J. Braz. Chem. Soc., Vol. 19, No. 1, 184-193, 2008.
Printed in Brazil - ©2008 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

Efficient Synthesis of New 1-[Alkyl(aryl)]-5-(3,3,3-trihalo-2-oxopropylidene)pyrrolidin-2-ones

Alex F. C. Flores,* Darlene C. Flores, Graciela Oliveira, Lucas Pizzuti, Rubia M. S. da Silva, Marcos A. P. Martins and Helio G. Bonacorso

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

Este trabalho mostra a síntese, em bons rendimentos (57-95%), de duas séries de 1-alquil(aril) amino-2-oxo-5-(2-oxo-3,3,3-trialopropiliden)-pirrolidinas **5** e **6**, a partir dos intermediários 4-[alquil(aril)amino]-6-oxo-7,7,7-trialo-4-hepteno-atos de metila **3** e **4** obtidos por substituição da metoxila-β nos precursores 4-metoxi-6-oxo-7,7,7-trialo-4-heptenoatos de metila **1** e **2,** pela série de aminas primárias RNH_2, onde R = $PhCH_2$, $PhCH_2CH_2$, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-piridnil, 5-metil-3-isoxazolil, 4-$NH_2C_6H_4$. A estrutura molecular dos produtos inéditos foi atribuída a partir dos dados de RMN ^1H, ^{13}C e espectrometria de massas. A configuração geométrica dos compostos **3d** e **5b** foi confirmada pelos dados de difração de raios-X em monocristal.

Reactions of methyl 4-methoxy-6-oxo-7,7,7-trihalo-4-heptenoates **1** and **2** with primary amines RNH_2, where R = $PhCH_2$, $PhCH_2CH_2$, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-pyridyl, 5-methyl-3-isoxazolyl, 4-$NH_2C_6H_4$ affording methyl 4-[alkyl(aryl)amino]-6-oxo-7,7,7-trihalo-4-heptenoates **3**, **4,** in good yields (57-95%), which suffer quantitative intramolecular cyclocondensation to produce 1-alkyl(aryl)-5-(2-oxo-3,3,3-trihalopropylidene)pyrrolidin-2-ones **5**, **6**, are reported. The structures of the isolated new products were assigned by means of ^1H, ^{13}C NMR measurements and mass spectrometry. The *Z* and *E* configuration of compounds **3d** and **5b** respectively were established from X-ray crystallography.

Keywords: pyrrolidin-2-ones, [CCCC+N] cyclisation, methyl 4-methoxy-6-oxo-7,7,7-trihalo-4-heptenoates

Introduction

We have systematically used the acetals acylation method for synthesis of wide range of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones. These 1,3-dielectrophilic precursors have proved to be important building blocks for regiospecific synthesis of heterocyclic compounds bearing trihalomethyl group[2,3] with important pharmacological[4,5] and synthetic applications.[6] The levulinic acid (4-oxopentanoic acid) is an important fine organic material from renewable source, with acetyl group attractive for us.[7] Our continuing interest in 1,3-dielectrophilic compounds has led us to study a new aspect of the application of the acetal acylation method for producing methyl 4-methoxy-6-oxo-7,7,7-trihalo-4-heptenoates **1** and **2**.[8]

On the other hand, the pyrrolidin-2-ones, have received considerable attention due to their activity in CNS as nootropic drugs. Piracetam-like nootropics revert amnesia induced by scopolamine and other amnesing drugs, electroconvulsive shock and hypoxia with an unknown mechanism.[9] In general, they show no affinity for the most important central receptors, but are able to modulate the action of these most important central neurotransmitters, in particular acetylcholine and glutamate. Extensive study of the modes of action of the 2-pyrrolidinones has revealed various pharmacological effects, with striking differences between drugs.[10,11]

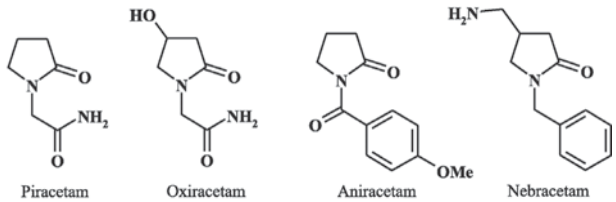


Figure 1. Structures of pyrrolidin-2-one drugs.

