Haloacetylated Enol Ethers: **15** [26]. Study of the Regiochemistry of the Cyclo-condensation of β-Alkoxyvinyl Trihalomethyl Ketones with *N*-Methyl Thiourea

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A study of the regiochemistry of the cyclo-condensation reaction of β-alkoxyvinyl trihalomethyl ketones with an unsymmetric dinucleophile *N*-methyl thiourea to afford a series of 1-methyl-3-(4,4,4-trifluoro-[chloro]-3-oxo-1-butenyl)thioureas and the corresponding *N*-methyl pyrimidinethione derivatives is reported. The absolute assignment of the position of the *N*-methyl group in the pyrimidine ring was obtained through a nmr study based on two dimensional HMBC and NOESY experiments.

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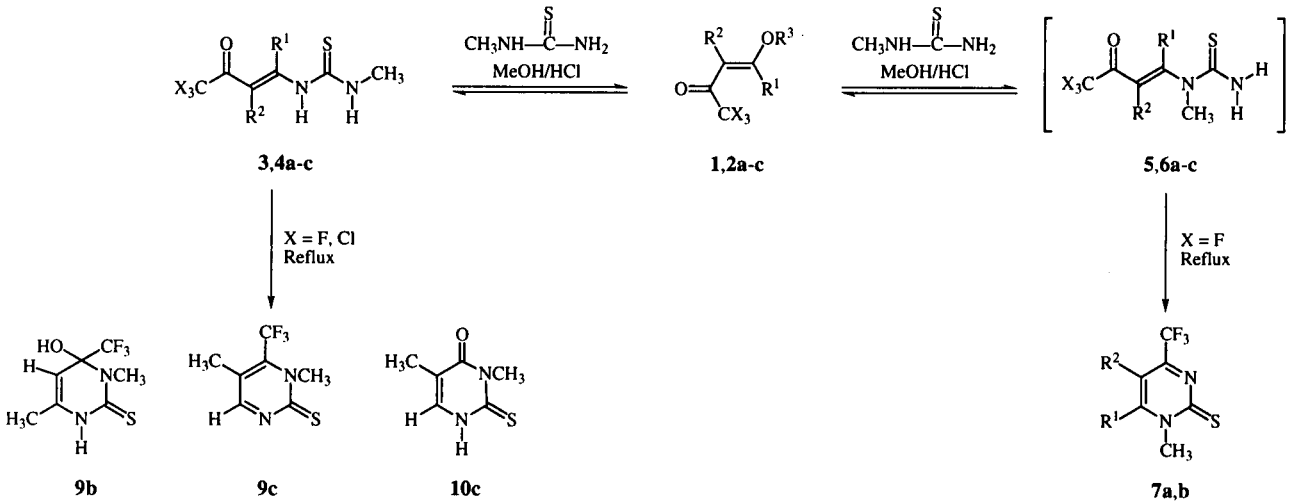
The β-alkoxyvinyl trihalomethyl ketones are versatile precursors of the trihalomethyl group containing compounds such as enones [1], enaminones [2-4], complex chelating [3], heterocycles [4,5-8] and alkadienyl ketones [9]. Many reactions have been developed by our research group in the past few years, for which the synthetic potential of β-alkoxyvinyl trihalomethyl ketones toward several dinucleophiles such as hydrazines, semicarbazides, hydroxylamine, ureas, 2-methylthiourea, guanidine, amidines, and phenylenediamine leading to pyrazoles [10-13], isoxazoles [14-18], pyrimidines [19-22], and benzoazepines [23] were explored.

In a previous work [20] a series of 4-trihalomethyl-2-methylthiopyrimidines, from the cyclo-condensation reaction of β-alkoxyvinyl trihalomethyl ketones and 2-methylisothiourea sulfate, were obtained. With the continuing interest for the investigation of the reactivity of β-alkoxyvinyl trihalomethyl ketones, the aim of this work is to study the regiochemistry of the cyclo-condensation reaction of a series of β-alkoxyvinyl trihalomethyl ketones (**1a-c**, **2a-c**) toward *N*-methylthiourea, an unsymmetric dinucleophile. Important information about the substituent effect of the ketones **1** and **2** on the regiochemistry of these cyclizations can be obtained by the observation of the structure of the intermediates and the final products. The reactions of β-alkoxyvinyl trifluoro[chloro]methyl ketones **1a-c**, **2a-c** with *N*-methylthiourea are presented in Scheme 1.

