Haloacetylated Enol Ethers: 4 [6]. Synthesis of 4-Trihalomethyl-2-methylthiopyrimidines

Claudia da C. Madruga, Edília Clerici, Marcos A. P. Martins, and Nilo Zanatta*

Departamento de Química, Universidade Federal de Santa Maria,
97.119-900 Santa Maria, RS, Brazil

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The synthesis of a series of 5- and 6-substituted 4-trihalomethyl-2-methylthiopyrimidines, prepared from the cyclocondensation reaction of β-alkoxyvinyl tri[fluoro]chloromethyl ketones with 2-methyl-2-thiopseudourea sulfate, are reported. A systematic study to find the best reaction conditions were carried out.

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Many analogues of thiopyrimidines were reported to exhibit effective biological activity [1]. However, it is relatively rare to find trihalomethylated pyrimidines because the introduction of halogens in the pyrimidine side chain, usually accomplished by free radical reaction, is poorly selective and in many cases opening of the pyrimidine ring was observed [2,3]. An alternative method to obtaining trihalomethylpyrimidines utilizes β-alkoxyvinyl trihalomethyl ketones which are condensed with dinucleophiles of the type N-C-N [4]. This method offers a clear advantage since the trihalomethyl group comes from a precursor which is obtained from the acylation of vinyl ethers [5], ketals [7], or enamines [8] with trichloroacetyl chloride or trifluoromethyl anhydride. The versatility of the β-alkoxyvinyl trihalomethyl ketones to synthesize halomethyl substituted heterocycles has been shown in recent publications [4-6,9].

Recently, 4-trifluoromethyl-2-methylthiopyrimidine was prepared from the condensation of 1,1,1-trifluoro-4-ethoxy-3-buten-2-one with thiourea followed by the methlylation of the intermediate 4-trifluoromethyl-2-thiopyrimidinone with iodomethane in 43% overall yield in a rather tedious procedure [10]. In this work we obtained the 4-trifluoromethyl-2-methylthiopyrimidine in 83% yield in just one reaction step which requires a relatively short reaction time and the product is very easy to isolate and purify. We also tested this reaction with four other β-alkoxyvinyl trifluoromethyl ketones **1b-e** to get information of the structure dependence of these cyclocondensation reactions with 2-methyl-2-thiopseudourea sulfate. Furthermore, we also studied the trichlorinated vinyl ketones **2a-e** to obtain the corresponding 4-trichloromethyl-2-methylthiopyrimidines which in preliminary tests exhibited much stronger biological activity than the fluorinated analogue [11].

The preparation of compounds **1,2a-e** was reported in reference 5.

The cyclo-condensation reactions of 4-alkoxy-1,1,1-trifluoro[chloro]methyl-3-alken-2-ones **1,2a-e** with 2-methyl-2-thiopseudourea sulfate were carried out under different conditions of solvent, *p*H, and temperature. Basic and acidic media had to be used since the reaction did not take place just by mixing the ketones **1** or **2** with 2-methyl-2-thiopseudourea sulfate in solvents such as water and methanol. Thus, four main methods were investigated: method A: water/pyridine, method B: methanol/water/pyridine, method C: methanol/water/hydrochloric acid, and method D: methanol/pyridine. The best results of these systematic studies are shown in Table 1 and physical and spectral data of the compounds synthesized are shown in Table 2.

Table 1

Optimized Yields of the Synthesis of 4-Trihalomethyl-2-methylthiopyrimidines

Educt	Method [a,b]	Product	Time (hours) [c]	Yield (%)
1a	A	**3a**	36	83
1b	A	**3b**	21	94
1b	B [d]	**3b**	24	70
1c	B	**3c**	48	14
1c	C	**3c**	24	34
1d	A	**3d**	18	[f]
1e	B	**3e, 5e**	78	[f]
2a	A [e]	**4a**	18	80
2b	A	**4b**	79	77
2c	A	**4c**	48	[g]
2d	D	**6d**	10	66
2e	B	**7e**	32	43

[a] Methods: A: H_2O/Py; B: MeOH/H_2O/Py; C: MeOH/H_2O/HCl; D: MeOH/Py. [b] Temperature of the reflux of the solvent. [c] Time which the mixture was stirred. [d] Temperature of 60°. [e] Temperature of 40°. [f] Structure derived from gc/ms and the compounds were not isolated. [g] Recovered traces of compound **4c** together with starting material.