*e-mail: alexflores@smail.ufsm.br

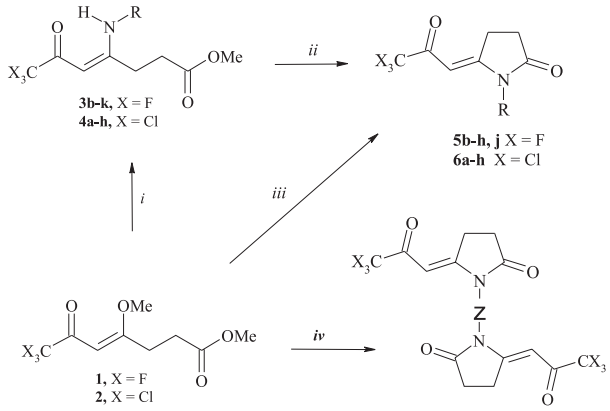
Continuing with our systematic studies on synthesis and application of 4-alkoxy-1,1,1-trihalo-3-alken-2-ones we report an efficient approach for synthesis of a series of 1-[alkyl(aryl)]-5-(3,3,3-trihalo-2-oxopropylidene)pyrrolidin-2-nes from **1** and **2**. This study deals with formation of the methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trihalo-4-heptenoates **3** and **4**, and their intramolecular cyclisations to new 1-alkyl[aryl]-5-(3,3,3-trihalo-2-oxopropylidene) pyrrolidin-2-ones **5** and **6**.

Results and Discussion

The precursors methyl 4-methoxy-6-oxo-7,7,7-trihalo-4-heptenoates **1** and **2** were obtained by acetal acylation method as described previously.[8]

The fluorinated enaminones **3** were synthesized and isolated by reaction of the methyl 4-methoxy-6-oxo-7,7,7-trifluoro-4-heptenoate (**1**) with primary alkyl[aryl]amines in CH_3CN at variable temperatures depending on used amine. The analytical data have demonstrated the formation of the methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trifluoro-4-heptenoates **3,b-k** (Table 1, Supplementary Information), with (*Z*)-4-alkyl[aryl]amino-1,1,1-trifluoro-3-alken-2-one moiety.[2] Primary alkylamines (**b, c**) reacted readily with 4-methoxy-1,1,1-trifluoro-3-alken-2-ones in MeOH, EtOH or *i*-PrOH by displacement of β-methoxy substituent, in these cases, the intramolecular cyclocondensation of the resulting methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3,b,c** to pyrrolidin-2-ones also took place, affording mixtures of products **3** and **5** at room temperature. However, when the least reactive primary arylamines were employed, and the reaction was carried out in MeOH or EtOH at room temperature, unreacted **1** or mixtures of methyl 4-ethoxy-6-oxo-7,7,7-trifluoro-4-heptenoate and **1** were recovered. The methyl 4-arylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3,d-j** were obtained in refluxing MeCN or at room temperature, by addition of equimolar amount of Et_3N or lutidine (Table 1, Supplementary Information). Reaction of the methyl 4-methoxy-6-oxo-7,7,7-trifluoro-4-heptenoate **1** with 1,4-diaminobenzene in a stoichiometric ratio 1:1 or in 2:1 mol-equiv ratio in MeCN at room temperature lead to the methyl 4-(4-aminophenylamino)-6-oxo-7,7,7-trifluoro-4-heptenoate **3k**, but under reflux conditions the intramolecular cyclisation took place under formation of only 1,1'-(1,4-phenylene)-bis(5-(3,3,3-trifluoro-2-oxopropylidene)-2-pyrrolidin-2-one) **5k** (Scheme 1).