Scheme 1



3,4a-c **1,2a-c** **5,6a-c**

9b **9c** **10c** **7a,b**

	R^1	R^2	R^3		
a	H	H	CH_2CH_3	X	Compound
b	CH_3	H	CH_3	F	**1, 3, 5, 7, 9**
c	H	CH_3	CH_3	Cl	**2, 4, 6, 10**

The cyclo-condensation reaction of compounds **1a-c**, **2a-c** with *N*-methyl thiourea was carried out in methanol under acid catalysis, a method successfully accomplished by our research group previously [19]. Depending on the temperature and the reaction time, the open chain Michael's adducts 1-methyl-3-(4,4,4-trifluoro[chloro]-3-oxo-1-butenyl)thioureas (**3a,c** and **4a**) or the *N*-methyl-2-pyrimidinethiones **7a,b**, **9b,c** and **10c** were obtained. In general, for low temperature and short reaction time, the open chain compounds **3a,c** and **4a** were obtained and for higher temperature and longer reaction time, the pyrimidinethiones were isolated. Table 1 shows the conditions used for several reactions.

Table 1

Reaction Conditions [a] for the Synthesis of Compounds **3a-c**, **4a**, **7a,b**, **9b,c**, **10c**

Substrate	Temperature (°C) Time (Hours)	Yield (%)	Compound
1a	0/0.2	77	**3a**
1a	10/18	68	**7a**
1b	0/0.2	–	**3b** [d]
1b	[b]/0.2	–	**7b** + **9b** (1:1) [e]
1b	[c]/0.5	50	**7b**
1b	[c]/26	58	**7b**
1c [f]	[b]/0.5	45	**3c**
1c [f]	[b]/2	–	**3c** + **9c** (1:2) [e]
2a	[c]/1	74	**4a**
2c	[c]/0.5	30	**10c**

[a] Reactions carried out in methanol (7 mL), HCl (1 mL); [b] Room temperature: 18-25 °C; [c] Reflux temperature of the solvent; [d] This compound was not obtained; [e] Mixture ratio of compounds obtained by pmr integrals; [f] Reactions carried out in methanol (5 mL) and hydrochloric acid (0.5 mL).

The open chain compounds **3a,c** and **4a** were isolated for the first time. These compounds are difficult to isolate because the cyclization after the Michael addition of the thiourea on the β-carbon of the β-alkoxyvinyl ketone is usually very fast. The open chain compounds were isolated probably due to the steric hindrance between the *N*-methyl and the trihalomethyl groups.

It was observed that substituents on the β-alkoxyvinyl trihalomethyl ketones have a major effect in both reactivity and the regiochemistry of the pyrimidine ring formation. The formation of compounds **7a,b** suggest a rearrangement of the intermediates **3a,b** to the intermediates **5a,b** which promptly cyclize to the pyrimidines **7a,b**, since the direct cyclization of **3** would lead to pyrimidines of the general structure **9** with the *N*-methyl group in the N-3 position. This study showed that when R^1 and R^2 are both hydrogens only the pyrimidine **7a** (*N*-methyl in N-1 position) was observed. When R^1 is an hydrogen and R^2 is a methyl only the pyrimidine **9c** (*N*-methyl in N-3 position) was isolated. But when R^1 is a methyl and R^2 is an hydrogen a 1:1 mixture of the pyrimidine **7b** (*N*-methyl in N-1 position) and the tetrahydro pyrimidine **9b** (*N*-methyl in N-3 position) was obtained.

The cyclization of the trichloromethylated intermediate **4a-c** are more difficult probably due to the bulkiness of the trichloromethyl group. The intermediate **4a** was obtained in good yields but did not cyclize even with elevated temperatures or prolonged reaction times. The cyclization of β-alkoxyvinyl ketone **2b** was tested under several reaction conditions such as increasing the temperature and reaction time and increasing the amounts of hydrochloric acid. The result, however was not satisfactory because neither the formation of the compounds **4b** or **6b** nor the corresponding pyrimidinethione was observed. The cyclization of **4c** was achieved with the cleavage of the trichloromethyl group affording 4-oxo-2-pyrimidinethione **10c** with the *N*-methyl group in N-3 position.

