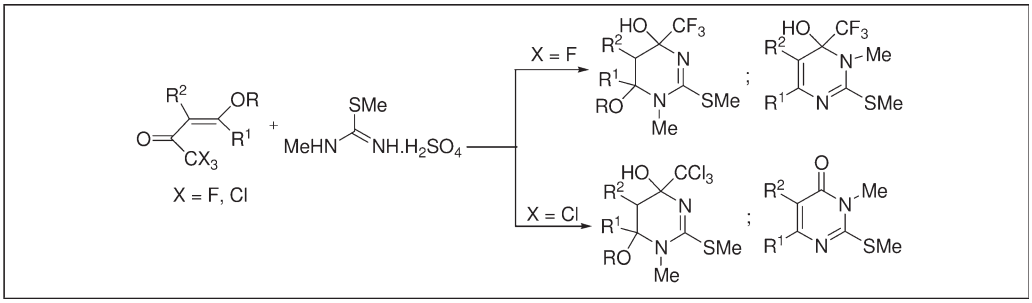
Synthesis and Structural Study of *N*-Methyl-2-methylthiopyrimidine Derivatives from Trihalomethylated Enones

Nilo Zanatta,* Claudia C. Madruga, Patricia C. Marisco, Luciana S. da Rosa, Fabio M. da Silva, Helio G. Bonacorso, and Marcos A. P. Martins

Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97.105-900, Santa Maria, RS, Brazil
*E-mail: zanatta@base.ufsm.br

Received November 26, 2009
DOI 10.1002/jhet.425
Published online 13 July 2010 in Wiley Online Library (wileyonlinelibrary.com).



The synthesis and chemoselective study of a novel series *N*-methyl-2-methylthio-tetrahydropyrimidines and or *N*-methyl-2-methylthiodihydropyrimidines, from the cyclocondensation reaction of β-alkoxyvinyl trihalomethyl ketones (enones) with 1,2-dimethylisothiourea sulfate is described. It was found that the chemoselectivity depends on both the reaction conditions and the steric and electronic effects of the substituents on the enones.

J. Heterocyclic Chem., **47**, 1234 (2010).

INTRODUCTION

Pyrimidines have a long history of biological activity in fields ranging from pharmaceutics to agriculture. The N^1-alkylation of pyrimidines is one way of functionalizing the pyrimidine ring to achieve important physical and bioactive properties. For example, *N*-alkylated nucleic acid bases are widely known for being the most effective antiviral [1] and antitumoral agents, [2] as well as for exhibiting anti-inflammatory [3] and herbicidal activity [4]. In addition, *N*-alkylated pyrimidines, obtained by alkylating agents, such as diazoalkanes [5], alkyl halides [6], and alkylsulfates, among others [7], are important compounds for mutagenic and carcinogenic studies in living systems.

Very few studies have reported on the synthesis of *N*-alkylated 2-methylthiopyrimidines by cyclocondensation reactions using nonsymmetric *S*-alkylthioureas. Probably, the main reason for this is that thioureas are weak nucleophiles, and they do not react very well with 1,3-dicarbonyl compounds or derivatives thereof in a [3 + 3] atom fragment synthesis, which is the main strategy for the preparation of pyrimidine compounds. β-Alkoxyvinyl ketones, however, allow the possibility of direct cyclization with weak nucleophiles because it has been demonstrated that these enones readily react with weak nucleophiles, such as ureas [8], *N*-methylurea [9], *N*-methylthioureas [10], and 2-methyl-2-thiopseudourea [11].

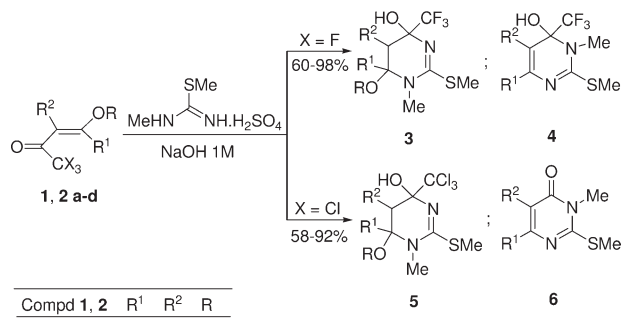
We have reported the synthesis of a series of 4-trihalomethyl-2-methylthiopyrimidines from the reaction of 1,1,1-trifluoro[chloro]-4-alkoxy-alk-3-en-2-ones (tri-halomethylated enones) with 2-methyl-2-thiopseudourea sulfate in the presence of pyridine or acid catalysis [12]. More recently, we reported the synthesis of a new series of 2-methylthiotetrahydropyrimidines from the same enones under a modified procedure [11].