The structures of fluorinated enaminones **3** were confirmed by elemental analysis, mass spectrometry and ^1H, ^{13}C NMR spectral data. The ^1H NMR spectra showed characteristic broad signals from N-H between 12.4-13.2 ppm, the vinylic hydrogen singlet at 5.47-5.68 ppm



R	a	b	c	d	e	f	g
	n-Pr	CH_2Ph	$(CH_2)_2Ph$	Ph	4-Me-C_6H_4	4-MeO-C_6H_4	4-Cl-C_6H_4

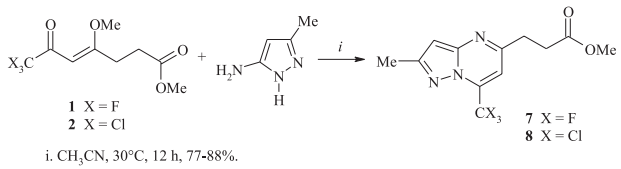
R	h	i	j	k
	4-Br-C_6H_4	5-methyl-3-isoxazolyl	2-pyridyl	4-H_2N-C_6H_4

i. RNH_2, MeCN, 25-80 °C, 6-24h. *ii*. Et_3N, MeCN, 80 °C, 24h, 75-95%.
iii. (a) RNH_2, MeCN, 25-80 °C, 12h; (b) Et_3N, 80 °C, 8-24h
iv. 1,4-diaminobenzene or ethylenediamine, MeCN, 25-80 °C, 12h.

Scheme 1.

and for methyl group of ester as intense singlet at 3.64-3.70 ppm.[12,13] The ^{13}C NMR spectra showed the signals of methoxy group at 51.5-51.9 ppm and carboxylic ester carbon at 169.8 –170.7 ppm confirming the propionyl chain, two characteristic quartets for carbonyl carbon C6, *ca.* 176-178 ppm, $^2J_{CF}$ 34 Hz and trifluoromethyl group C7, *ca.* 116.5-117.5 ppm, $^1J_{CF}$ 288 Hz, all confirming acyclic enaminone structures **3b-k** .

Reacting **1** or **2** with 5-amino-3-methyl-1*H*-pyrazole under conditions described above, the products of cyclocondensation [3 + 3], the methyl 3-(2-methyl-7-(trihalomethyl) pyrazolo[1,5-*a*]pyrimidin-5-yl)propanoates **7** and **8** (Scheme 2). Their structures were confirmed by elemental analysis and ^1H, ^{13}C NMR data.[15]



Scheme 2. 5-amino-3-methyl-1*H*-pyrazole lead to [CCC + NCN] cyclisation.

The easy intramolecular cyclization of methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3b,c** to pyrrolidin-2-ones **5b,c** occurred in MeOH, EtOH or MeCN. The intramolecular cyclisation of methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates **3d-j** to 5-(3,3,3-trifluoro-2-oxopropylidene)-pyrrolidin-2-ones **5d-j** occurred only

in refluxing MeCN in the presence of equimolar amount of Et_3N for reaction periods varying between 8-24 h. The products **5,b-k** can be obtained in *one pot* process by the reaction of precursor **1** and amine in MeCN followed by Et_3N addition and/or reflux (85 °C) affording similar yields.

The 1-Alkyl(aryl)-5-(3,3,3-trifluoro-2-oxopropylidene) pyrrolidin-2-ones **5,b-k** were characterised by elemental analysis, mass spectrometry and ^1H, ^{13}C NMR data. The ^1H NMR spectra showed characteristic signals for vinylic hydrogen at 5.66-5.94 ppm and the signals for cyclic CH_2 as multiplet at 2.67-2.83 and 3.33-3.57 ppm. The ^{13}C NMR spectra showed the signals of amide carbon at 167.8-169.2 ppm, two characteristic quartets of carbonyl carbon at propylidene chain *ca.* 178-179.3 ppm, $^2J_{CF}$ 34 Hz, for trifluoromethyl group CF_3 *ca.* 116.2-116.4 ppm, $^1J_{CF}$ 291 Hz and for vinylic carbon at 90.3-93.7 ppm, all confirming 1-alkyl[aryl]-5-(3,3,3-trifluoro-2-oxopropylidene) pyrrolidin-2-one structures **5,b-k**.