In methods **A** and **B**, pyridine was used in an amount equivalent to the 2-methyl-2-thiopseudourea sulfate. A mild base such as pyrimidine was sufficient to liberate the dinucleophile (2-methyl-2-thiopseudourea sulfate), from its salt form and the reaction then takes place. In method C, hydrochloric acid was used with the intention to activate the vinyl ketone instead of the thiourea sulfate. This method provided better results only for the cyclization of compound **1c**. In method D, methanol was used as the sol-

Table 2

Selected Physical and Spectral [a] Data for **3a-c, 4a,b**

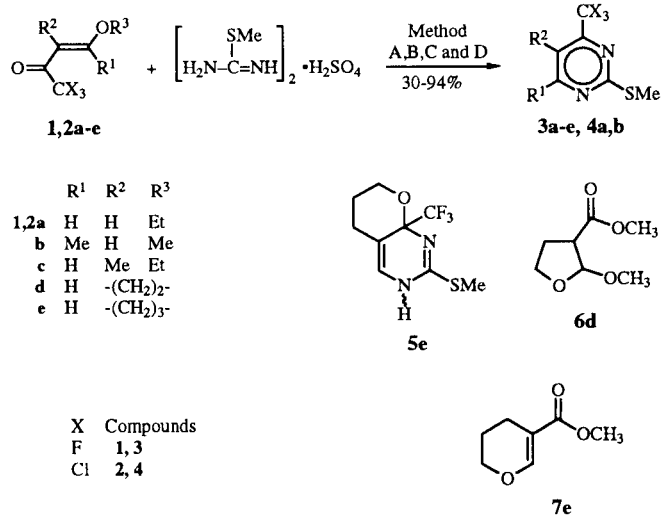
No	Yield [b] (%)	Mp [c] (°C)	Molecular Formula	Analysis(%) Calcd/Found C	H	N	^{1}H-NMR δ, J (Hz)	^{13}C NMR δ, J_{C-F} (Hz)	MS (70 ev) m/z
3a	83	oil	$C_6H_5N_2F_3S$ 194.2	37.11	2.60 [d]	14.43	7.2 (d, 1H, J = 4.9), 8.7 (dq, 1 H, J = 4.9), 2.6 (s, 3H, S-CH_3)	174.7 (C-2), 155.7 (-C4, J = 36.5), 111.3 (C-5), 159.2 (C-6), 120.1 (C-7, J = 275.1), 13.9 (C-8)	195 (M^+, 100), 174 (14), 148 (22), 136 (30), 69 (42)
3b	94	48	$C_7H_7N_2F_3S$ 208.2	40.38	3.38	13.45	7.1 (s, 1H), 2.5 (d, 3H, J < 1, CH_3), 2.6 (s, 3H, S-CH_3)	173.8 (C-2), 155.2 (C-4, J = 35.8), 111.2 (C-5), 169.9 (C-6), 120.4 (C-7, J = 275.1), 13.9 (C-8), 24.1 (C-9)	208 (M^+, 100), 188 (6), 162 (43), 147 (18), 93 (52), 69 (53)
				40.39	3.39	13.52			
3c	34	oil	$C_7H_7N_2F_3S$ 208.2	40.38	3.38	13.45	8.6 (s, 1H), 2.4 (q, 3H, J < 1, CH_3), 2.6 (s, 3H, S-CH_3)	170.6 (C-2), 153.2 (C-4, J = 34.6), 122.7 (C-5), 161.2 (C-6), 121.0 (C-7, J = 276.7), 13.9 (C-8), 14.2 (C-9)	209 (M^++1, 100), 188 (10), 162 (13), 93 (7), 69 (12)
				40.50	3.53	13.20			
4a	80	52	$C_6H_5N_2Cl_3S$ 243.5	29.59	2.07	11.50	7.5 (d, 1H, J = 5), 8.7 (d, 1H, J = 5), 2.6 (s, 3H, S-CH_3)	173.4 (C-2), 165.8 (C-4), 110.4 (C-5), 159.2 (C-6), 95.5 (C-7), 14.1 (C-8)	243 (M^+, 13), 207 (100), 171 (12), 107 (10), 45 (45)
				29.72	2.20	11.31			
4b	77	62	$C_7H_7N_2Cl_3S$ 257.6	32.64	2.74	10.88	7.4 (s, 1H), 2.5 (d, 3H, J < 1, CH_3), 2.6 (s, 3H, S-CH_3)	172.8 (C-2), 169.9 (C-4), 109.9 (C-5), 165.5 (C-6), 95.7 (C-7), 14.1 (C-8), 24.4 (C-9)	258 (M^+, 7), 221 (100), 185 (13), 115 (13), 45 (48)
				32.80	2.87	10.81			