Continuing in our interest in the synthesis of pyrimidine derivatives from trihalomethylated enones, this article aims to study the chemoselectivity and yields of the synthesis of a series of *N*-methyl-2-methylthio-pyrimidines carried out by the cyclocondensation of trihalomethylated enones with the nonsymmetric dinucleophile 1,2-dimethylisothiourea. A detailed NMR study of the structure of the pyrimidines derivatives was carried out to determine the correct position of the *N*-methyl group on the pyrimidine scaffold and to understand the factors that led to such chemoselectivity.

RESULTS AND DISCUSSION

The reaction of enones **1a–d** and **2a–d** with 1,2-dimethylisothiourea sulfate, carried out in the presence of 1 *M* sodium hydroxide solution under mild conditions, furnished *N*-methyl-2-methylthiotetrahydropyrimidines or *N*-methyl-2-methylthiodihydropyrimidines depending

Scheme 1



Compd **1**, **2**	R^1	R^2	R
a	H	H	Et
b	Me	H	Me
c	H	-$(CH_2)_2$-	
d	H	-$(CH_2)_3$-	

on the reaction conditions and the type and positions of the substituents on the trihalomethylated enones (Scheme 1). Table 1 reports the optimized reaction conditions, the yields, and the correct structure of the obtained compounds.

The reaction of enones **1a** and **2a** with 1,2-dimethylisothiourea sulfate in the presence of 1 *M* sodium hydroxide solution at room temperature furnished tetrahydropyridines **3a** and **5a**, respectively. Both products **3a** and **5a** were composed of two diastereo-isomers, whose structure and composition are described in the next section. When the reaction of enone **2a** was carried out at 50°C for 5 h, 3-methyl-2-(methyl-thio)pyrimidin-4-(3*H*)-one (**6a**) was obtained in 92% yield.

Enones bearing a methyl group at the β-position (R^1 = Me) such as **1b** and **2b** reacted with 1,2-dimethyl-isothiourea sulfate in the presence of sodium hydroxide solution furnishing dihydropyrimidine **4b** and **6b** with the *N*–methyl group at the N^3–position of the pyrimidine ring. We speculate that a steric effect between the *N*–methyl group and β-methyl group of enones **1b** and **2b** was responsible for the formation of compounds **4b** and **6b** (N^3**–**regioisomers). In addition, the methoxy group was eliminated because hemi-aminals from ketones are less stable than those from aldehydes. Furthermore, in compound **6b** the elimination of the CCl_3 group was expected for reactions carried out under aqueous basic conditions [13]. In a previous study, compound **4b** exhibited significant inhibition of ATP and ADP hydrolysis in synaptosomes from rat cerebral cortex [14].

The reaction of enones **1c** and **1d** with 1,2-dimethylisothiourea sulfate in the presence of 1 *M* sodium hydroxide solution furnished hexahydrofuro[2,3-*d*]pyrimidin-4-ol (**3c**) and hexahydro-1*H*-pyrano[2,3-*d*]pyrimidin-4-ol (**3d**), respectively. Although, products **3c** and **3d** show three stereogenic centers and additionally the possibility of two regioisomers due to the N^1**–** and N^3–methylation, only a single compound of each product was isolated, which means that the reactions were highly stereoselective and regioselective for these two enones under the conditions given in Table 1.

Enone **2d** reacted with 1,2-dimethylisothiourea sulfate in the presence of 1 *M* sodium hydroxide solution to furnish 3-methyl-2-(methylthio)-4a,5,6,7-tetrahydro-3*H*-pyrano[2,3-*d*]pyrimidin-4(8a*H*)-one (**5d**) in good yields. Under the same condition used to obtain compound **5d**, the enone **2c** failed to give the expected product **5c** and only starting material was isolated. One can observe that enones **2a**–**d** showed the elimination of the trichloro-methyl group instead of the hydroxyl group, except for the reaction of enone **2a** when carried out at room temperature. The elimination of the trichloromethyl group under basic reaction conditions has been reported previously [13].

STRUCTURAL STUDIES

All compounds were fully analyzed by ^{1}H and ^{13}C NMR as well as 2D NMR experiments such as COSY HH [15], NOESY [16], HMQC [17], and HMBC [18]. Figure 1 shows the atom numbering used for NMR assignment of compounds **3**–**6**. Yields, selected physical and ^{1}H and ^{13}C NMR spectral data are presented in the experimental part.

