# Synthesis and Structural Study of a New Series of 2-Methylsulfanyl-Tetrahydropyrimidines from β-Alkoxyvinyl Trihalomethyl Ketones



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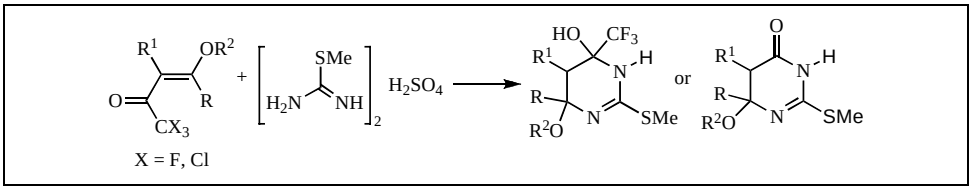


This work describes the synthesis of a novel series of 2-methylsulfanyl-tetrahydropyrimidines, from the cyclocondensation reaction of β-alkoxyvinyl trihalomethyl ketones with 2-methyl-2-thiopseudourea sulfate, in good yields. A detailed $^{1}$H- and $^{13}$C-NMR study was performed on the 2-methylsulfanyl-tetrahydropyrimidines obtained and 3D structures were proposed based on AM1 calculations supported by $^{1}$H NMR coupling constants and NOESY experiments.

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## INTRODUCTION

Tetrahydropyrimidines are relatively rarely reported compounds, when compared with aromatic pyrimidines, mainly due to the fact that their attainment depends on special synthetic strategies as well as specific substituents that can stabilize their partially saturated structures. Strategies that have been developed to obtain the tetrahydropyrimidine ring include: *i*) dialkylation of both nitrogen atoms of the pyrimidine ring [1] or one of the backbone carbons [2], *ii*) reduction of the parent pyrimidine [3], *iii*) condensation of 1,5-diamines with cyanogen bromide or aldehydes [4-7], *iv*) reaction of α,β-unsaturated carbonyl compounds or acrylates with dinucleophiles of the N-C-N type [8-12], and *v*) addition reactions to pyrimidines [13-15]. An interesting method, based on a triad of reaction components such as 3-oxo esters, 1,3-diketones or β-alkoxyvinyl trichloromethyl ketones with benzaldehyde and (thio)urea, resulting in the formation of a series of 4-fluoroalkyl [16] and 4-trichloromethyl [17] substituted tetrahydropyrimidines, has been reported. Another method that appeared recently in the literature for the preparation of 4-trifluoromethyl substituted tetrahydropyrimidines consists of the cyclo-condensation of β-alkoxyvinyl trifluoromethyl ketones with acetamidine- and benzamidine-hydrochloride in the presence of a base. [18] Although many reactions of β-alkoxyvinyl trihalomethyl ketones with dinuclephiles of the N-C-N type have been reported, [19] only acetamidine- and benzamidine-hydrochloride and 2-methyl-2-thiopseudourea sulfate, whose synthesis is reported in this work, have been known to furnish tetra-hydropyrimidines.

Tetrahydropyrimidines have been shown to possess a diverse range of biological activities including antiviral (with activity against viruses of the trachoma group), antibacterial, antitumor (found against Walker carci-nosarcoma in rats and mice), antiinflammatory, analgesic, antihypertensive, calcium channel blocker, and blood platelet aggregation inhibitory activity [20].

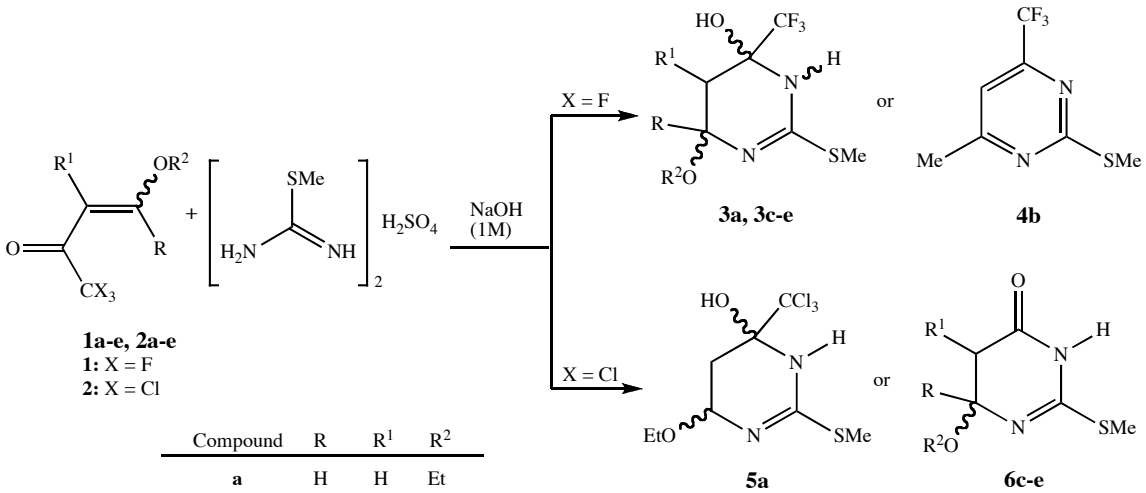
In light of the relatively few methods available to obtain stable tetrahydropyrimidines and the possible biological significance of these compounds, we wish to report the synthesis and structural study of a new series of tetrahydropyrimidines obtained from the cyclocondensation reaction of enones **1a**-**e**, **2a**-**e** with 2-methyl-2-thiopseudourea sulfate in the presence of base (Scheme 1). The utility of β-alkoxyvinyl trihalomethyl ketones (enones) as potential building blocks for the synthesis of many heterocyclic systems such as isoxazoles [21], pyrazoles [22], pyrimidines [23], pyridines [24], pyrrolidinones [25], and diazepines [26] has been demonstrated in previous publications from our group. β-alkoxyvinyl trihalomethyl ketones have been successfully used to obtain several series of bi-heterocycles [27].