[a] The nmr spectra were recorded on a Bruker AC 80 (^{1}H at 80.13 MHz and ^{13}C at 20.15 MHz) in deuteriochloroform/TMS. [b] Yields of isolated compounds. [c] Melting points determined with a Reichert Thermovar apparatus and are uncorrected. [d] Known compound, see ref 10.

vent based on the satisfactory results obtained in the cyclocondensation of compounds **1** and **2** with urea and methylurea [4], where both ketones and ureas were soluble in methanol. In this work, reactions were carried out in heterogeneous phase since the 2-methyl-2-thiopseudourea sulfate was not totally soluble even in hot methanol. Method D, however, did not give the same positive results as observed for the cyclization of compounds **1** or **2** with urea [4]. Although, in most cases it was possible to isolate the expected pyrimidine, the yields were always lower than with the other methods. We speculated that the low yields exhibited by method D relative, for example, to method A, could be related to the lack of solubility of the sulfate salt in methanol. To overcome this problem, water was used to dissolve the sulfate salt, but in this case, the vinyl ketones were no longer soluble in this solvent. In most instances, reactions carried out in water/pyridine (method A) gave better yields than the reactions carried out in methanol/pyridine (method D), however, in some cases, for example, for compounds **1c**, method A furnished the expected pyrimidine in very low yield, **2c** failed to react, and in the condensation of the cyclic enol ethers **2d,e** with 2-methyl-2-thiopseudourea sulfate, only starting materials were isolated from the reaction. Method D, in turn, also gave poor results with the cyclization of **1c**; **2c** failed to react, and the reaction of the ketones **2d,e**, afforded compounds **6d** and **7e** respectively, in moderate yields (Table 1).

Since neither methanol nor water in the case of pyrimidine provided satisfactory results for the cyclization of compounds **1,2c-e** with 2-methyl-2-thiopseudourea sulfate, it occured to us to use solvent mixtures. A mixture of methanol and water in a proportion of 70:30 respectively, is a convenient solvent because in this mixture both vinyl ketone and sulfate salt are soluble and the reaction could be carried out under homogeneous phase conditions, making it easy to follow the course of the reaction by hplc or tlc. Methods B and C that use this mixture of solvents, however, provided better results only for the cyclization of compound **1c**.