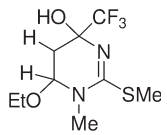
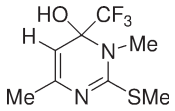
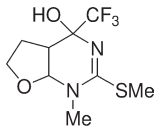
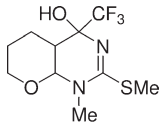
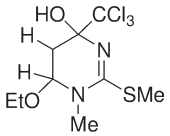
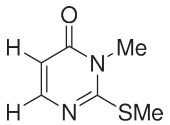
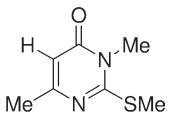
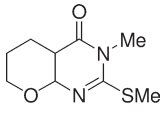
The correct position of the *N*–methyl group (N^1– or N^3–positions) of all *N*–methyl-2-methylthiopyrimidines was determined by two-dimensional HMBC NMR experiments, as shown in Figure 1 [9,10]. In this experiment, when the *N*–methyl group is at the N^1–position, two cross-peaks between the hydrogen atoms of the *N*–methyl group and C–2 and C–6 are observed (Fig. 1, structure **I**). When the *N*–methyl group is at the N^3–position, two cross-peaks between the hydrogen atoms of the *N*–methyl group and C–2 and C–4 are observed (Fig. 1, structure **II**). The cross-peak between the hydrogens of the SMe group and the C–2 assigns this carbon in both structures **I** and **II**. The same strategy was used to assign all the other compounds obtained in this study.

Compound **3a** was obtained as a mixture of two stereoisomers (**3a** and **3a′**), as shown in Figure 2.

The major isomer, isolated in 82%, shows both hydroxy- and ethoxy-groups in an axial position whereas the minor isomer shows the hydroxyl group at an axial position and the ethoxy group at an equatorial position. Compound **3a** was obtained as the major isomer probably because of the formation of a hydrogen-bond between the hydroxyl hydrogen and the oxygen atom of the ethoxy group, which could stabilize this structure. The structure of **3a** and **3a′** was proposed from the interpretation of the coupling constant of H–6 with H–5 and H–5′ as reported previously [11]. A similar trend as observed for **3a** was observed for **5a**.

Table 1

Optimized reaction conditions and structure of the obtained compounds.

Entry	Enone	Reaction conditions[a]		Structure of the obtained products	Yield (%)[d]
		Molar ratio[b] Enone/Nu[c]/Base	*T* (°C)/ time (h)		
1	**1a**	1.0:1.5:1.5	r.t./1	 **3a**[e]	77
2	**1b**	1.0:1.5:1.5	0/2.2	 **4b**	98
3	**1c**	1.0:1.1:1.1	10/0.7	 **3c**	64
4	**1d**	1.0:1.1:1.1	0/1	 **3d**	60
5	**2a**	1.0:2.0:2.0	r.t./1	 **5a**[e]	58
6	**2a**	1.0:1.5:1.5	50/5	 **6a**	92
7	**2b**	1.0:2.0:2.0	30/2.4	 **6b**	95
8	**2d**	1.0:1.1:1.1	0/1.2	 **5d**	70

[a] Reaction conditions: NaOH 1M.
[b] Molar ratio: enone/dinucleophile/base.
[c] Nu = 1,2-dimethylisothiourea sulfate.
[d] Yields of isolated products.
[e] Obtained as a mixture of two diastereoisomers.

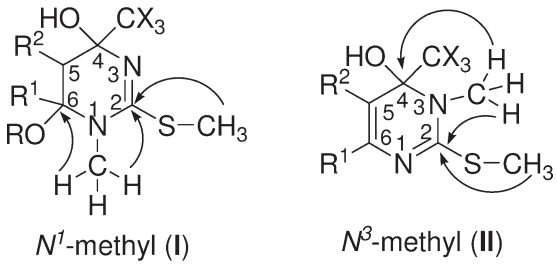


Figure 1. Strategy for the assignment of the position of the *N*-methyl group by HMBC.

Compound **3c** has, besides three asymmetric carbons, the possibility of two regioisomers due to the N^1– and/or N^3–alkylation. However, this compound showed only one set of signals in both ^{1}H and ^{13}C NMR spectra indicating that the reaction was both highly stereoselective and regioselective. Observation of a strong cross-peak between H–4a and H–7a in the NOESY experiment indicates that these hydrogens are close in space, which suggests that the furopyrimidine ring closure was accomplished with *cis* configuration. The most probable structure for **3d** is the furopyrimidine rings in the *cis* configuration, the CF_3 group in pseudo-equatorial positions *cis* to H–4a and *trans* to C–5, and the methyl group bound to N^1 because three bond cross-peaks between the hydrogens of the *N*–methyl group and C–2 and C–7a were observed in the HMBC spectrum (Fig. 3). Compound **3d** also has three asymmetric carbons and the possibility of N^1–Me and/or N^3–Me isomers. As observed for **3c**, **3d** also showed only one set of signals in both ^{1}H and ^{13}C NMR spectra indicating that the reaction was both highly stereoselective and regioselective. The coupling constant between H–4a and H–8a of 12.2 Hz indicates a *trans*-diaxial position of these two hydrogens, consequently, the pyranopyrimidine ring closure occurred with *trans* configuration. The methyl