## SYNTHESIS OF COMPOUNDS

Scheme 1 outlines the reaction of enones **1a-e** with 2-methyl-2-thiopseudourea sulfate carried out in the presence of 1 *M* sodium hydroxide solution furnishing 6-alkoxy-4-hydroxy-4-trifluoromethyl-2-methylsulfanyl tetrahydropyrimidines **3a** and **3c-e**, in good yields. The reactions were carried out at room temperature under vigorous stirring. The course of the reactions was monitored by the formation of a precipitate, which

appears soon after the addition of the reactants, and the solid was collected by filtration, washed with distilled water, and dried in a desiccator. The reaction of ketone **1b** with 2-methyl-2-thiopseudourea sulfate in 1 *M* sodium hydroxide solution led to the corresponding tetrahydropyrimidine but the product was unstable and rapidly lost an alcohol and a water molecule to give the parent aromatic pyrimidine **4b**.

**Scheme 1.**




| Compound | R | $R^1$ | $R^2$ |
|---|---|---|---|
| **a** | H | H | Et |
| **b** | Me | H | Me |
| **c** | H | Me | Et |
| **d** | H | $(-CH_2-)_2$ | |
| **e** | H | $(-CH_2-)_2$ | |

The reaction of ketone **2a** with 2-methyl-2-thiopseudourea sulfate carried out in the presence of 1 *M* sodium hydroxide solution furnished a mixture of stereoisomers called 6-alkoxy-2-methylsulfanyl-4-trichloromethyl-tetrahydropyrimidin-4-ol (**5a** and **5a'**), in good yields. The cyclization reaction of ketones **2c-e** with 2-methyl-2-thiopseudourea sulfate showed the elimination of the trichloromethyl group furnishing tetrahydropyrimidines **6c-e** with a carbonyl group in the 4-position of the pyrimidine ring.

## NMR STUDY

All compounds were fully analyzed by $^1$H- and $^{13}$C-NMR as well as 2D-NMR experiments such as COSY H-H [28], NOESY [29], HMQC [30], and HMBC [31]. Figure 1 shows the atom numbering used for NMR assignment of compounds **3**, **5**, and **6**. Yields, selected physical, and $^1$H- and $^{13}$C-NMR spectral data are presented in the experimental part.

Compound **3a** showed $^1$H vicinal coupling constants of H-6 with H-5' and H-5 of 12.4 and 3.9 Hz, respectively (Figure 2). The coupling constant of 12.4 Hz indicates a *trans-diaxial* position for H-6 and H-5' and the coupling constant of 3.9 Hz indicates an *axial-equatorial* position for H-6 and H-5. Since the tetrahydropyrimidine is in a *half-chair like* form [32], these values indicate that the ethoxy group is in an *equatorial* position and the amino hydrogen is attached to the N-3, giving that since the coupling between H-6 and the N-H was not observed. Figure 2 shows the structure of **3a** proposed from the observed $^1$H NMR coupling constants.

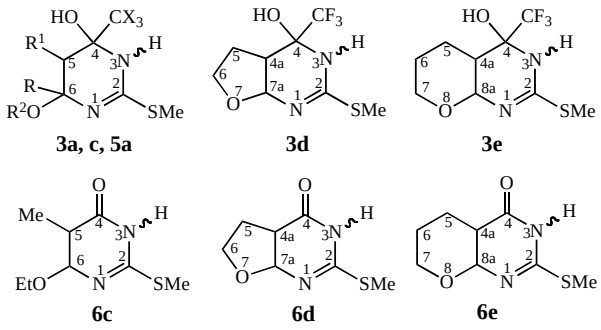



**Figure 1**. Structure of compounds **3**, **5**, and **6** showing the atom numbering used for the NMR assignment.

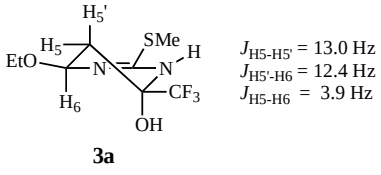



**Figure 2.** Structure of **3a** proposed from the observed $^1$H NMR coupling constants.

Compound **3c** showed two sets of signals in the NMR spectra registered in $CDCl_3$ at a ratio of approximately 60:40% (determined by $^1$H-NMR integrals) which were designated as **3c** and **3c'**, respectively. The major compound **3c** showed a vicinal coupling constant of H-6 with H-5 of 8.4 Hz, which indicates a *trans-diaxial* position for these two hydrogens and, consequently, both 5-Me and 6-OEt substituents occupy *equatorial* positions. Compound **3c'** showed a vicinal coupling constant between H-6 and H-5 of 2.0 Hz, which indicates an *axial-equatorial* position for H-6 and H-5. Therefore, the substituent of either C-5 or C-6 is *equatorial* and the other is *axial*. AM1 energy minimization showed that the isomer with the ethoxy group in the *axial* position and the methyl group in the *equatorial* position is 0.13 Kcal/mol more stable than when the ethoxy group is *equatorial* and the methyl group is *axial*. The amino hydrogen is attached to the N-3 because a coupling constant between H-6 and the N-H was not observed in either **3c** or **3c'**.

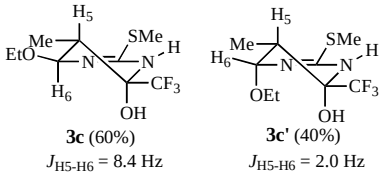



**Figure 3.** Structure of compounds **3c** and **3c'** proposed from the observed $^1$H NMR coupling constants.

Compound **3d** has three asymmetric carbons but it showed only one set of signals in both $^1$H- and $^{13}$C-NMR spectra indicating that the reaction was highly stereoselective. The observation of a strong cross peak between H-4a and H-7a in the NOESY experiment indicates that these hydrogens are close in space, suggesting that the furopyrimidine ring closure was accomplished with *cis* configuration. The most probable structure for **3d** presents the furopyrimidine rings in *cis* configuration, the $CF_3$ group in *pseudo-equatorial* positions *cis* to H-4a and *trans* to C-5, and the amino hydrogen bound to N-3, since no coupling between the NH-3 and H-7a was observed. Compound **3e** also has three asymmetric carbons but it showed only one set of signals in both $^1$H- and $^{13}$C-NMR spectra indicating that the reaction was also highly stereoselective. The coupling constant between H-4a and H-8a of 9.2 Hz indicates a *trans-diaxial* position for these two hydrogens and, consequently, that the pyrano-pyrimidine ring closure occurred with *trans* configuration. The lack of a coupling constant between H-8a and the N-H suggests that this hydrogen is bound to the N-3.