Compounds **3d** and **5b** were subjected to single crystal X-ray analysis (Tables 4 and 5). This measurement has showed in solid state the molecular structure with *Z*-configuration on alkene moiety and intramolecular hydrogen bond O3---H1—N1 for methyl 6-oxo-4-phenylamino-7,7,7-trifluoro-4-heptenoate (**3d**) (Figure 2). X-ray diffraction analysis performed on 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5b**) showed the *E*-configuration for enaminoketone moiety (Figure 3), confirming that the intramolecular cyclisation occurred with the inversion of configuration. In both structures the trifluoromethyl group suffers a rotational disorder and was refined as two components as approximately 60%/40% occupancy (Tables 1 and 2).

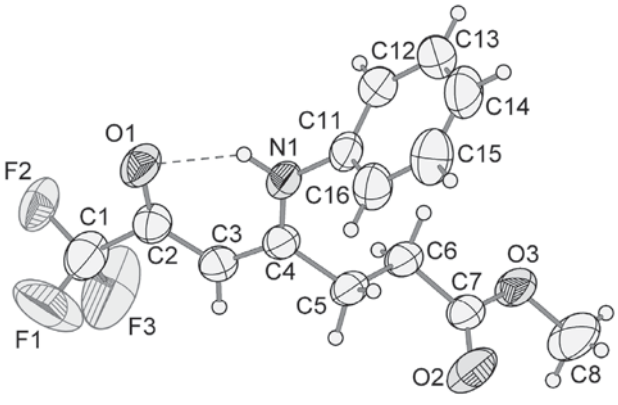


Figure 2. ORTEP representation of the X-ray molecular structure of methyl 4-benzylamino-2-oxo-7,7,7-trifluoro-4-heptanoate (**3d**).

The methyl 4-methoxy-6-oxo-7,7,7-trichloro-4-heptenoate demonstrated high reactivity for nucleophilic attack of alkylamines at β-carbon of the vinyl group, taking place of methoxy group, followed by fast intramolecular

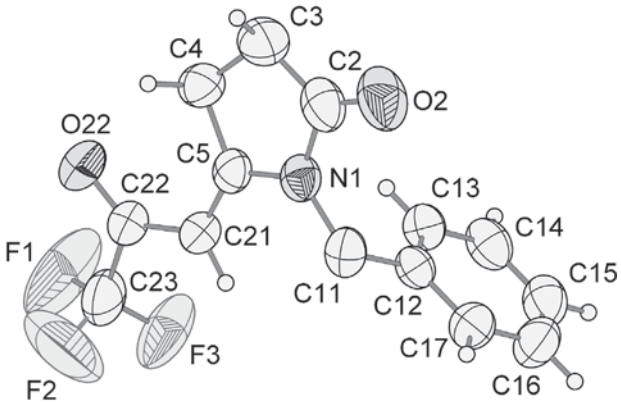


Figure 3. ORTEP representation of the X-ray molecular structure of 1-benzyl-5-(3,3,3-trifluoro-2-oxopropylidene)pyrrolidin-2-one (**5b**).

cyclisation to 1-alkyl-5-(3,3,3-trichloro-2-oxopropylidene)-pyrrolidin-2-ones. With the intention to isolate of the methyl 4-alkylamino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c**, the heptanoate precursor **2** was reacted with primary alkylamines in dichloromethane or chloroform at -5 - 0 ºC for 2 hours. Primary arylamines were reacted in MeCN at room temperature (Scheme 1) for 6 hours, and 4-arylamino-6-oxo-7,7,7-trichloro-4-heptenoates **4,d-j** were isolated in good yields and in high purity (Table 2, Supplementary Information). Reactions in EtOH or *i*-PrOH gave poor yields with complex mixtures of unidentified products, maybe involving transesterication and/or chloroform elimination.

The molecular structures of methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c-j** were confirmed by elemental analysis, mass spectrometry and ^1H, ^{13}C NMR spectral data. The ^1H NMR spectra showed characteristic broad signals for N-H between 13.4-13.8 ppm, the vinylic hydrogen at 5.85-5.89 ppm and for methoxy group as intense singlet at 3.60-3.67 ppm.[12,13] The ^{13}C NMR spectra showed the signals of methoxy group at characteristic region 51.9-52.9 ppm, for the carboxylic ester carbon at 181.2-181.7 ppm and low intense signal at 96-99.1 for trichloromethyl carbon confirming the attributed structure for methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a,c-j**.