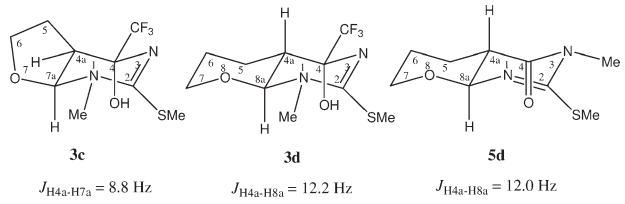


Figure 3. Structure of compounds **3c**, **3d**, and **5d**.

group is attached to N^1 because three bond cross-peaks between the hydrogens of the *N*–methyl group and C–2 and C–8a were observed on the HMBC spectrum (Fig. 3). Compound **5d** showed the same general structure as **3d**, however, **5d** exhibited the N^3–methyl group and the CCl_3 group was eliminated with the formation of a carbonyl group, which was the tendency for all trichloromethyl-bearing enones when the reaction was carried out in basic medium [13].

The tridimensional structure of tetrahydropyrimidines proposed in this study are consistent with the structure of related pyrimidines proposed by Saloutin, *et al*. [19]

Presumably, the reaction starts with the Michael addition of the amino groups of the 1,2-dimethylisothiourea at the β-carbon atom of enone **1** or **2** furnishing both structures **I** (path 1) and/or **II** (path 2), as shown in Scheme 2.

Both hemi-aminals and trifluoromethyl groups are stable under basic conditions, although, hemi-aminals derived from aldehydes are more stable than those from ketones. Thus, after the addition of the first nitrogen of 1,2-dimethylisothiourea at the carbon–carbon double

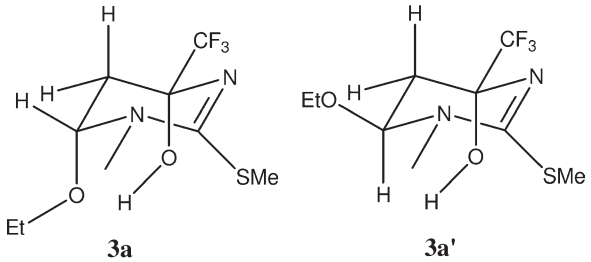
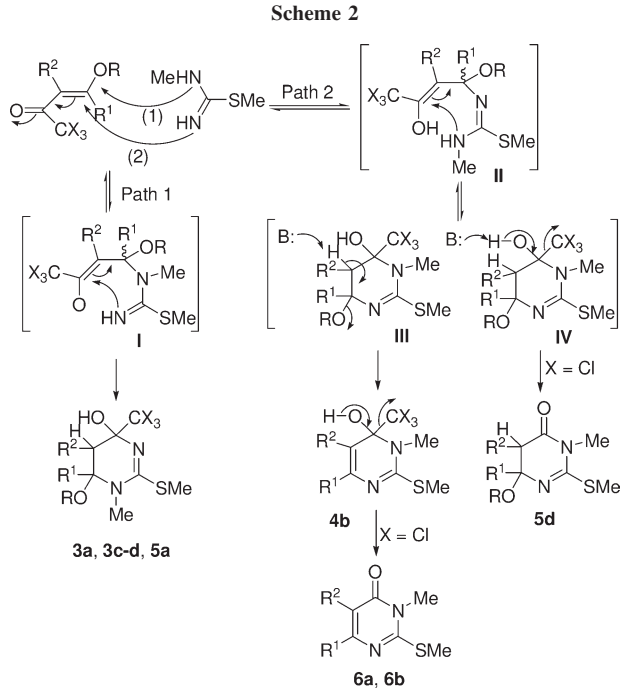


Figure 2. Structure of compounds **3a** and **3a′**.

Scheme 2



bond, the carbonyl becomes activated for the addition of the second nitrogen furnishing the tetrahydropyrimidines **3a**, **3c–d**, and **5a**. When enones **1** and **2** were β-methyl substituted (R^1 = Me), they reacted with 1,2-dimethylisothiourea giving N^3-methyldihydropyrimidines **4b** and **6b**, probably due to a steric effect between the *N*-methyl group and β-methyl group of enones **1b** and **2b**. In addition, the formation of compounds **4b** and **6b** occurred with the elimination of the methoxy group because hemi-aminals from ketones are less stable than those from aldehydes. Enones **2** bearing a trichloromethyl group also furnished N^3-methylpyrimidines because of the easy elimination of the trichloromethyl group under basic conditions [13].