Compound **5a** was obtained as a mixture of 2 stereoisomers (**5a** and **5a'**) at a ratio of 54:46%, respectively. The coupling constants of H-6 with H-5 and H-5' show that the structure of the major isomer **5a** bears the 6-ethoxy group in an *equatorial* position and the amino hydrogen bound to the N-3, while the structure of the minor isomer **5a'** presents the 6-ethoxy group in an *axial* position and the amino hydrogen also bound to the N-3. This structure is supported by $^1$H-NMR coupling constants as shown in Figure 4.

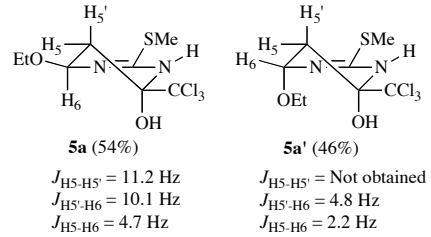



**Figure 4.** Structure of compounds **5a** and **5a'** proposed from the observed $^1$H NMR coupling constants.

Compound **6c** shows an $^1$H NMR coupling constant between H-6 and H-5 of 10 Hz indicating a *trans-diaxial* position for these atoms and, consequently, both 5-methyl and 6-ethoxy groups are in *equatorial* positions. A simple doublet observed for H-6 indicates that the N-H is bound to the N-3.

Compounds **6d**, and **6e** have the pyrimidine ring fused with a tetrahydrofuran and a hexahydropyran, respectively. Both products were isolated as single compounds. From the $^1$H NMR coupling constants we concluded that compound **6d** has the furopyrimidine rings fused in *cis* configuration and **6e** has the pyrano-pyrimidine rings fused in *trans* configuration, as described for compounds **3d** and **3e**, respectively.

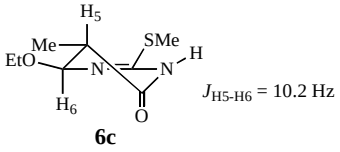
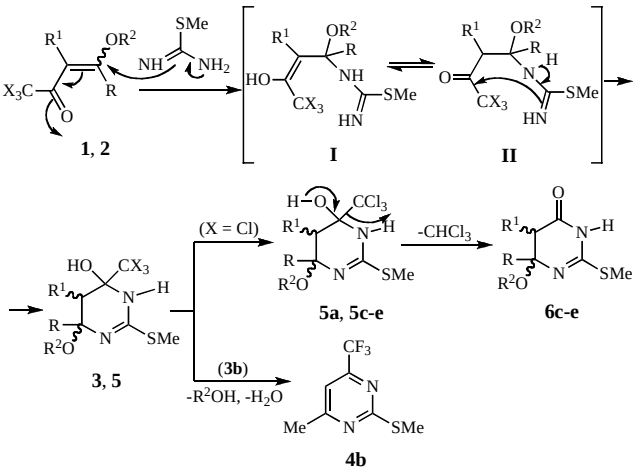



**Figure 5.** Structure of **6c** proposed from the observed $^1$H NMR coupling constants.

The mechanism of formation of 2-methylsulfanyl-tetrahydropyrimidines **3**, **5**, and **6** probably entails the addition of a nitrogen atom from 2-methyl-2-thiopseudourea to the β-carbon of the β-alkoxyvinyl ketones **1** and **2** furnishing the structure **I**, Scheme 2 that is a tautomer of the structure **II**. Once the addition on the C-C double was carried out (slow reaction step), the carbonyl becomes activated for the addition of the second nitrogen of the 2-methyl-2-thiopseudourea, which should be the fast reaction step, furnishing the tetrahydro-pyrimidines **3** and **5**. It is has been reported that the

trichloromethyl group is a good leaving group [33] and under basic medium is eliminated to give the 2-methylsulfanyl-5,6-dihydro-3*H*-pyrimidin-4-ones **6c-e**. When there is a methyl group besides than a methoxy group attached to the C-6, both the methoxy and the hydroxy groups are in the *axial*-position, which is the favorable conformation for the elimination of these groups under basic reaction condition. Thus, compound **3b** was not stable and the fully aromatic pyrimidine **4b** was isolated.

**Scheme 2.** Reaction mechanism




## STRUCTURAL CONSIDERATIONS

Structural energy minimization based on the Austin Model 1 (AM1) was performed in order to better understand the three dimensional structure of the tetrahydropyrimidines obtained in this work. The starting structure layout for the energy minimization was provided by detailed $^1$H-NMR studies based on hydrogen coupling constant measurements and NOESY experiments. Single crystal x-ray diffraction was not performed because the obtained compounds were either powders or they formed inadequate crystals for this measurement. The AM1 program used was based on previous experiments where a good fit was observed between single crystal X-ray diffraction and AM1 data of a series of structure related heterocycles [22b,34-36]. The 3D structure of selected compounds, calculated by AM1, can be obtained from the authors, under request.

The minimized energy of compounds **3a**, **3c-e**, **5a**, **5a'**, and **6c-e** are presented in Table 3 and selected torsion angles of selected compounds are presented in Tables 1 and 2. Bond angles for compounds **3a**, **3c-e**, **5a**, **5a'**, and **6c-e** can be obtained from the authors, under request.

The study shows that part of the pyrimidine ring defined by the N1-C2-N3 atoms is considerably planar since its bond angle is close to 127º for all tetrahydropyrimidines. The planarity of the N1-C2-N3 atoms of the pyrimidine ring is probably due to the double bond between N1 and C2. The atoms C4, C5, and C6 are out of the ring plane since their bond angles are close to 110º, almost a perfect tetrahedron. The bond angle of a six membered ring can only achieve this value upon distortion of the bond angle in a *chair-like* form. The bond angles of C4, C5, and C6 with their respective substituents are all close to 108º, which further suggests a distortion of this part of the ring in a *chair-like* conformation.

The torsion angles between C6-N1-C2-N3 ($\omega_{12}$) of close to 5° and between C4-N3-C2-N1 ($\omega_{23}$) of nearly 7° (average value) confirm that this part of the pyrimidine ring is reasonably planar. However, the torsion angle defined by C4-C5-C6-N1 ($\omega_{56}$) and C6-C5-C4-N3 ($\omega_{45}$) showing average values of 40º and 35º, respectively, suggest that this part of the ring is distorted in a *chair-like* form (Table 1).