The open chain compound **3a** was refluxed in chloroform, in the presence of hydrochloric acid, in an attempt to obtain the 3-methyl-4-trifluoromethyl-2-pyrimidinethione (**7a**). With these conditions, the intramolecular cyclization did not occur and compound **3a** was recovered. However, when compound **3a** was refluxed in methanol in the presence of hydrochloric acid, compound **7a** was obtained. This suggests that compound **3a**, in methanol and hydrochloric acid, is first converted to the intermediate **5a**, which was not observed, to lead to compound **7a**. The product from the direct cyclization of **3a** seems not to occur under the given conditions. Selected physical data of **3a,c**, **4a**, **7a,b**, **9b,c** and **10c**, are shown in Table 2.

The nmr spectra of the open chain compounds **3a** and **4a**, in dimethylsulfoxide-d_6, exhibited two isomers each comprised of the *E* and *Z* forms in a ratio of 3:2 respectively. The *E* and *Z* isomer were assigned by the coupling constant of the olefinic protons. The *E* isomer exhibits a coupling constant of about 13 Hz while the *Z* isomer shows a coupling constant of about 8.5 Hz. The remaining protons of each isomer were assigned from the integrals according to the different isomeric ratio. The compound **3a** (*E*) does exist in equilibrium with **3a** (*Z*) in DMSO-d_6 solution, however, in low polarity solvents these compounds exist only in the *Z* form due to the hydrogen bonding among the N-H and the carbonyl oxygen [4]. The cmr signals of each isomer were assigned based on the different intensities of the resonance peaks. For compound **3c** only the *E* isomer was observed. The NOESY spectrum of **3c** shows no cross-peaks between the methyl group α-carbonyl and the β-proton which indicates that the methyl group α-carbonyl and the β-proton occupy opposite positions around the double bond and, therefore, only the *E* isomer was observed in DMSO-d_6. Table 3 shows the ^{1}H- and ^{13}C-nmr data of compounds **3a,c**, **4a** and Table 4 shows ^{1}H- and ^{13}C-nmr spectral data of compounds **7a,b**, **9b,c**, and **10c**.

Table 2

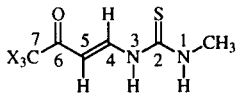
Selected Physical Data for **3a,c**, **4a**, **7a,b**, **9b,c**, and **10c**

Compound	Yield (%) [a]	Mp (°C)	Molecular Formula (MW)	Analysis (%) Calcd./Found C	H	N
3a	77	119-121	$C_6H_7F_3N_2OS$ (212.18)	33.96	3.33	13.20
				33.96	3.36	13.24
3c	45	140-142	$C_7H_9F_3N_2OS$ (226.22)	37.17	4.01	12.38
				37.00	4.08	12.22
4a	73	115-117	$C_6H_7Cl_3N_2OS$ (261.55)	27.55	2.70	10.71
				27.34	2.64	10.53
7a	68	189-191	$C_6H_5F_3N_2S$ (194.17)	37.11	2.60	14.43
				36.84	2.69	14.16
7b	58	122-125	$C_7H_7F_3N_2S$ (208.20)	40.38	3.39	13.45
				40.36	3.68	13.07
9b	35	145-147	$C_7H_9F_3N_2OS$ (226.11)	37.17	4.01	12.38
				36.97	3.96	12.27
9c	32	107-109	$C_7H_7F_3N_2S$ (208.20)	40.38	3.39	13.45
				40.36	3.43	13.52
10c	30	213-215	$C_7H_8N_2OS$ (156.20)	46.14	5.16	17.93
				45.95	4.93	17.61

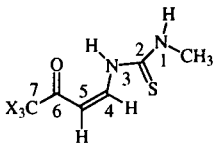
[a] Yields of compounds after purification.