The intramolecular cyclisation of isolated methyl 4-alkyl[aryl]amino-6-oxo-7,7,7-trichloro-4-heptenoates **4,a**,**c** to 5-(3,3,3-trichloro-2-oxopropylidene)pyrrolidin-2-ones **6,a**,**c** occurred in MeCN, affording quantitative yields without Et_3N addition. The products **6,d-f** and **6h** were obtained in good yields by stirring of **4** in MeCN at variable temperatures for 2 to 6 h. In general, the products **6** can be readily obtained in excellent yields without isolation of enaminones intermediates, by the reaction of precursor **2** and appropriate amine in MeCN under reflux

temperature (80-85 ºC). The 1,1'-(ethane-1,2-diyl)bis(5-(3,3,3-trichloro-2-oxopropylidene)pyrrolidin-2-one) **6l** was obtained by the reaction of **2** and ethylenediamine in 2:1 equiv ratio in MeCN at room temperature (Scheme 1).

The 1-alkyl[aryl]-5-(3,3,3-trichloro-2-oxopropylidene) pyrrolidin-2-ones **6a, 6c-f** and **6h** were characterised by elemental analysis, mass spectrometry and ^{1}H, ^{13}C NMR data. 2D COSY (HH and CH) and DEPT experiments were used for signal assignment.

Table 1. Crystal data and structure refinement for **3d** and **5b**

Crystal data	**3d**	**5b**
CCDC No.a	615368	615367
Formula	C14H14F3NO3	C14H12F3NO2
Habit	Colorless	Colorless
Size (mm)	0.15 x 0.15 x 0.1	0.35 x 0.15 x 0.13
Symmetry	Monoclinic, P2(1)/c	Orthorhombic, Pbca
Unit cell dimensions (Å)		
a, α	11.2299(5), 90°	9.6444(7), 90°
b, β	5.9503(2), 104.22°	15.5012(7), 90°
c, γ	22.8256(10), 90°	17.7423(9), 90°
Volume (A3), Z	1478.46(10), 4	2652.5(3), 8
Dc (g.cm-3)	1.353	1.419
μ (mm-1)	0.119	0.123
θ range for data collection (º)	3.55 < θ < 30.09	2.74 < θ < 27.0
Index ranges	-15 ≤ h ≤ 15 -8 ≤ k ≤ 8 -31 ≤ l ≤ 29	-5 ≤ h ≤ 12 -19 ≤ k ≤ 18 -22 ≤ l ≤ 22
Reflexions collected	17625	14247
Independent reflexions (Rint)	4275 (0.0313)	2895 0.0396
Completeness to θ	98.4 %	99.8 %
Tmin- Tmax	0.864 - 1.0	0.6937 - 1.0
Solution	Direct methods SHELXS-97	
Refinement method	Full-matrix least-squares on F2	
Data, restraints, parameters	4275, 48, 228	2895, 0, 195
Goodness-of-fit on F2	1.043	1.072
Final R indices [I > 2σ (I)]	R1 = 0.0494 wR2 = 0.1343	R1 = 0.0662 wR2 = 0.1951
R índices (all data)	R1 = 0.0975 wR2 = 0.1576	R1 = 0.1047 wR2 = 0.2254
Largest diff. peak and hole (e. Å-3)	0.23 and -0.227	0.337 and -0.535

[a] CCDC 286548 contains the supplementary crystallographic data for this paper. These data can be made available free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk or by contacting CCDC.