The torsion angles defined by R1-C5-C4-$CX_3$ of 68º (average value excluding **3d**) and H5-C5-C4-$CX_3$ of 47º (average value) suggest that the CX3 group is in a *pseudo-equatorial* position. The torsion angles defined by the atoms H5-C5-C4-O4 (average 154º, excluding the 4-carbonyl compounds) and R1-C5-C4-O4 (average 35º, excluding the 4-carbonyl compounds) suggest that

**Table 1**

Torsion angles of tetrahydropyrimidine rings of selected compounds

| Compound[a] | Torsion Angles | | | | | |
|---|---|---|---|---|---|---|
| | $\omega_{12}$ | $\omega_{23}$ | $\omega_{34}$ | $\omega_{45}$ | $\omega_{56}$ | $\omega_{16}$ |
| **3a** | -6.08 | 10.98 | -30.60 | 44.23 | -40.23 | 21.67 |
| **3d** | -4.81 | 8.05 | 9.27 | -26.79 | 30.02 | -15.08 |
| **3e** | 2.63 | -13.91 | -9.45 | 38.28 | -49.78 | 30.38 |
| **6c** | -2.97 | -5.56 | -2.92 | 17.40 | -24.92 | 18.51 |
| **5a** | -6.13 | 10.82 | -31.20 | 46.15 | -40.53 | 23.01 |
| **5a'** | -4.64 | 11.19 | -26.32 | 35.17 | -29.92 | 14.73 |
| **6d** | -1.00 | -2.81 | -2.47 | 10.19 | -13.47 | 9.27 |
| **6e** | -2.71 | -11.10 | -6.64 | 33.18 | -46.09 | 31.70 |

[a] For compounds **3d** and **6d** the atoms C-4a and C-7a and for compounds **3e** and **6e** the atoms C-4a and C-8a were considered as C-5 and C-6, respectively.

**Table 2**

Torsion angles of the substituents of C4-C5 and C5-C6 of selected compounds.

| | Compounds[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Torsion Angles | **3a** | **3d** | **3e** | **5a** | **5a'** | **6c** | **6d** | **6e** |
| H5-C5-C4-O4 | 157 | 88 | 156 | 162 | 151 | 76 | -50 | 92 |
| H5-C5-C4-$CX_3$ | -75 | -25 | 42 | 74 | 35 | -- | --- | --- |
| H5-C5-C4-N3 | 165 | -147 | -80 | 165 | -86 | -102 | 131 | -84 |
| R2-C5-C4-O4 | 40 | -33 | 35 | 43 | 32 | -41 | 70 | -27 |
| R2-C5-C4-$CX_3$ | 43 | -146 | -79 | 45 | -84 | -- | --- | --- |
| R2-C5-C4-N3 | 77 | 92 | 159 | -75 | 156 | 141 | 109 | 156 |
| O4-C4-C5-C6 | -81 | -152 | -86 | -76 | -89 | -165 | -171 | -150 |
| $CX_3$-C4-C5-C6 | 165 | 95 | 160 | 167 | 156 | -- | --- | --- |
| H5-C5-C6-H6 | -159 | 25 | -171 | -160 | -28 | -146 | -10 | -169 |
| H5-C5-C6-O6 | -48 | -88 | -54 | -49 | -143 | -36 | 103 | -52 |
| H5-C5-C6-N1 | -160 | 150 | 67 | 79 | 92 | 93 | -133 | 70 |
| R2-C5-C6-H6 | -39 | 141 | -53 | -41 | 91 | 28 | -128 | -51 |
| R2-C5-C6-O6 | 71 | 28 | 65 | -70 | -25 | 82 | -15 | 66 |
| R2-C5-C6-N1 | -160 | -94 | -175 | -162 | -150 | -149 | 109 | -172 |
| H6-C6-C5-C4 | 81 | -95 | 72 | 78 | -149 | 96 | 110 | 75 |
| O6-C6-C5-C4 | -169 | 152 | -170 | -174 | 95 | -154 | -137 | -168 |

[a] For compounds **3d** and **6d** the atoms C-4a and C-7a and for compounds **3e** and **6e** the atoms C-4a and C-8a were considered as C-5 and C-6, respectively.

**Table 3**

Energy minimization (AM1) of tetrahydropyrimidines

| Compound | Heat of Formation[a] | Compound | Heat of Formation[a] | Compound | Heat of Formation[a] |
|---|---|---|---|---|---|
| **3a** | -228.46 | **3e** | -221.95 | **6c** | -67.07 |
| **3c** | -230.48 (91%) | **5a** | -85.25 (67%) | **6d** | -56.84 |
| **3c'** | -229.06 (9%) | **5a'** | -84.83 (33%) | **6e** | -59.80 |
| **3d** | -217.58 | | | | |

[a] Heat of formation in Kcal.mol$^{-1}$ (calculated percentage ratio of isomers).

the OH group occupies a *pseudo-axial* position since the $R^2$ was defined as the substituent of C5 in an *equatorial* position (Table 2). When both substituents on C5 are hydrogens, $R^2$ was defined as the hydrogen in an *equatorial* position.

In summary, this study presented the synthesis of a stable new series of tetrahydropyrimidines from 1,1,1-trihalo-4-alkoxy-3-alken-2-ones with 2-methyl-2-thio-pseudourea sulfate, in good yields. Most reactions showed high stereoselectivity furnishing a single isomer. Data from $^1$H NMR coupling constants and NOESY experiments allowed for the attainment of reliable information about the structure of the tetrahydropyrimidines. 3D structures of tetrahydro-pyrimidines were obtained from AM1 calculations using structural information derived from the NMR experiments and the composition of isomers (e.g. 3c and 3c', and 5a and 5a') calculated with AM1 followed the same trend of the population of isomers determined by $^1$H NMR integrals

## EXPERIMENTAL

The 1,1,1-trihalo-4-alkoxy-3-alken-2-ones (**1**, **2**) were prepared according to reference [37]. 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. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a pentium PC. The GC was equipped with a split-splitless injector, autosampler, cross-linked HP-5 capillary column (30m, 0.32mm of internal diameter), and helium was used as the carrier gas. $^1$H- and $^{13}$C-NMR spectra were acquired on a Bruker DPX 400 spectrometer ($^1$H at 400.13 MHz and $^{13}$C at 100.62 MHz) in DMSO-$d_6$ or $CDCl_3$, using TMS as the internal reference.

