound	Yield[a] (%)	Melting point (mp)[b] (°C)	Molecular formula and weight	Analysis (%)[c] calcd/found		
				C	H	N
2a	76	139–140	$C_5H_6N_3OF_3S$	28.17	2.84	19.71
			213.18	28.38	2.82	19.64
2b	96	143–144	$C_6H_8N_3OF_3S$	31.72	3.55	18.49
			227.20	31.85	3.46	18.45
2c	74	143–144	$C_6H_8N_3OF_3S$	31.72	3.55	18.49
			227.20	31.90	3.50	18.17
2d	73	158–159	$C_{11}H_{10}N_3OF_3S$	45.67	3.48	14.53
			289.28	45.63	3.47	14.55
2e	87	178–179	$C_{12}H_{12}N_3OF_3S$	47.52	3.99	13.85
			303.30	47.65	3.93	13.84
2f	87	207–208	$C_{11}H_9N_3OF_3SBr$	35.89	2.46	11.41
			368.17	35.91	2.50	11.40
2g	90	235–236	$C_{11}H_9N_4O_3F_3S$	39.50	2.70	16.80
			334.27	39.38	2.88	16.63

[a]Yields of isolated compounds.
[b]The melting points are uncorrected.
[c]Elemental analysis were performed on a CHN-Elementar Analysensysteme Vario EL.

Table 3
Selected physical data of 3-aryl[alkyl]-5-trifluoromethyl-1*H*-pyrazoles (**3a–g**)

Compound	Yield[a]	Melting point (mp)[b]		Molecular formula and weight	Analysis (%)[c] calcd/found		
	(%)	(°C)			C	H	N
3a	57	44–46	48[d]	$C_4H_3F_3N_2$ 136.08		[e]	
3b	67	85–87	86–87[d]	$C_5H_5F_3N_2$ 150.11		[e]	
3c	72	102–103	102–104[d]	$C_5H_5F_3N_2$ 150.11		[e]	
3d	72	122–123		$C_{10}H_7F_3N_2$ 212.17	56.60 56.66	3.30 3.34	13.20 13.11
3e	75	168–169		$C_{11}H_9F_3N_2$ 226.20	58.40 58.45	4.00 3.92	12.40 12.30
3f	75	147–148		$C_{10}H_6BrF_3N_2$ 291.07	41.30 41.00	2.10 2.48	9.60 9.81
3g	75	154–155		$C_{10}H_6F_3N_3O_2$ 257.17	46.70 46.53	2.40 2.54	16.30 16.15

[a]Yields of isolated compounds.
[b]The melting points are uncorrected.
[c]Elemental analysis were performed on a CHN-Elementar Analysensysteme Vario EL.
[d]Data in Ref. [12] led the mp for **3a**, **3b** and **3c** exchanged; they are presented correctly here.
[e]Known compounds, see Ref. [12].

Table 2
Selected ^{1}H and ^{13}C NMR spectral data[a] of compounds **2a–g**

Compound	^{1}H-NMR, δ (ppm), J (Hz) ^{13}C-NMR, δ (ppm), J (Hz)
2a	8.76 (s, 1H, NHa), 8.41 (s, 1H, O–H), 8.24 (s, 1H, NHb), 7.39 (s, 1H, H3), 3.55 (dd, 1H, J=20.0, H4a), 3.34 (dd, 1H, J=20.0, H4b). 177.0 (C=S), 146.6 (C3), 123.5 (q, J=289.9, CF_3), 90.7 (q, J=33.2, C5), 45.7 (C4).
2b	8.58 (s, 1H, NHa), 8.48 (s, 1H, O–H), 8.03 (s, 1H, NHb), 3.51 (d, 1H, J=19.2, H4a), 3.36 (d, 1H, J=19.2, H4b), 2.04 (s, 3H, CH_3). 176.0 (C=S), 156.2 (C3), 123.6 (q, J=289.9, CF_3), 91.99 (q, J=32.2, C5), 56.1 (C4), 15.2 (CH_3).
2c	8.84 (s, 1H, NHa), 8.78 (s, 1H, O–H), 8.30 (s, 1H, NHb), 7.38 (s, 1H, H3), 3.53 (q, 1H, J=7.4, H4), 1.08 (d, 3H, J=7.4, CH_3). 177.1 (C=S), 151.0 (C3), 123.7 (q, J=290.3, CF_3), 90.9 (q, J=32.2, C5), 48.2 (C4), 10.6 (CH_3).
2d	8.84 (s, 1H, NHa), 8.50 (s, 2H, NHb e O–H), 7.99−7.87, 7.58−7.40 (m, 5H, aromatic-H), 4.06 (d, 1H, J=20.0, H4a), 3.80 (d, 1H, J=20.0, H4b). 176.2 (C=S), 152.6 (C3), 123,5 (q, J=290.3, CF_3), 131.2; 129.4; 128.7; 127.3 (aromatic-C), 92.7 (q, J=32.7, C5), 43.9 (C4).
2e	8.82 (s, 1H, NHa), 8.53 (s, 1H, O–H), 8.45 (s, 1H, NHb), 7.83−7.81, 7.31−7.29 (m, 4H, aromatic-H), 4.01 (d, 1H, J=19.0, H4a), 3.75 (d, 1H, J=19.0, H4b), 2.36 (s, 3H, p-CH_3). 176.1 (C=S), 152.6 (C3), 141.4, 129.3, 127.3, 126.6 (aromatic-C), 123.6 (q, J=289.7, CF_3), 92.6 (q, J=33.2, C5), 43.9 (C4), 21.0 (p-CH_3).
2f	8.87 (s, 1H, NHa), 8.54 (s, 1H, NHb), 8.49 (s, 1H, O–H), 7.92−7.87, 7.73−7.68 (m, 4H, aromatic-H), 4.07 (d, 1H, J=20.0, H4a), 3.79 (d, 1H, J=20.0, H4b). 176.3 (C=S), 151.6 (C3), 131.6, 129.2, 128.6, 124.8 (aromatic-C), 123.4 (q, J=290.3, CF_3), 92.9 (q, J=32.2, C5), 43.8 (C4).
2g	8.96 (s, 1H, NHa), 8.66 (s, 1H, NHb), 8.44 (s, 1H, O–H), 8.34−8.30, 8.21−8.17 (m, 4H, aromatic-H), 4.15 (d, 1H, J=19.0, H4a), 3.85 (d, 1H, J=19.0, H4b). 176.8 (C=S), 150.6 (C3), 148.5, 135.5, 128.4, 123.7 (aromatic-C), 123.3 (q, J=290.0, CF_3), 93.3 (q, J=33.1, C5), 43.8 (C4).