Table 3

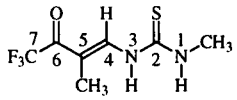
^{1}H- and ^{13}C-NMR Spectral Data of Compounds **3a,c** and **4a**



3a (*E*), **4a** (*E*)



3a (*Z*), **4a** (*Z*)

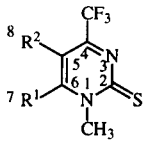


3c

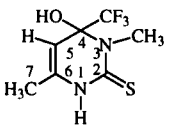
Compound	^{1}H-NMR, δ_{ppm}, (Multiplicity, Number of Protons, J_{Hz}, Assignment) ^{13}C-NMR, δ_{ppm}, J_{CF} (Hz)
3a (*E*)	11.30 (d, 1H, $J_{H3\text{-}H4}$ = 12.2, H3), 8.89 (q, 1H, $J_{H1\text{-}CH3}$ = 4.4, H1), 8.78 (dd, 1H, $J_{H4\text{-}H3}$ = 12.2, $J_{H4\text{-}H5}$ = 13.4, H4), 6.11 (dq, 1H, $J_{H5\text{-}H4}$ = 13.4, $J_{H5\text{-}F}$ = 0.9, H5), 3.04 (d, 3H, $J_{CH3\text{-}H1}$ = 4.4, N-CH_3)
	180.54 (C2), 149.01 (C4), 96.47 (C5), 178.36 (q, $J_{C\text{-}F}$ = 33.0, C6), 116.63 (q, $J_{C\text{-}F}$ = 289.9, CF_3), 32.15 (N-CH_3)
3a (*Z*)	11.62 (d, 1H, $J_{H3\text{-}H4}$ = 11.8, H3), 10.12 (q, 1H, $J_{H1\text{-}CH3}$ = 4.4, H1), 8.51 (dd, 1H, $J_{H4\text{-}H3}$ = 11.8, $J_{H4\text{-}H5}$ = 8.5, H4), 5.87 (dq, 1H, $J_{H5\text{-}H4}$ = 8.5, $J_{H5\text{-}F}$ = 0.8, H5), 3.02 (d, 3H, $J_{CH3\text{-}H1}$ = 4.4, N-CH_3
	180.77 (C2), 150.59 (C4), 99.33 (C5), 178.76 (q, $J_{C\text{-}F}$ = 33.0, C6), 116.26 (q, $J_{C\text{-}F}$ = 288.7, CF_3), 31.90 (N-CH_3)
3c	8.75 (q, 1H, $J_{H1\text{-}CH3}$ = 4.4, H1), 10.28 (d, 1H, $J_{H3\text{-}H4}$ = 12.0, H3), 8.85 (d, 1H, $J_{H4\text{-}Hc}$ = 12.0, H4), 1.83 (s, 3H, CH_3), 3.06 (d, 3H, $J_{H1\text{-}CH3}$ = 4.4, N-CH_3)
	180.97 (C2), 145.40 (C4), 107.54 (C5), 178.41 (q, $J_{C\text{-}F}$ = 31.9, C6), 9.66 (C7), 117.19 (q, $J_{C\text{-}F}$ = 291.1, CF_3), 31.74 (N-CH_3)
4a (*E*)	8.88 (q, 1H, $J_{H1\text{-}CH3}$ = 4.3, H1), 11.45 (d, 1H, $J_{H3\text{-}H4}$ = 11.8, H3), 8.73 (dd, 1H, $J_{H4\text{-}H3}$ = 11.8, $J_{H4\text{-}H5}$ = 13.2, H4), 6.40 (d, 1H, $J_{H5\text{-}H4}$ = 13.2, H5), 3.02 (d, 3H, $J_{CH3\text{-}H1}$ = 4.3, N-CH_3)
	180.87 (C2), 148.48 (C4), 94.92 (C5), 180.63 (C6), 96.83 (CCl_3), 31.95 (N-CH_3)
4a (*Z*)	9.98 (q, 1H, $J_{H1\text{-}CH3}$ = 4.3, H1), 11.39 (d, 1H, $J_{H3\text{-}H4}$ = 12.0, H3), 8.51 (dd, 1H, $J_{H4\text{-}H3}$ = 12.0, $J_{H4\text{-}H5}$ = 8.7, H4), 6.07 (d, 1H, $J_{H5\text{-}H4}$ = 8.7, H5), 3.04 (d, 3H, $J_{CH3\text{-}H1}$ = 4.3, N-CH_3)
	181.59 (C2), 149.64 (C4), 91.11 (C5), 180.68 (C6), 95.92 (CCl_3), 31.79 (N-CH_3)