In summary, from these results it can be concluded that steric and electronic effects determined the position of the methyl group at the N^1– *versus* N^3–positions of the pyrimidine ring according to the following observations: when R^1 = H, N^1–methyltetrahydropyrimidines were the only regioisomer isolated (**3a**, **3c–d**, **5a**, and **5d**). This is because hemi-aminals from aldehydes are more stable than those from ketones. An exception to this rule was observed when X = Cl. In this case, due to the facile elimination of the CCl_3 group under basic conditions only N^3–methylpyrimidinones **6a**, **6b**, and **5d** were obtained. We speculate that a steric effect between the *N*–methyl group and β-methyl group of the enones **1b** was responsible for the formation of compounds **4b**, where N^3–methyldihydropyrimidines were obtained.

EXPERIMENTAL

The 1,1,1-trihalo-4-alkoxy-3-alken-2-ones (**1**, **2**) were prepared according to ref. [20]. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. IR spectra were measured on a Bruker IFS 28 spectrophotometer on KBr pellets. Elemental analysis was performed on a Vario EL Elementar Analysensysteme. 1H, 13C, and 2D NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) in $CDCl_3$ or DMSO-d_6, using TMS as the internal reference.

General procedure for the synthesis of *N*-methyl-2-methylthio-pyrimidines (3–6). A solution of 1.0 *M* sodium hydroxide (7.5 mL, 7.5 mmol) and 1,2-dimethylisothiourea sulfate (1.14 g, 7.5 mmoles) was added drop wise under vigorous magnetic stirring to the enones **1a–d, 2a–d** (5.0 mmoles). The mixture was stirred for a period of time and temperature specified at Table 1 and extracted with chloroform (3 × 15 mL). The organic layer was dried under anhydrous sodium carbonate, filtered, and the solvent evaporated. Products were purified by recrystallizations and the solvent used for the purification is reported for each compound together with the melting point.

6-Ethoxy-1-methyl-2-(methylthio)-4-(trifluoromethyl)-1,4,5,6-tetrahydro-pyrimidin-4-ol (3a, 3a′). This compound was obtained as an orange powder in 77% yield, mp 68°C (hexane/ethyl acetate, 9:1). **3a**: ^{1}H NMR: δ 1.24 (t, 3H, *J* = 7.0 Hz, CH_3), 2.02 (dd, 1H, *J* = 14.0, 3.6 Hz, H–5), 2.37 (s, 3H, S-CH_3), 2.47 (dd, 1H, *J* = 14.0, 3.0 Hz, H–5), 3.04 (s, 1H OH), 3.14 (s, 3H, *N*–CH_3), 3.62 (qua, 2H, *J* = 7.0 Hz, CH_2), 4.62 (dd, 1H, *J* = 3.6, 3.0 Hz, H–6); ^{13}C NMR: δ = 13.7 (S–CH_3), 15.0 (CH_3), 30.1 (C–5), 37.6 (*N*–CH_3), 64.2 (CH_2), 80.3 (q, $J_{C\text{-}F}$ = 31.0 Hz, C–4), 86.4 (C–6), 123.7 (q, $J_{C\text{-}F}$ = 283.2 Hz, CF_3), 160.1 (C–2). **3a′**: ^{1}H NMR: δ 1.24 (t, 3H, *J* = 7.0 Hz, H–8), 2.03 (dd, 1H, *J* = 13.8, 9.0 Hz, H–5), 2.15 (s, 1H OH), 2.33 (s, 3H, S–CH_3), 2.40 (dd, 1H, *J* = 13.8, 0.8 Hz, H–5), 2.98 (s, 3H, *N*–CH_3), 3.70 (q, 2H, *J* = 7.0 Hz, CH_2), 4.39 (dd, 1H, *J* = 9.6, 0.8 Hz, H–6); ^{13}C NMR: δ 14.5 (S–CH_3), 15.0 (CH_3), 30.8 (C–5), 32.1 (*N*–CH_3), 64.2 (CH_2), 80.5 (q, $J_{C\text{-}F}$ = 31.0 Hz, C–4), 83.7 (C–6), 123.9 (q, $J_{C\text{-}F}$ = 284.0 Hz, CF_3), 158.4 (C–2). Anal. Calcd. for $C_9H_{15}O_2N_2F_3S$ (272.29): C, 39.70; H, 5.55; N, 10.29 Found: C, 39.28; H, 5.23; N, 10.02.