Scheme



The cyclization of **2c** with 2-methyl-2-thiopseudourea sulfate led to the least satisfactory results compared to its analog **1c**, giving only traces of the expected pyrimidine **4c** together with starting materials by the method A. A complex mixture of unidentified compounds were obtained by both methods B and C. It was observed that, in general, β-alkoxyvinyl ketones bearing substituents on the α-carbonyl carbon did not give satisfactory results in the cyclization reactions with 2-methyl-2-thiopseudourea sulfate. Another example of this trend is the cyclic vinyl ketones **1,2d,e**. For these compounds, no one method utilized was successful and in most of the cases only traces of the expected pyrimidines were obtained together with a complex mixture of unidentified products. For example, compound **1d**, using the methods A and D produced compound **3d** in very low yield, together with a mixture of several unidentified compounds. The structure of compound **3d**, which was not isolated from the reaction mixture, was derived from the gc/ms data. Cyclization of compound **2d** furnished, by both methods B and D, compound **6d** in 56% and 66% respectively. This reaction by method C afforded compound **6d** and starting materials in a proportion of 1:2 respectively.

By the method A, reaction of compound **1e** with 2-methyl-2-thiopseudourea sulfate led to compounds **3e** and **5e**, identified by gc/ms, together with a mixture of several unidentified compounds. This reaction when carried out by methods C and D, starting materials together with a mixture of unidentified compounds were recovered at the end of the reaction.

Tentative of cyclization of **2e** with 2-methyl-2-thiopseudourea sulfate by method B furnished the compound **7e** in 43% yield. By all the other methods only starting materials were recovered at the end of the reaction.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker AC80 spectrometer (^{1}H at 80.13 MHz and ^{13}C at 20.15 MHz) in deuteriochloroform/TMS. Capillary gc analyses were performed on a Carlo Erba, Mega Series 5400 chromatograph equipped with a split/splitless injector and FID detector. The gc/ms data were obtained on a Fininigan-mat ITD 80A connected to a Varian 3400 GC. Elemental analysis were carried out in the Institute of Organic Chemistry, University of Stuttgart, Germany.

The β-alkoxyvinyl trihalomethyl ketones **1** and **2** were prepared according to reference [5].

4-Trifluoro(chloro)methyl-2-methylthiopyrimidines **3a-e**, **4a-c**.

General Procedure:

Method A.

To a mixture of β-alkoxyvinyl ketones **1** or **2** (5 mmoles) and 1.04 g (3.75 mmoles) of 2-methyl-2-thiopseudourea sulfate in 10 ml of distilled water was added 0.6 ml (7.5 mmoles) of pyridine. The mixture was stirred and then refluxed for 18-36 hours (see Table 1). The product was isolated by extraction with chloroform. The chloroform layer was washed with 0.1 *N* hydrochloric acid (3 x 15 ml), then with water (15 ml), and dried with sodium carbonate and evaporated in a rotavapor to give **3a,b, 4a,b**. Compound **3a** was purified by column chromatography in neutral alumina and dichloromethane as the mobile phase. Compounds **3b** and **4b** were recrystallized from hexane, and compound **4a** was purified by column chromatography using silica gel and hexane-ethyl acetate (9:1) as the mobile phase. Compounds **3d** and **4c** were identified by gc/ms and they have not been isolated from the crude mixture of products.

Compound **3d**.

This compound had ms: (70 eV) m/z (%) = 238 (M^+, 72), 207 (100), 193 (16), 137 (40), 107 (27), 69 (22), 57 (25), 45 (47).

Compound **4c**.

This compound had ms: (70 eV) m/z (%) = 256 (M^+, 10), 221 (100), 185 (35), 150 (10), 139 (17), 105 (10), 85 (42), 45 (77).

Method B.