Table 4

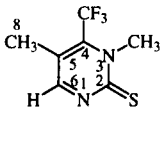
^{1}H- and ^{13}C-NMR Spectral Data of Compounds **7a,b**, **9b,c** and **10c**



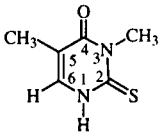
7a,b



9b



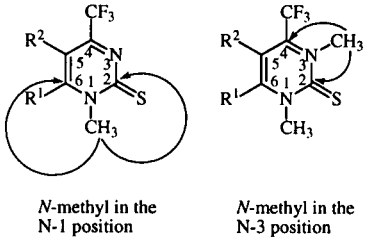
9c



10c

Compound	^{1}H-NMR, δ_{ppm}, (Multiplicity, Number of Protons, J_{Hz}, Assignment) ^{13}C-NMR, δ_{ppm}, J_{CF} (Hz)
7a	3.83 (s, 3H, N-CH_3), 7.31 (d, 1H, J_{H5-H6} = 5.4, H5), 8.85 (d, J_{H6-H5} = 5.4, H6)
	181.02 (C2), 154.70 (q, J_{C-F} = 36.0, C4), 104.46 (C5), 155.33 (C6), 119.64 (q, J_{C-F} = 275.0, CF_3), 46.42 (N-CH_3)
7b	3.98 (s, 3H, N-CH_3), 7.39 (s, 1H, H5), 2.68 (s, 3H, CH_3)
	182.45 (C2), 152.55 (q, J_{C-F} = 35.4, C4), 106.53 (C5), 165.79 (C6), 22.24 (CH_3), 119.83 (q, J_{C-F} = 276.9, CF_3), 40.81 (N-CH_3)
9b	3.34 (s, 3H, N-CH_3), 10.53 (s, 1H, N1-H), 4.73 (s, 1H, OH), 7.96 (s, 1H, H5), 1.83 (s, 3H, CH_3)
	175.51 (C2), 82.60 (q, J_{C-F} = 32.2, C4), 93.93 (C5), 136.26 (C6), 17.24 (CH_3), 123.39 (q, J_{C-F} = 291.2, CF_3), 33.78 (N-CH_3)
9c	3.05 (s, 3H, N-CH_3), 8.85 (s, 1H, H6), 1.83 (s, 3H, CH_3)
	181.16 (C2), 178.42 (q, J_{C-F} = 31.8, C4), 107.54 (C5), 145.78 (q, J_{C-F} = 4.4, C6), 9.73 (CH_3), 117.2 (q, J_{C-F} = 292.2, CF_3), 31.81 (N-CH_3)
10c	3.52 (s, 3H, N-CH_3), 7.36 (d, 1H, J_{H6-NH} = 5.6, H6), 1.82 (s, 3H, CH_3)
	175.34 (C2), 161.62 (C4), 112.36 (C5), 136.75 (C6), 12.72 (CH_3), 33.21 (N-CH_3)

The correct determination of the *N*-methyl group position in pyrimidines has been considered by some authors as a difficult task [24]. In this work a simple and reliable method was used to unambiguously assign the position of the *N*-methyl group in *N*-methyl pyrimidines. The correct position of the *N*-methyl group of the *N*-methyl-2-pyrimidinethiones **7a,b**, **9b,c**, and **10c** was determined by two-dimensional Heteronuclear Multiple Bond Coherence (HMBC) nmr experiment [25]. In this experiment when the *N*-methyl group is in the N-1-position two cross-peaks between the *N*-methyl protons and the carbons 2 and 6 should be observed. When the *N*-methyl is in the N-3 position cross-peaks between the methyl protons and the carbons 2 and 4 should be observed (see Figure 1). The



N-methyl in the N-1 position

N-methyl in the N-3 position

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

position of the *N*-methyl group of compound **7a** was also confirmed by the NOESY experiment. In this spectrum a cross-peak between the methyl group and the H-6 confirms that the *N*-methyl group is in the N-1 position. In Scheme 1 the pyrimidinethiones show the *N*-methyl group in the correct position.

Conclusions.