**AM1 calculations.** The calculations were carried out by the Austin Model 1 (AM1) semiempirical method [38], implemented in the CS MOPAC 97 package [39]. Geometries were completely optimized without fixing any parameter, thus bringing all geometric variables to their equilibrium values. The energy minimization protocol employs the Eigenvector

Following routine, a conjugated gradient method. Convergence to a local minimum is achieved when the energy gradient is ≤ 0.01 kcal.mol$^{-1}$. The calculations were performed on a PC Pentium III-550MHz .

**General Procedure for the Preparation of 6-Alkoxy-2-methylsulfanyl-4-trifluoro [chloro]methyl-tetrahydropyrimidin-4-ol (3a, 3c-e, 5a) and 6-Alkoxy-2-methylsulfanyl-tetrahydropyrimidin-4-ones (6c-e).** General Procedure: To a solution of **1a-e** or **2a-e** (5.0 mmol) and 2-methyl-2-thiopseudourea sulfate (1.04 g, 7.5 mmol) in distilled water (3 mL) a solution of sodium hydroxide (0.3 g in 7.5 mL of distilled water, 7.5 mmol) was added dropwise under vigorous magnetic stirring. During the course of the reaction (from 15 minutes to 4 hours) a white solid precipitated and it was collected by filtration, washed with distilled water, dried, and recrystallized (chloroform/methanol) to give **3a, 3c-e**, **4b**, and **5a**, **6c-e**.

**6-Ethoxy-2-methylsulfanyl-4-trifluoromethyl-3,4,5,6-tetrahydro-pyrimidin-4-ol (3a).** This compound was obtained as a white powder in 87% yield; Mp. 120-121 °C; IR (KBr) 3687, 3412, 1600; $^1$H NMR ($CDCl_3$): δ = 5.26 (br s, 2 H, NH, OH), 4.51 (dd, 1 H, $^3J_{H6\text{-}H5'}$ = 12.4, $^3J_{H6\text{-}H5}$ = 3.9, H-6), 3.73 (m, 2 H, -$OCH_2$-), 2.28 (dd, 1 H, $^3J_{H5\text{-}H5'}$ = 13.0, $^3J_{H5'\text{-}H6}$ = 12.4, H-5'), 1.81 (dd, 1 H, $^3J_{H5\text{-}H5'}$ = 13.0, $^3J_{H5\text{-}H6}$ = 3.9, H-5), 1.25 (t, 3 H, *J* = 7.0, -$OCCH_3$); $^{13}$C NMR ($CDCl_3$): δ = 161.35 (C-2), 124.28 (q, $^1J_{CF}$ = 284.7, $CF_3$), 81.69 (q, $^2J_{CF}$ = 31.1, C-4), 77.21 (C-6), 51.99 (-$OCH_2$-), 31.01 (C-5), 13.26 (-$OCCH_3$), 10.89 (-SMe); MS: *m/z* (%) 258 ($M^+$, 26), 243 (18), 229 (69), 213 (41), 189 (98), 140 (68), 99 (100), 71 (84). *Anal.* Calcd. for $C_8H_{13}F_3N_2O_2S$ (258.26): C, 37.21; H, 5.07; N, 10.85%. Found: C, 37.21; H, 5.06; N, 10.79 %.

**6-Ethoxy-5-methyl-2-methylsulfanyl-4-trifluoromethyl-3,4,5,6-tetrahydropyrimidin-4-ol (3c).** This compound was obtained as a white powder in 47% yield. **3c** is comprised by two stereoisomers which were not possible to separate by recrystallization or column chromatography. The melting point, elemental analysis, and the spectral data were acquired from the mixture of isomers. Mp. 119-121 °C; IR (KBr) 3688, 3430, 1617; 3c: $^1$H NMR ($CDCl_3$): δ = 5.80 (br s, 2 H, NH, OH), 4.35 (d, 1 H, $^3J_{H6\text{-}H5}$ = 8.4, H-6), 3.78 – 3.73, 3.47 – 3.43 (m, 2 H, -$OCH_2$-), 2.44 (dq, 1 H, $^3J_{H5\text{-}CH3}$ = 7.2, $^3J_{H5\text{-}H6}$ = 8.4, H-5), 2.35 (s, 3 H, -SMe), 1.15 (t, 3 H, $^3J$ = 7.0, -$OCCH_3$), 0.92 (d, 3 H, $^3J_{CH3\text{-}H5}$ = 7.2, -$CH_3$); $^{13}$C NMR ($CDCl_3$) δ 155.53 (C-2), 121.85 (q, $^1J_{CF}$ = 283.5, -$CF_3$), 85.04 (C-6), 82.62 (q, $^2J_{CF}$ = 29.5, C-4), 62.95 (-$OCH_2$-), 34.30 (C-5) 14.53 (-$CH_3$), 12.67 (-SMe), 12.58 (-$OCCH_3$); 3c': $^1$H NMR ($CDCl_3$): δ = 5.80 (2 H, br s, NH, OH), 4.37 (1 H, d, $^3J_{H6\text{-}H5}$ = 2.0, H-6), 3.78 – 3.73, 3.60 – 3.58 (2 H, m, -$OCH_2$-), 2.39 (3 H, s, -SMe), 1.95 (1 H, dq, $^3J_{H5\text{-}CH3}$ = 7.2, $^3J_{H5\text{-}H6}$ = 2.0, H-5), 1.17 (3 H, t, $^3J$ = 7.0, -$OCCH_3$), 1.11 (3 H, d, $^3J_{CH3\text{-}H5}$ = 7.2, -$CH_3$); $^{13}$C NMR ($CDCl_3$): δ = 155.53 (C-2), 124.06 (q, $^1J_{CF}$ = 286.3, -$CF_3$), 84.84 (C-6), 82.57 (q, $^2J_{CF}$ = 33.4, C-4), 63.53 (-$OCH_2$-), 35.33 (C-5), 14.82 (-$CH_3$), 12.76 (-$OCCH_3$), 12.69 (-SMe); MS: *m/z* (%) 272 ($M^+$, 12), 257 (18), 243 (60), 227 (17), 203 (52), 187 (11), 154 (31), 113 (40), 99 (52), 86 (100), 74 (81). *Anal.* Calcd. for $C_9H_{15}F_3N_2O_2S$ (272.29): C, 39.70; H, 5.55; N, 10.29 %. Found: C, 39.95; H, 5.41; N, 10.23 %.