Table 2. Bond lengths [Å] and angles [º] for **3d** and **5b**

3d		**5b**	
C7-F1	1.3215(10)	N1-C2	1.398(4)
C7-F2	1.3219(10)	N1-C5	1.369(3)
C7-F3	1.3224(10)	N1-C11	1.454(3)
C7-C6	1.528(2)	C2-O2	1.209(4)
N1-C4	1.3339(19)	C2-C3	1.488(5)
N1-C11	1.4287(19)	C3-C4	1.517(5)
N1-H1	0.86	C3-H3A	0.97
C6-O3	1.2350(18)	C3-H3B	0.97
C6-C5	1.400(2)	C4-C5	1.503(4)
C1-O1	1.190(2)	C4-H4A	0.97
C5-C4	1.378(2)	C4-H4B	0.97
C5-H5	0.93	C5-C21	1.356(4)
C4-C3	1.505(2)	C21-C22	1.432(4)
C3-C2	1.510(2)	C21-H21	0.93
C3-H3A	0.97	C22-O22	1.214(3)
C3-H3B	0.97	C22-C23	1.566(4)
C2-C1	1.499(2)	C11-C12	1.505(4)
C2-H2A	0.97	C11-H11A	0.97
C2-H2B	0.97	C11-H11B	0.97
C1-O1	1.322(5)	C12-C13	1.372(4)
C1-O2	1.33(2)	C12-C17	1.386(4)
O2-C8	1.434(5)	C13-C14	1.386(4)
C8-H8A	0.96	C13-H13	0.93
C8-H8B	0.96	C14-C15	1.365(5)
C8-H8C	0.96	C14-H14	0.93
C11-C16	1.378(2)	C15-C16	1.366(5)
C11-C12	1.380(2)	C15-H15	0.93
C12-C13	1.379(2)	C16-C17	1.379(5)
C12-H12	0.93	C16-H16	0.93
C13-C14	1.376(3)	C17-H17	0.93
C13-H13	0.93	C23-F1	1.3207 (10)
C14-C15	1.374(3)	C23-F2	1.3210 (10)
C15-C16	1.378(3)	C23-F3	1.3215 (10)
F1-C7-F2	106.95(16)	C2-N1-C5	112.6(2)
F1-C7-C6	115.2(4)	C5-N1-C11	125.9(2)
C4-N1-C11	126.6(13)	C2-N1-C11	121.5(2)
C4-N1-H1	116.7	O2-C2-N1	122.3(3)
C11-N1-H1	116.7	O2-C2-C3	129.4(3)
O3-C6-C5	127.01(15)	N1-C2-C3	108.3(3)
O3-C6-C7	115.67(14)	C2-C3-C4	105.4(3)
C5-C6-C7	117.26(13)	C2-C3-H3A	110.7
C4-C5-C6	123.25(14)	C4-C3-H3A	110.7
C4-C5-H5	118.4	H3A-C3-H3B	108.8
C6-C5-H5	118.4	C5-C4-C3	105.0(2)

Table 2. continuation

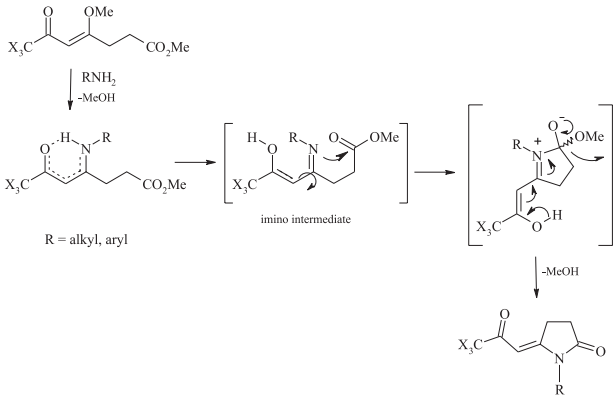
3d		5b	
N1-C4-C5	121.74(14)	C5-C4-H4A	110.8
N1-C4-C3	119.16(14)	C3-C4-H4A	110,8
C5-C4-C3	119.08(13)	H4A-C4-H4B	108.8
C4-C3-C2	113.15(13)	C21-C5-N1	123.8(2)
C4-C3-H3A	108.9	C21-C5-C4	127.5(2)
C2-C3-H3A	108.9	N1-C5-C4	108.7(2)
H3A-C3-H3B	107.8	N1-C11-C12	115.0(2)
C1-C2-C3	111.48(13)	N1-C11-H11A	108.5
O1-C1-O2	122.2(3)	C12-C11-H11A	108.5
O1-C1-C2	124.75(15)	C12-C11-H11B	108.5
O2-C1-C2	113.0(3)	C13-C12-C17	118.5(3)
C1-O2-C8	116.9(4)	C13-C12-C11	123.0(2)
C16-C11-C12	120.13(16)	C17-C12-C11	118.5(2)
C16-C11-N1	121.01(15)	C12-C13-C14	120.6(3)
C12-C11-N1	118.83(15)	C12-C13-H13	119.7
C13-C12-C11	120.06(18)	C14-C13-H13	119.7
C11-C12-H12	120.0	C15-C14-C13	120.2(3)
C14-C13-C12	119.83(19)	C14-C15-C16	120.0(3)
C15-C14-C13	119.93(19)	C15-C16-C17	120.0(3)
C14-C15-C16	120.6(2)	C16-C17-C12	120.7(3)
C11-C16-C15	119.44(19)	C5-C21-C22	122.3(2)
C13-C12-H12	120.0	O22-C22-C21	128.4(3)
C14-C13-H13	120.1	O22-C22-C23	115.7(2)
C14-C15-H15	119.7	C21-C22-C23	116.0(2)