This work allowed the isolation of the open chain Michael's adducts of the general type of **3** and **4** which have not been reported before. The open chain intermediate of type **5** and **6**, however, were not observed. This work showed that the substituents on the β-alkoxyvinyl trihalomethyl ketones have a major effect in both reactivity and the regiochemistry of the pyrimidine ring formation as described in the discussion section.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. The β-alkoxyvinyl trifluoro[chloro]methyl ketones (**1a-c**, **2a-c**) were prepared according to reference [2,14]. All melting points were determined on a Reichert

Thermovar apparatus and are uncorrected. ^{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 and TMS as the internal reference. The HMBC spectra were acquired as 4096 x 256 hypercomplex files using the pulse sequence described by Bax and Summers [25]. Spectral widths in F_2 and F_1 were approximately 0.5–9.0 ppm for proton and 5–190 ppm for ^{13}C, respectively. The long range delay was optimized for 7 Hz (70 msec). A total of 16–64 scans were accumulated with a 2 second inter-pulse delay. Microanalysis were performed in a Vario EL Elementar Analysensysteme.

1-Methyl-3-(4,4,4-trifluoro-3-oxo-1-butenyl)thioureas (**3a**,**c**) and (**4a**).

General Procedure Described for Compound **3a**.

To a round bottomed flask cooled in an ice bath was added the ketone **1a** (0.84 g, 5.0 mmoles), *N*-methylthiourea (0.68 g, 7.5 mmoles), methanol (10 mL), and hydrochloric acid (1 mL). The reaction was stirred for 10 minutes and the methanol was partially evaporated in rotary evaporator. The reaction conditions for the other reactions are presented in Table 1. With the addition of cold water (20 mL) a yellow precipitate was formed which was filtered off. The filtrate was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried under sodium carbonate. The solvent was evaporated and the resulting yellow solid was recrystallized from hexane and ethyl acetate to obtain yellow crystals identified as pure **3a** in 77% yield. Compound **3a** (*E* isomer) exist in equilibrium with **3a** (*Z* isomer) in DMSO-d_6 solution. The same procedure of isolation and purification was also applied to compounds **3c** and **4a**.

1-Methyl-4-trifluoromethyl-1,2-dihydro-2-pyrimidinethione (**7a**,**b**, **9b**,**c**).

General Procedure Described for Compound **7a**.

Compound **7a** was obtained using a similar procedure for the preparation of **3a**. The reaction mixture was stirred at 10 °C for 18 hours. The reaction conditions for the other reactions are presented in Table 1. The methanol was partially evaporated, distilled water was added, and the product extracted with ethyl acetate. The organic phase was dried with sodium carbonate and evaporated to obtain **7a** as a yellow solid which was recrystallized from hexane/ethyl acetate (3:1). Compound **7b** was isolated and purified using the same procedure as **7a**.

Compound **9b**.

A mixture of **7b** and **9b** (4-hydroxy-3,6-dimethyl-4-trifluoromethyl-1,2,3,4-tetrahydro-2-pyrimidinethione) was obtained and the products were separated by their different solubility. Chloroform was added to the mixture of compounds and only **7b** became soluble. Compound **9b** was separated by filtration and recrystallized from methanol.

Compound **9c**.

A mixture of **3c** and **9c** (3,5-dimethyl-4-trifluoromethyl-1,2-dihydro-2-thiopyrimidinone) was obtained in a ratio of 1:2, respectively and the products were separated by their different solubility. To the mixture of **3c** and **9c** was added chloroform. Compound **9c** dissolved and **3c** was removed by filtration. Compound **9c** was recrystallized from hexane/chloroform.

3,5-Dimethyl-4-oxo-1,2,3,4-tetrahydro-2-pyrimidinethione (**10c**).

A solution of **2c** (1.08 g, 5 mmoles), *N*-methylthiourea (0.68 g, 7.5 mmoles) in methanol (10 mL), and hydrochloric acid (1 mL) was stirred for 30 minutes. The methanol was evaporated obtaining a dark oil which was dissolved in ethyl acetate (20 mL) and washed with a saturated solution of sodium chloride (15 mL). The organic layer was dried with anhydrous magnesium sulfate and concentrated to furnish **10c** as a light yellow solid which was recrystallized from hexane/ethyl acetate.

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REFERENCES AND NOTES

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[1] M. Hojo, R. Masuda, S. Sakaguchi and M. Takagawa, *Synthesis*, 1016 (1986).

[2] E. Okada, R. Masuda, M. Hojo and R. Inoue, *Synthesis*, 533 (1992).