[a]The NMR spectra were recorded on a Bruker DPX-200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in DMSO-d_6/TMS.

4. Experimental

^{1}H- and ^{13}C-NMR spectra, at 200.13 and 50.32 MHz respectively, were recorded on a Bruker DPX-200 in a 5 mm probe in DMSO (dimethylsulfoxide)-d_6 and TMS was used as an internal reference. The melting points were taken on Reichert–Thermovar melting point microscope and are uncorrected. The elemental analysis were performed on a CHN-Elementar Analysensysteme Vario EL.

*4.1. Preparation of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-pyrazolethiocarboxyamide (**2a–g**)*

4.1.1. General procedure

To a stirred solution of thiosemicarbazide (10 mmol) in 50 ml of methanol, kept at 20–25°C, pure 4-alkoxy-4-aryl-[alkyl]-1,1,1-trifluoro-3-buten-2-one **1a–g** (10 mmol) was added and the mixture was stirred for 24 h at 20–25°C for

Table 4
Selected ^{1}H and ^{13}C NMR spectral data[a] of compounds **3a–g**

Compound	^{1}H-NMR, δ (ppm), J (Hz) ^{13}C-NMR, δ (ppm), J (Hz)
3a	13.57 (s, 1H, NH), 7.86 (d, 1H, J=2.0, H3), 6.60 (d, 1H, J=2.0, H4).
	141.3 (q, J=36.7, C5), 130.5 (C3), 122.1 (q, J=267.7, CF_3), 103.2 (C4).
3b	13.29 (s, 1H, NH), 6.40 (s, 1H, H4), 2.30 (s, 3H, CH_3).
	141.2 (q, J=36.2, C5), 140.6 (C3), 122.0 (q, J=267.6, CF_3), 102.1 (C4), 10.1 (CH_3).
3c	13.29 (s, 1H, NH), 7.73 (s, 1H, H3), 2.12 (s, 3H, CH_3).
	138.7 (q, J=34.2, C5), 129.8 (C3), 122.5 (q, J=268.7, CF_3), 113.5 (C4), 7.62 (CH_3).
3d	14.08 (s, 1H, NH), 7.86−7.82, 7.51−7.42 (m, 5H, aromatic-H), 7.19 (s, 1H, H4).
	144.2 (C3), 142.2 (q, J=35.2, C5), 121.8 (q, J=268.2, CF_3), 129.0, 128.8, 128.3, 125.6 (aromatic-C), 100.9 (C4).
3e	14.01 (s, 1H, NH), 7.75−7.71, 7.32−7.28 (m, 4H, aromatic-H), 7.12 (s, 1H, H4), 2.35 (s, 3H, p-CH_3).
	144.2 (C3), 141.9 (q, J=38.2, C5), 138.5, 129.6, 125.4 (aromatic-C), 121.8 (q, J=268.2, CF_3), 100.5 (C4), 20.7 (p-CH_3).
3f	14.17 (s, 1H, NH), 7.84−7.79, 7.73−7.68 (m, 4H, aromatic-H), 7.22 (s, 1H, H4).
	142.9 (C3), 142.2 (q, J=37.2, C5), 132.0, 127.4, 127.2, 122.1 (aromatic-C), 121.6 (q, J=268.2, CF_3), 101.2 (C4).
3g	14.42 (s, 1H, NH), 8.43−8.30, 8.21−8.09 (m, 4H, aromatic-H), 7.45 (s, 1H, H4).
	147.0 (C3), 142.2 (C5), 134.2, 126.4, 124.2 (aromatic-C), 121.4 (q, J=268.3, CF_3), 103.0 (C4).

[a]The NMR spectra were recorded on a Bruker DPX-200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz) in DMSO-d_6/TMS.

2a–b and 20 h at 40–45°C for **2c–g**. The solvent was evaporated and hot chloroform was added to the solid residue. The insoluble thiosemicarbazide was filtered off. The products (**2a–g**) were crystallized by addition of cyclohexane to the chloroform solution (1:2).

*4.2. Preparation of 3-aryl[alkyl]-5-trifluoromethyl-1H-pyrazole (**3a–g**)*

4.2.1. General procedure

In a 25 ml flask a mixture of 10 mmol of 3-aryl[alkyl]-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1*H*-1-pyrazolethiocarboxyamide (**2a–g**), and concentrated sulfuric acid (40 mmol) was stirred at reflux for 4 h. The mixture was poured slowly on 50 ml of ice water and the solution was extracted with dichloromethane (3×30 ml). The combined organic fractions were washed with water, dried with anhydrous magnesium sulfate and the solvent removed in a rotavapor. The solid products **3a–g** were recrystallized hexane or cyclohexane.

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