The synthesis of 5-(3,3,3-trifluoro-2-oxopropylidene) pyrrolidin-2-ones from methyl 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates and primary amines can be characterised as an Paal-Knorr process for pyrrole heterocyclic from [CCCC + N] building blocks. Mechanistically, it is conceivable that the reaction involves an initial attack from amines to β-position, leading to enaminoketone moiety,[14] then an imino intermediate as shown in Scheme 3, which allow the rotation of trihalocarbonyl group around C4-C5 bond on 4-amino-6-oxo-7,7,7-trihalo-4-heptenoates, and intramolecular nucleophilic attack of imino nitrogen to ester carbonyl lead to pyrrolidin-2-ones.

Experimental

General

EtOH, MeOH, MeCN and Et_3N were purchased from Merck and Aldrich, R^1NH_2 was purchased from Aldrich, all used as obtained from suppliers. The methyl 7,7,7-trifluoro



Scheme 3.

[chloro]-4-methoxy-6-oxo-4-heptenoates **1** and **2** were prepared according to reference 8. All melting points were determined on a Reichert Thermovar instrument and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz and ^{13}C at 100.62 MHz) 5 mm sample tubes, 298 K, digital resolution ± 0.01 ppm, in $CDCl_3$ 0.02-0.05 g.mL^{-1}, using TMS as internal standard. Mass spectra were registered with a HP 6890 GC connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. The elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyser (São Paulo University/Brazil).

*Methyl 4-alkylamino-6-oxo-7,7,7-trifluoro-4-heptenoates (***3b** *and* **3c***)*

To a stirred solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-3-heptenoate 1 (5 mmol, 1.28 g) in MeCN (5 mL), kept at 25 ºC, was added benzylamine (5.1 mmol, 0.56 mL) or phenethylamine (5.1 mmol, 0.62 mL) in MeCN (5 mL). The mixture was stirred for 6 h. The solvent was evaporated and the solid residue was dried under vacuum. The enaminones **3b** and **3c** were purified on silica-gel chromatographic column using chloroform-hexane (2:1) as eluent, yield refers to purified product.

3b:Yield 57 %; oil; Anal. Calcd. for $C_{15}H_{16}F_3NO_3$ (315.29 g.mol^{-1}): C, 57.14; H, 5.11, N, 4.44. Found: C, 58.10; H, 5.40; N, 4.65. ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (m, H2), 2.67 (m, H3), 5.37 (s, H5), 3.69 (s, OMe), 4.61 (d, $^2J_{HH}$ 6.0 Hz, CH_2), 7.26 - 7.4 (m, Ph), 11.49 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2 (q, $^2J_{CF}$ 33 Hz, C6), 171.6 (C4), 171.3 (C1), 135.9 (C1, Ph), 129.0 (C3 and C5, Ph), 128.1 (C4, Ph), 126.9 (C2 and C6, Ph), 117.5 (q, $^1J_{CF}$ 288 Hz, C7), 87.5 (C5), 51.9 (OMe), 47.2 (-CH_2-), 31.2 (C2), 26.7 (C3). MS (EI, 70 eV) *m/z* (%): 315 (M^+, 29), 284 (5), 246(68), 218 (36), 91 (100), 65 (75).