1-Methyl-2-(methylthio)-4-(trifluoromethyl)-1,4,4a,5,6,7a-hexahydrofuro-[2,3-d]pyrimidin-4-ol (3c). This compound was obtained as a white powder in 64% yield, mp 82–86°C (hexane); ^{1}H NMR: δ 2.06–2.11 (m, 2H, H–4a, H–5), 2.15–2.24 (m, 2H, H–5), 2.37 (s, 3H, S–CH_3), 2.89 (s, 1H, OH), 3.01 (s, 3H, *N*–CH_3), 4.13 (dd, 2H, *J* = 9.0, 5.0 Hz, H–6), 4.49 (d, 1H, *J* = 8.8 Hz, H–7a); ^{13}C NMR: δ 14.6 (S–CH_3), 23.9 (C–5), 32.2 (*N*–CH_3), 44.4 (C–4a), 68.3 (C–6), 82.4 (q, $J_{C\text{-}F}$ = 30.8 Hz, C–4), 86.3 (C–7a), 124.4 (q, $J_{C\text{-}F}$ = 283.0 Hz, CF_3), 163.6 (C–2). Anal. Calcd. for $C_9H_{13}O_2N_2F_3S$ (270.27): C, 40.00; H, 4.85; N, 10.36. Found: C, 39.92; H, 4.94; N, 10.50.

1-Methyl-2-(methylthio)-4-(trifluoromethyl)-1,4a,5,6,7,8a-hexahydro-1H-pyrano[2,3-d]pyrimidin-4-ol (3d). This compound was obtained as a white powder in 60%, yield, mp 158–161°C (hexane); ^{1}H NMR: δ 1.51–1.65 (m, 4H, H–4a, H–5, H–6), 1.85 (br s, 1H, H–5), 2.28 (s, 3H, S–CH_3), 2.86 (s, 3H, *N*–CH_3), 3.48 (m, 1H, H–7), 3.95 (m, 1H, H–7), 4.25 (d, 1H, *J* = 13.2 Hz, H–8a), 6.38 (s, 1H, OH); ^{13}C NMR: δ 13.8 (S–CH_3), 22.8 (C–5), 25.2 (C–6), 32.1 (*N*–CH_3), 40.9 (C–4a), 66.6 (C–7), 82.4 (q, $J_{C\text{-}F}$ = 29.0 Hz, C–4), 86.1 (C–8a),125.9 (q, $J_{C\text{-}F}$ = 286.0 Hz, CF_3), 155.1 (C–2). Anal. Calcd. for $C_{10}H_{15}O_2N_2F_3S$ (284.30): C, 42.25; H, 5.32; N, 9.85. Found: C, 42.34; H, 5.27; N, 9.86.

6-Ethoxy-1-methyl-2-(methylthio)-4-(trichloromethyl)-1,4,5,6-tetrahydropyrimidin-4-ol (4a, 4a′). This compound was obtained as a brown powder in 58% yield, mp 105–106°C (hexane), Ir: ν(cm^{-1}) 3440, 2998, 1678. **4a**: ^{1}H NMR: δ 1.25 (t, 3H, *J* = 7.0 Hz, CH_3), 2.40 (s, 3H, S–CH_3), 2.41 (dd, 1H, *J* = 14.0, 3.6 Hz, H–5), 2.74 (dd, 1H, *J* = 14.0, 2.4 Hz, H–5), 3.16 (s, 3H, *N*–CH_3), 3.21 (s, 1H, OH), 3.62 (qua, 2H, *J* = 7.0 Hz, CH_2), 4.63 (dd, 1H, *J* = 3.6, 2.4 Hz, H–6); ^{13}C NMR: δ 13.8 (S–CH_3), 14.9 (CH_3), 31.3 (C–5), 37.4 (*N*–CH_3), 64.2 (CH_2), 86.9 (C–6), 87.0 (C–4), 107.1 (CCl_3), 161.9 (C–2). **4a′**: ^{1}H NMR: δ 1.26 (t, 3H, *J* = 7.0 Hz, CH_3), 2.35 (s, 3H, S–CH_3), 2.41 (dd, 1H, *J* = 13.0, 10.0 Hz, H–5), 2.43 (s, 1H, OH), 2.67 (dd, 1H, *J* = 13.0, 5.2 Hz, H–5), 2.98 (s, 3H, *N*–CH_3), 3.60 (qua, 2H, *J* = 7.0 Hz, CH_2), 4.68 (dd, 1H, *J* = 10.0, 5.2 Hz, H–6); ^{13}C NMR: δ 14.31 (S–CH_3), 15.04 (CH_3), 31.52 (*N*–CH_3), 31.7 (C–5), 62.9 (CH_2), 85.0 (C–6), 88.8 (C–4), 108.2 (CCl_3), 163.7 (C–2). Anal. Calcd. for $C_9H_{15}O_2N_2Cl_3S$ (321.65): C, 33.61; H, 4.70; N, 8.71. Found: C, 33.30; H, 4.49; N, 8.39.