[3] I. I. Gerus, M. G. Gorbunova and V. P. Kukhar, *J. Fluorine Chem.*, 195 (1994).

[4] I. I. Gerus, M. G. Gorbunova, S. I. Vdovenko, Y. U. L. Yagupol'skii and V. P. Kukhar, *Chem. Heterocyclic Compounds*, 1623 (1991).

[5a] M. Hojo, R. Masuda and E. Okada, *Synthesis*, 215 (1989); [b] Y. Kamitori, M. Hojo, R. Masuda, M. Fujishiro, I. Nakamura and K. Yamamoto, *J. Heterocyclic Chem.*, **30**, 389 (1993).

[6] Y. Kamitori, M. Hojo, R. Masuda, T. Fujitani, T. Kobuchi and T. Nishigaki, *Synthesis*, 340 (1986).

[7] W. Spiegler and N. Götz, *Synthesis*, 69 (1986).

[8] I. I. Gerus, S. I. Vdovenko, M. G. Gorbunova and V. P. Kukhar, *Chem. Heterocyclic Compounds*, 398 (1991).

[9] S. Hara, N. Kato, E. Takada and A. Sukuki, *Synlett*, 961 (1994).

[10] M. E. F. Braibante, G. Clar and M. A. P. Martins, *J. Heterocyclic Chem.*, **30**, 1159 (1993).

[11] H. G. Bonacorso, A. D. Wastowski, N. Zanatta, M. A. P. Martins, J. A. Naue, *J. Fluorine Chem.*, **92**, 23 (1998).

[12] H. G. Bonacorso, M. R. Oliveira, A. P. Wentz, A. D. Wastowski, A. B. Oliveira, M. Hoerner, N. Zanatta, M. A. P. Martins, *Tetrahedron*, **55**, 345 (1999).

[13] M. A. P. Martins, R. Freitag, A. F. C. Flores and N. Zanatta, *Synthesis*, 1491 (1995).

[14] A. Colla, M. A. P. Martins, G. Clar, S. Krimmer and P. Fischer, *Synthesis*, 483 (1991).

[15] M. A. P. Martins, A. N. Zoch, A. F. C. Flores, G. Clar, N. Zanatta and H. G. Bonacorso, *J. Heterocyclic Chem.*, **32**, 739 (1995).

[16] M. A. P. Martins, A. F. C. Flores, R. Freitag and N. Zanatta, *J. Heterocyclic Chem.*, **32**, 731 (1995).

[17] M. A. P. Martins, G. M. Siqueira, G. P. Bastos, H. G. Bonacorso and N. Zanatta, *J. Heterocyclic Chem.*, **33**, 1619 (1996).

[18] M. A. P. Martins, A. F. C. Flores, R. A. Freitag and N. Zanatta, *J. Heterocyclic Chem.*, **33**, 1223 (1996).

[19] I. L. Pacholski, I. Blanco, M. A. P. Martins and N. Zanatta, *J. Braz. Chem. Soc.*, **2**, 118 (1991).

[20] C. C. Madruga, E. Clerici, M. A. P. Martins and N. Zanatta, *J. Heterocyclic Chem.*, **32**, 735 (1995).

[21] N. Zanatta, M. F. M. Cortelini, M. J. S. Carpes, H. G. Bonacorso and M. A. P. Martins, *J. Heterocyclic Chem.*, **34**, 509 (1997).

[22] N. Zanatta, M. B. Fagundes, R. Ellensohn, M. Marques, H. G. Bonacorso and M. A. P. Martins, *J. Heterocyclic Chem.*, **35**, 451 (1998).

[23] H. G. Bonacorso, S. T. Bittencourt, A. D. Wastowski, A. P. Wentz, N. Zanatta and M. A. P. Martins, *Tetrahedron Letters*, **37**, 9155 (1996).

[24] I. I. Gerus, S. I. Vdovenko, M. G. Gorbunova and V. P. Kukhar, *Chem. Heterocyclic Compounds*, 398 (1992).

[25] A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, **108**, 2093 (1986).

[26] M. A. P. Martins, A. F. C. Flores, G. P. Bastos, N. Zanatta and H. G. Bonacorso, *J. Heterocyclic Chem.*, **36**, 837 (1999).