Compounds **1** or **2** (5 mmoles) and 1.04 g (3.75 mmoles) of 2-methyl-2-thiopseudourea sulfate, were dissolved in a mixture 7 ml of methanol and 3 ml of distilled water. To the mixture was added 0.6 ml (7.5 mmoles) of pyridine, and it was heated for 24-79 hours (see Table 1). The methanol was evaporated and to the residue was added distilled water (20 ml) and extracted with chloroform (3 x 15 ml). The chloroform layer was washed with 1*N* hydrochloric acid (3 x 15 ml), then with 15 ml at distilled water, dried with sodium carbonate, and evaporated in rotavapor to give **3b,c,e, 5e** and **7e**. Compond **7e** was purified by column chromatography on silica gel and hexane-ethyl acetate (9:1) as the mobile phase, resulting in a colorless oil, in 43% yield. Compounds **3e** and **5e** were identified by gc/ms and they have not been isolated.

Compound **3e**.

This compound had ms: (70 eV) m/z (%) = 251 (M^+-1, 100), 205 (5), 180 (10), 152 (8), 115 (10), 74 (28), 45 (44).

Compound **5e**.

This compound had ms: (70 eV) m/z (%) = 252 (M^+, 73), 207 (62), 187 (20), 162 (20), 137 (100), 107 (20), 74 (30), 57 (42), 45 (84).

Compound **7e**.

This compound had ^{1}H nmr (deuteriochloroform/TMS): δ = 1.67 (m, 2H, CH_2), 2.26 (t, J = 7.85, CH_2), 3.70 (s, 3H, OCH_3), 4.00 (t, J = 5.07, CH_2), 7.57 (m, 1H, =CH); ^{13}C nmr (deuteriochloroform/TMS): δ = 19.0 (CH_2), 20.9 (CH_2), 50.7 (OCH_3), 66.3 (CH_2), 105.6 (=C), 155.2 (=CH), 168.0 (C=O); ms: (70 eV) m/z (%) = 142 (M^+, 30), 127 (120), 111 (73), 83 (100), 55 (96).

Method C.

β-Alkoxyvinyl ketones **1** or **2** (5 mmoles) and 2-methyl-2-thiopseudourea sulfate 1.04 g (3.75 mmoles), were dissolved in 7 ml of methanol and 3 ml of distilled water. After the solubilization of the salt, 1 ml of concentrated hydrochloric acid was added and then refluxed for 24 hours. The methanol was evaporated and to the residue was added 20 ml of distilled water and extracted with chloroform (3 x 15 ml). The chloroform layer was washed with 15 ml of distilled water, dried over sodium carbonate, and evaporated in a rotavapor to give **3c**. Compound **3c** was purified by column chromatography on neutral alumina and dichloromethane was the mobile phase.

Method D.

To a mixture of β-alkoxyvinyl ketones **1** or **2** (5 mmoles) and 1.04 g (3.75 mmoles) of 2-methyl-2-thiopseudourea sulfate in 10 ml of methanol was added 0.6 ml (7.5 mmoles) of pyridine. The mixture was stirred and then refluxed for 10 hours. The product was isolated by extraction with chloroform. The chloroform layer was washed with 0.1*N* hydrochloric acid (3 x 15 ml), then with water (15 ml), and dried over sodium carbonate and evaporated in a rotavapor to give **6d**. Compound **6d** was purified by column chromatography on silica gel and hexane-ethyl acetate (9:1) was the mobile phase resulting in a colorless oil in 66% yield; ^{1}H nmr (deuteriochloroform/TMS): δ = 2.24 (qua, 2H, 6.79, H3), 3.05 (dt, 1H, J = 1.70, 6.79, H2), 3.35 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.95 (m, 2H, CH_2), 5.18 (d, J = 1.70 Hz, CH); ^{13}C nmr (deuteriochloroform/TMS): δ = 27.41 (CH_2), 50.6 (OCH_3), 51.1 (OCH_3), 54.8 (CH), 66.8 (CH_2), 106.4 (CH), 172.5 (C=O); ms: (70 eV) m/z (%) = 159 (M^+-1, <1)$^+$, 145 (8), 129 (20), 117 (12), 99 (25), 69 (100), 41 (68).

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* Author to whom correspondence should be addressed.

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