**2-Methylsulfanyl-4-trifluoromethyl-3,4,4a,5,6,7a-hexahydrofuro[2,3-*d*]pyrimidine-4-ol (3d).** This compound was obtained as a white powder in 66% yield; Mp. 100-104 °C; IR (KBr) 3787, 3392, 1598; $^1$H NMR (DMSO-$d_6$): δ = 8.00 (br s, 1 H, NH), 6.50 (br s, 1 H, OH), 4.55 (d, 1 H, $^3J_{H7a\text{-}H4a}$ = 12.0, H-7a), 3.60 – 3.40 (m, 2 H, H-6), 2.20 (s, 3 H, -SMe), 2.10 – 1.70 (m, 2 H, H-5), 1.68 – 1.50 (m, 1 H, H4a); $^{13}$C NMR (DMSO-$d_6$): δ = 153.10 (C-2), 124.00 (q, $^1J_{CF}$ = 288.0, -$CF_3$), 89.80 (C-7a), 80.50 (q, $^2J_{CF}$ = 30.30, C-4), 65.90 (C-6), 43.00 (C-4a), 22.50 (C-5), 12.40 (-SMe); MS: *m/z* (%) decomposed in the GC column. *Anal.* Calcd. for $C_8H_{11}N_2O_2F_3S$ (256.24): C, 37.50; H, 4.37; N, 10.93 %. Found: C, 37.72; H, 4.39; N, 11.13 %.

**2-Methylsulfanyl-4-trifluoromethyl-3,4a,5,6,7,8a-hexahydro-4*H*-pyran[2,3-*d*]pyri midin-4-ol (3e).** This compound was obtained as a white powder in 72% yield; Mp. 167-169 °C; IR (KBr) 3685, 3404, 1605; $^1$H NMR (DMSO-$d_6$): δ = 8.21 (br s, 1 H, NH), 6.35 (br s, 1 H, OH), 4.43 (d, 1 H, $^3J_{H8a\text{-}H4a}$ = 9.2, H-8a), 3.87, 3.47 (m, 2 H, H-7), 2.27 (s, 3 H, -SMe) 1.60 - 1.50 (m, 4 H, H-5, H-6), 1.46 (m, 1 H, H-4a); $^{13}$C NMR (DMSO-$d_6$): δ = 157.70 (C-2), 125.30 (q, $^1J_{CF}$ = 286.3, $CF_3$), 81.95 (C-8a), 81.95 (q, $^2J_{CF}$ = 30.0, C-4), 65.65 (C-7), 40.07 (C-4a), 25.02 (C-6), 21.98 (C-5), 12.22 (-SMe); MS: *m/z* (%) 270 ($M^+$, 27), 201 (78), 187 (42), 111 (100), 84 (86), 69 (57), 55 (55). *Anal.* Calcd. for $C_9H_{13}N_2O_2F_3S$ (270.27): C, 39.99; H, 4.85; N, 10.36 %. Found: C, 40.13; H, 4.87; N, 10.38 %.

**6-Methyl-2-methylsulfanyl-4-trifluoromethyl-pyrimidine (4b).** This compound was obtained as a yellow powder in 70% yield. Physical and spectral data was reported in reference 19a.

**6-Ethoxy-2-methylsulfanyl-4-trichloromethyl-3,4,5,6-tetrahydropyrimidin-4-ol (5a).** This compound was obtained in a mixture of stereoisomers as a white powder in 82% yield. The melting point, elemental analysis, and the spectral data were acquired from the mixture of isomers. Mp. 130-134 ºC; IR (KBr) 3688, 3431, 1615; **5a**: $^1$H NMR (DMSO-$d_6$): δ = 7.40 (br s, 1 H, NH), 7.00 (br s, 1 H, OH), 4.75 (dd, 1 H, $^3J_{H6\text{-}H5'}$ = 10.1, $^3J_{H6\text{-}H5}$ = 4.7, H-6), 3.57 – 3.51, 3.38 – 3.51 (m, 2 H, -$OCH_2$-), 2.30 – 2.50 (m, 1 H, H-5'), 2.33 (s, 3 H, -SMe) 1.84 (dd, 1 H, $^3J_{H5\text{-}H5'}$ = 11.2, $^3J_{H5\text{-}H6}$ = 4.7, H-5), 1.06 (t, 3 H, $^3J$ = 7.0, -$CH_3$); $^{13}$C NMR (DMSO-$d_6$): δ = 158.34 (C-2), 109.26 ($CCl_3$), 89.54 (C4), 80.62 (C-6), 63.00 (-$OCH_2$-), 33.39 (C-5), 15.22 (-$OCCH_3$), 12.32 (-SMe). **5a'**: $^1$H NMR (DMSO-$d_6$): δ = 8.51 (br s, 1 H, NH-3), 5.92 (br s, 1 H, OH), 4.68 (dd, 1 H, $^3J_{H6\text{-}H5\text{-}H5'}$ = 4.8, 2.2, H-6), 3.78 – 3.72, 3.57 – 3.51 (m, 2 H, -$OCH_2$-), 2.35 – 2.31 (m, 1 H, H-5'), 2.30 (s, 3 H, -SMe), 2.26 – 2.19 (m, 1 H, H-5), 1,14 (t, 3 H, $^3J$ = 7.0, -$CH_3$); $^{13}$C NMR (DMSO-$d_6$): δ = 156.83 (C-2), 109.57 ($CCl_3$), 87.34 (C-4), 77.29 (C-6), 62.00 (-$OCH_2$-), 31.67 (C-5), 14.99 (-$OCCH_3$), 12.03 (-SMe); MS: *m/z* (%) decomposed in the GC column. *Anal.* Calcd. for $C_8H_{13}N_2O_2Cl_3$ (275.56): C, 31.23; H, 4.26; N, 9.11 %. Found: C, 31.03; H, 4.22; N, 9.24%.