3,6-Dimethyl-2-(methylthio)-4-(trifluoromethyl)-3,4-dihydropyrimidin-4-ol (4b). This compound was obtained as dark yellow powder in 98% yield, mp 58–60°C (hexane/ethyl acetate, 9:1); Ir: ν(cm^{-1}) 3432, 1684. ^{1}H NMR: δ 1.85 (d, 3H, *J* = 1.6 Hz, CH_3), 2.37 (s, 3H, S–CH_3), 3.15 (qua, 3H, $J_{H\text{-}F}$ = 1.6 Hz,

N–CH_3), 3.15–3.16 (s, 1H, OH, underneath to *N*–CH_3), 4.82 (m, 1H, H–5); ^{13}C NMR: δ 14.5 (S–CH_3), 22.9 (CH_3), 30.45 (q, $J_{C\text{-}F}$ = 2.1 Hz, *N*–CH_3), 84.5 (q, $J_{C\text{-}F}$ = 31.8 Hz, C–4), 96.8 (C–5), 124.6 (q, $J_{C\text{-}F}$ = 288.0 Hz, CF_3), 147.2 (C–6), 160.3 (C–2). Anal. Calcd. for $C_8H_{11}ON_2F_3S$ (240.25): C, 39.99; H, 4.61; N, 11.66. Found: C, 39.59; H, 4.41; N, 11.59.

3-Methyl-2-(methylthio)pyrimidin-4(3H)-one (6a). This compound was obtained as light yellow powder in 92% yield, mp 113–115°C (hexane); ^{1}H NMR: δ 2.57 (s, 3H, S–CH_3), 3.51 (s, 3H, *N*–CH_3), 6.19 (d, 1H, *J* = 6.0 Hz, H–5), 7.76 (d, 1H, *J* = 6.4 Hz, H–6); ^{13}C NMR: δ 15.0 (S–CH_3), 30.2 (*N*–CH_3), 109.8 (C–5), 151.7 (C–6), 162.0 (C–4), 163.7 (C–2). Anal. Calcd. for $C_6H_8ON_2S$ (156.20): C, 48.32; H, 5.69; N, 18.79. Found: C, 48.12; H, 5.50; N, 18.52.

3,6-Dimethyl-2-(methylthio)pyrimidin-4(3H)-one (6b). This compound was obtained as yellow powder in 95% yield, mp 83–85°C (hexane); ^{1}H NMR: δ 2.22 (CH_3), 2.57 (s, 3H, S–CH_3), 3.48 (s, 3H, *N*–CH_3), 6.05 (d, 1H, H–5); ^{13}C NMR: δ 14.9 (S–CH_3), 23.6 (CH_3), 29.8 (*N*–CH_3), 107.2 (C–5), 161.8 (C–6), 162.2 (C–2), 162,3 (C–4). Anal. Calcd. for $C_7H_{10}ON_2S$ (170.23): C, 49.39; H, 5.92; N, 16.46. Found: C, 49.51; H, 5.67; N, 16.38.

3-Methyl-2-(methylthio)-1,4a,5,6,7,8a-hexahydro-4H-pyrano-[2,3-d]pyrimidin-4-one (5d). This compound was obtained as white powder in 70% yield, mp 85–86°C (hexane/ethyl acetate, 9:1); ^{1}H NMR: δ 1.45–1.56 (m, 1H, H–5), 1.66–1.73 (m, 2H, H–6), 2.20 (dd, 1H, *J* = 12.0, 4.0 Hz, H–4a), 2.32–2.40 (m, 1H, H–5), 2.45 (s, 3H, S–CH_3), 3.21 (s, 3H, *N*–CH_3), 3.50–3.60 (m, 1H, H–7), 4.10–4.16 (m, 1H, H–7), 4.52 (d, 1H, *J* = 12.0 Hz, H–8a); ^{13}C NMR: δ 142 (S–CH_3), 22.7 (C–5), 24.8 (C–6), 29.1 (*N*–CH_3), 42.3 (C–4a), 67.1 (C–7), 88.7 (C–8a), 155.1 (C–2), 170.4 (C–4). Anal. Calcd. for $C_9H_{14}O_2N_2S$ (214.28): C, 50.45; H, 6.59; N, 13.07. Found: C, 50.27; H, 6.43; N, 13.25.

Acknowledgments. The authors thank the financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico Universal (CNPq), grant No. 476634/06-7 and fellowships from CAPES (C. C. Madruga, L. S. da Rosa, F. M. da Silva).

REFERENCES AND NOTES

[1] (a) Amblard, F.; Nolan, S. P.; Schinazi, R. F.; Agrofoglio, L. A. Tetrahedron 2005, 61, 537; (b) Maruenda, H.; Johnson, F. J Med Chem 1995, 38, 2145; (c) Faul, M. M.; Huff, B. E.; Dunlap, S. E.; Frank, S. A.; Fritz, J. E.; Kaldor, S. W.; Le-Torneau, M. E.; Staszak, M. A.; Ward, J. A.; Werner, J. A.; Winneroski, L. L. Tetrahedron 1997, 53, 8085; (d) Bronson, J.; Ghazzouli, J. I.; Hitchcock, M. J. M.; Webb, R. R.; Martin, J C. J Med Chem 1989, 32, 1457.

[2] Hattori, H.; Nozawa, E.; Iino, T.; Yoshimura, Y.; Shuto, S.; Shimamoto, Y.; Nomura, M.; Fukushima, M.; Tanaka, M.; Sasaki, T.; Matsuda, A. J Med Chem 1998, 41, 2892.

[3] Senda, S.; Hirota, K.; Banno, K. J Med Chem 1972, 15, 471.

[4] (a) Tice, C. M.; Bryman, L.; Roemmele, M. R. C. Eur. Pat. 733622 (1994); (b) Tice, C. M.; Bryman, L.; Roemmele, M. R. C. Chem Abstr 1996, 125, 275903s; (c) Tice, C. M. (1994) U.S. Pat. 5300477; (d) Tice, C. M. Chem Abstr 1994, 122, 31543w.

[5] Wong, J. L.; Fuchs, D. S. J Org Chem 1971, 36, 848.

[6] (a) Danel, K.; Larsen, E.; Pedersen, B. E.; Vestergaard, B. F.; Nielsen, C. J Med Chem 1996, 39, 2427; (b) Jane, D. E.; Hoo, K.; Kamboj, R.; Deverill, M.; Bleakman, D.; Mandelzys, A. J Med Chem 1997, 40, 3645; (c) Ogilvie, K. K.; Beaucage, S. L. Tetrahedron Lett 1978, 19, 1663.

[7] Yamauchi, K.; Kinoshita, M. J Chem Soc Perkin Trans 1 1973, 391.

[8] Pacholski, I. L.; Blanco, I.; Martins, M. A. P.; Zanatta, N. J Braz Chem Soc 1991, 2, 118.

[9] Zanatta, N.; Faoro, D.; Fernandes, L. da, S.; Brondani, P. B.; Flores, D. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. Eur J Org Chem. 2008, 5832.

[10] Zanatta, N.; Madruga, C. C.; Marisco, P. C.; Flores, D. C.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 2000, 37, 1213.

[11] Zanatta, N.; Madruga, C. C.; Marisco, P. C.; da Rosa, L. S.; Fernandes, L. da S. Flores, D. C.; Flores, A. F. C.; Burrow, R. A.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 2008, 45, 221.

[12] Zanatta, N.; Madruga, C. C.; Clerice, E.; Martins, M. A. P. J Heterocycl Chem 1995, 32, 735.

[13] (a) Zanatta, N.; da Silva, F. M.; da Rosa, L. S.; Jank, L.; Bonacorso, H. G.; Martins, M. A. P.Tetrahedron Lett 2007, 48, 6531. (b) Bonacorso, H. G.; Lourega, R. V.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 2007, 48, 4835; (c) Zanatta, N.; Amaral, S. S.; Esteves-Souza, A.; Echevarria, A.; Brondani, P. B.; Flores, D. C.; Bonacorso, H. G.; Flores, A. F. C.; Martins, M. A. P. Synthesis 2006, 2305; (d) Zanatta, N.; Lopes, E. C. S.; Fantinel, L.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 2002, 39, 943; (e) Bonacorso, H. G.; Lourega, R. V.; Wastowski, A. D.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 9315; (f) Flores, A. F. C.; Zanatta, N.; Rosa, A.; Brondani, S.; Martins, M. A. P. Tetrahedron Lett 2002, 43, 5005; (g) Zanatta, N.; Cortelini, M. F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. J Heterocycl Chem 1997, 34, 509.

[14] Cechin, S. R.; Schetinger, M. R. C.; Zanatta, N.; Madruga, C. C.; Pacholski, I. L.; Flores, D. C.; Bonacorso, H. G.; Martins, M. A. P.; Morsch, V. M. Chem Res Toxicol 2003, 16, 1433.

[15] Nagayama, K; Kumar, A.; Wüthrich, K.; Ernst, R. R. J Magn Reson 1980, 40, 321.

[16] Wagner, G.; Wüthrich, K. J Mol Biol 1982, 155, 347.

[17] Bax, A.; Subramanian, S. J Magn Reson 1986, 67, 565.

[18] Bax, A.; Summers, M. F. J Am Chem Soc 1986, 108, 2093.

[19] Saloutin, V. I.; Burgart, Ya. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin, O. N. J Fluor Chem 2000, 103, 17–23.

[20] Colla, A.; Martins, M. A. P.; Clar, G.; Krimmer, S.; Fischer, P. Synthesis 1991, 483.