**6-Ethoxy-5-methyl-2-methylsulfanyl-5,6-dihydro-3*H*-pyrimidin-4-one (6c).** This compound was obtained as a yellow powder in 59% yield; Mp. 97-101 ºC; **6c**: $^1$H NMR ($CDCl_3$): δ = 7.40 (br s, 1 H, NH), 4.54 (d, 1 H, $^3J_{H6\text{-}H5}$ = 10.2, H-6), 4.20, 3.66 (q, 2 H, $^3J$ = 7.0, -$OCH_2$-), 2.66-2.37 (m, 1 H, H-5, superimposed with –$SCH_3$), 2.44 (s, 3 H, -SMe), 1.26 (d, 3 H, $^3J_{CH3\text{-}H5}$ = 7.0, -$CH_3$), 1,24 (t, 3 H, $^3J$ = 7.0, -$OCCH_3$); $^{13}$C NMR ($CDCl_3$): δ = 172.29 (C=O), 150.63 (C-2), 91.46 (C-6), 54.44 (-$OCH_2$-), 39.84 (C-5), 13.75 (-$CH_3$), 12.21 ($OCCH_3$), 10.14 (-SMe); MS: *m/z* (%) 202 ($M^+$, 9), 187 (93), 173 (100), 159 (18), 147 (20), 116 (35), 99 (49), 74 (52), 71 (69), 57 (19).

**2-Methylsulfanyl-3,4,4a,5,6,7a-hexahydrofuro[2,3-*d*]-pyrimidin-4-one (6d).** This compound was obtained as a white powder in 83% yield; Mp. 123-126 ºC; $^1$H NMR (DMSO-$d_6$): δ = 8.25 (br s, 1 H, NH), 4.70 (d, 1 H, $^3J_{H7a\text{-}H4a}$ = 12.0, H-7a), 3.95 (dd, 2 H, $^3J_{H6\text{-}H5\text{-}H5'}$ = 8.2, 6.1, H-6), 2.70 – 2.20 (m, 1 H, H-4a) 2.10 – 1.70 (m, 2 H, H-5), 2.30 (s, 3 H, -SMe); $^{13}$C NMR (DMSO-$d_6$): δ = 170.50 (C=O), 153.90 (C-2), 93.00 (C-7a), 66.20 (C-6), 44.70 (C-4a), 21.80 (C-5), 12.40 (-SMe); MS: *m/z* (%) 186 ($M^+$, 28), 168 (28), 156 (100), 107 (30), 82 (55). *Anal.*

Calcd. for $C_7H_{10}N_2O_2S$ (186.23): C, 45.15; H, 5.41; N, 15.04 %. Found: C, 45.09; H, 5.13; N, 14.75 %.

**2-Methylsulfanyl-3,4a,5,6,7,8a-hexahydro-4*H*-pyran[2,3-*d*]-pyrimidin-4-one (6e).** This compound was obtained as a white powder in 40% yield; mp 189-192 ºC; $^1$H NMR (DMSO-$d_6$): δ = 8.33 (br s, 1 H, NH), 4.41 (d, 1 H, $^3J_{H8a\text{-}H4a}$ = 9.2, H-8a), 3.90, 3.48 (m, 2 H, H-7), 2.30 (s, 3 H, -SMe), 1.92 (m, 1 H, H-4a), 1.69-1.60 (m, 2 H, H-5), 1.60 – 1.50 (m, 2 H, H-6); $^{13}$C NMR (DMSO-$d_6$): δ = 170.98 (C=O), 151.50 (C-2), 89.35 (C-8a), 65.79 (C-7), 42.05 (C-4a), 25.35 (C-5), 23.95 (C-6), 12.42 (-SMe); MS: *m/z* (%) 200 ($M^+$, 32), 185 (40), 172 (24), 143 (90), 98 (29), 55 (100). *Anal.* Calcd. for $C_8H_{12}N_2O_2S$ (200.26): C, 47.98; H, 6.04; N, 13.99 %. Found: C, 47.46; H, 5.87; N, 14.05 %.

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## REFERENCES

[1] Zhao, F. L.; Liu, J. T. *J. Fluorine Chem.* **2004**, *125*, 1491; [b] Prelli, L. R.; Garcia, M. B.; Perillo, I. A. *Heterocycles*, **2000**, ***53***, 2437.

[2] Habermeier, J.; Porret, D.; Baumann, D. *Ger. Offen.*, (1973); CA: 79:79781.

[3a] Baskaran, S.; Hanan, E.; Byun, D.; Shen, W. *Tetrahedron Lett.* **2004**, *45*, 2107; [b] Dunbar, P. G.; Durant, G. J.; Fang, Z.; Abuh, Y. F.; El-Assadi, A. A.; Ngur, D. O.; Periyasamy, S.; Hoss, W.; W. S. Messer Jr. *J. Med. Chem.* **1993**, *36*, 842.

[4] Russel, J. R.; Garner, C. D.; Joule J. A. *J. Chem. Soc., Perkim Trans.* **1992**, *1*, 409.

[5] Shu, K. S.; Negrete, G. R.; Konopelski, J. P.; Lakner, F. A.; Woo, N.–T.; Olmstead M. M. *J. Am. Chem. Soc.* **1992**, *114*, 1800.

[6] Barluenga, J.; Olano, B.; Fustero, S.; Foces-Foces, M.–C.; Cano F. H. *J. Chem. Soc. Chem. Commun.* **1980**, 410.

[7] Veeraraghavan, S.; Bhattacharjee, D.; Popp F. D. *J. Heterocycl. Chem.* **1981**, *18*, 443.

[8] Weis A. L. *Synthesis* **1985**, 528.

[9] Weis, A. L.; Zamir D. *J. Org. Chem.* **1987**, *52*, 3421.

[10] Wendelin, W.; Schermanz K. *J. Heterocycl. Chem.* **1984**, *21*, 65.

[11] Remennikov, G. Y.; Boldyrev, I. V.; Kravchenko, S. A.; V. V. Pirozhenko *Chem. Heterocyclic Comp.* **1993**, *29*, 1200.

[12] Schutalev, A. D.; Komarova, E. N.; Pagaev, M. T.; L. A. Ignotova *Chem. Heterocyclic Comp.* **1993**, *29*, 1259.

[13] Veeraraghavan, S.; Bhattacharjee, D.; Popp, F. D. *J. Heterocycl. Chem.* **1981**, *18*, 443.

[14] Yamamoto, Y.; Sakaguchi, A.; Yoshida, H.; Akiba K. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 725.

[15] Snider, B. B.; Shi Z. *J. Org. Chem.* **1992**, *57*, 2526.

[16] Saloutin, V. I.; Burgart, Y. V.; Kuzueva, O. G.; Kappe, C. O.; Chupakhin O. N. *J. Fluor. Chem.* **2000**, *103*, 17.

[17] Martins, A. P. M.; Teixeira M. V. M.; Cunico, W.; Scapin, E.; Mayer, R.; Pereira, C. M. P.; Zanatta, N.; Bonacorso, H. G.; Peppe, C.; Yuan Y. F. *Tetrahedron Lett.* **2004**, *45*, 8991.

[18] Zanatta, N.; Fagundes, M.; Hellensohn, R.; Martins, M. A. P.; Bonacorso H. G. *J. Heterocycl. Chem.* **1998**, *35*, 451.

[19a] Zanatta, N.; Madruga, C. C.; Clerice, E.; Martins, M. A. P. *J. Heterocycl. Chem.* **1995**, *32*, 735; [b] Zanatta, N.; Cortelini, M. F. M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509; [c] Bonacorso, H. G.; Lopes, L. S.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P. *J. Fluor. Chem.* **2003**, *120*, 29; [d] Bonacorso, H. G.; Martins, D. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. *Synthesis* **2005**, 809;

[20] Cappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

[21a] Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Zanatta, N.; Bonacorso, H. G. *J. Heterocycl. Chem.* **1999**, *36*, 837; [b] Martins, M. A. P.; Sinhorin, A. P.; Zimmermann, N. E. K.; Zanatta, N.; Bonacorso, H. G.; Bastos, G. P. *Synthesis* **2001**, 1959; [c] Martins, M. A. P.; Neto, M.; Sinhorin, A. P.; Bastos, G. P.; Zimmermann, N. E. K.; Rosa, A.; Bonacorso, H. G.; Zanatta, N. *Synth. Commun.* **2002**, *32*, 425.

[22a] Martins, M. A. P.; Freitag, R.; Flores, A. F. C.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 1491; [b] Bonacorso, H. G.; Oliveira, M. R.; Wentz, A. P.; Oliveira, A. B.; Hörner, M.; Zanatta, N.; Martins, M. A. P. *Tetrahedron* **1999**, *55*, 345; [c] Flores, A. F. C.; Martins, M. A. P.; Rosa, A.; Flores, D. C.; Zanatta, N.; Bonacorso, H. G. *Synth. Commun.* **2002**, *32*, 1585.

[23a] Pacholski, I. L.; Blanco, I.; Zanatta, N.; Martins, M. A. P.; *J. Braz. Chem. Soc.* **1992**, *2*, 118; [b] Zanatta, N.; Madruga, C. C.; Marisco, P. C.; Flores, D. C.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2000**, *37*, 1213; [c] Zanatta, N.; Cortelini, M. F.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocyclic Chem.* **1997**, *34*, 509.

[24] Zanatta, N.; Barichello, R.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **1999**, 765.

[25a] Zanatta, N.; Rosa, L. S.; Loro, E.; Bonacorso, H. G.; Martins, M. A. P. *J. Fluorine Chem.* **2001**, *107*, 149; [b] Zanatta, N.; Rosa, L. S.; Cortelini, M. F. M.; Beux, S.; Santos, A. P. D.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2002**, 2404.

[26a] Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **1996**, *37*, 9155; [b] Bonacorso, H. G.; Bittencourt, S. R. T.; Wastowski, A. D.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **1999**, *36*, 45.

[27a] Bonacorso, H. G.; Wentz, A. P.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2001**, 1505; [b] Bonacorso, H. G.; Wastowski, A. D.; Muniz, M. N.; Zanatta, N.; Martins, M. A. P. *Synthesis*, **2002**, 1079; [c] Bonacorso, H. G.; Duarte, S. H. G.; Zanatta, N.; Martins, M. A. P. *Synthesis* **2002**, 1037; [d] Zanatta, N.; Lopes, E. C. S.; Fantinel, L.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2002**, *39*, 943; [e] Zanatta, N.; Flores, D. C.; Madruga, C. C.; Faoro, D.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *Synthesis* **2003**, 894.

[28] Nagayama, K.; Kumar, A.; Wüthrich, K.; Ernst, R. R. *J. Mag. Res.* **1980**, *40*, 321.

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

[30] Bax, A.; Subramanian, S. *J. Mag. Res.* **1986**, *67*, 565.

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

[32] Eliel, E. L.; Wilen, S. H.; Doyle, M. P.; *Basic Organic Stereochemistry*, Wiley Interscience Publishers, New York, NY, 2001, pp 474.

[33a] Zanatta, N; Barichell, R.; Pauletto, M. M.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2003**, *44*, 961; [b] Zanatta, N.; Faoro, D.; Silva, S. C.; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2004**, *45*, 5689.

[34] Bonacorso, H. G.; Martins, M. A. P.; Zanatta, N.; Oliveira, M. R.; Wentz, A. P.; Hörner, M.; Bortuluzzi, A. *J. Spectrosc. Lett.* **1999**, *32*, 851.

[35] Martins, M. A. P.; Zanatta, N.; Pacholski, I. L.; Bonacorso, H. G.; Hörner, M.; Bortuluzzi, A. J.; Oliveira, A. B. *Spectrosc. Lett.* **1998**, *31*, 1125.

[36] Martins, M. A. P.; Flores, A. F. C.; Freitag, R. A.; Zanatta, N.; Hörner, M.; Bortuluzzi, A. *J. Spectrosc. Lett.* **1997**, *30*, 661.

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

[38] Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1990**, *107*, 3902.

[39] CambridgeSoft Corporation, 100 Cambridge Park Drive – Suite 4, Cambridge, MA 02140-9802 USA.