3c: Yield 92 %; oil; Anal. Calcd. for $C_{16}H_{18}F_3NO_3$ (329.32 g.mol^{-1}): C, 58.36; H, 5.51, N, 4.25. Found: C, 57.70; H, 5.11; N, 4.44. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (t, $^3J_{HH}$ 7.0 Hz, H2), 2.48 (m, 4H, H3, CH_2), 5.25 (s, H5), 3.66 (s, OMe), 3.64 (t, $^3J_{HH}$ 7.5 Hz, CH_2), 7.18 - 7.3 (m, Ph), 11.25 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 (q, $^2J_{CF}$ 33 Hz, C6), 171.5 (C4), 171.1 (C1), 137.2 (C1, Ph), 128.6 (C3 and C5, Ph), 128.5 (C2 and C6, Ph), 126.8 (C4, Ph), 117.5 (q, $^1J_{CF}$ 288 Hz, C7), 87.1 (C5), 51.7 (OMe), 44.9 (NCH_2-), 36.0 (-CH_2Ph), 31.0 (C2), 26.3 (C3). MS (EI, 70 eV): *m/z* (%): 329 (M$^+$, 38), 298 (23), 238 (92), 206 (92), 178 (84), 104 (100), 77 (39).

Methyl 4-arylamino-6-oxo-7,7,7-trifluoro-4-heptenoates (***3,d-k***)

To a stirred solution of methyl 7,7,7-trifluoro-4-methoxy-6-oxo-3-heptenoate **1** (5 mmol, 1.28 g) in MeCN (5 mL), was added the appropriate arylamine (Aldrich, 5.1 mmol) in MeCN (5 mL). The mixture was refluxed for 6 to 24 h. Then the solvent was evaporated and solid residue was dried under vacuum. Enaminones **3,d-k** were recrystallised from hexane-chloroform (2:1), yield refers to purified product.

3d: Yield 76 %; mp 51-53 ºC; Anal. Calcd. for $C_{14}H_{14}F_3NO_3$ (301.27 g.mol^{-1}): C, 55.82; H, 4.68, N, 4.65. Found: C, 56.07; H, 4.65; N, 4.35. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (t, $^3J_{HH}$ 7.5 Hz, H2), 2.72 (t, $^3J_{HH}$ 7.6 Hz, H3), 5.54 (s, H5), 3.64 (s, OMe), 7.14 - 7.5 (m, Ph), 12.6 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (q, $^2J_{CF}$ 33 Hz, C6), 171.5 (C4), 170.0 (C1), 136.4 (C1, Ph), 129.6 (C3 and C5, Ph), 127.1, (C4, Ph), 125.7 (C2 and C6, Ph), 117.3 (q, $^1J_{CF}$ 288 Hz, C7), 88.6 (C5), 51.8 (OMe), 31.4 (C2), 27.1 (C3). MS (EI, 70 eV): *m/z* (%): 301 (M$^+$, 39), 270 (19), 200 (82), 172 (78), 144 (48), 130 (49), 77 (100).

3e: Yield 92 %; mp 43-45 ºC; Anal. Calcd. for $C_{15}H_{16}F_3NO_3$ (315.29 g.mol^{-1}): C, 57.14; H, 5.11, N, 4.44. Found: C, 57.48; H, 4.99; N, 4.65. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, $^3J_{HH}$ 7.0 Hz, H2), 2.70 (t, $^3J_{HH}$ 7.2 Hz, H3), 5.51 (s, H5), 3.66 (s, OMe), 2.38 (s, 4-CH_3), 7.07 (m, 2H, Ph), 7.23 (m, 2H, Ph), 12.5 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (q, $^2J_{CF}$ 33 Hz, C6), 170.6 (C4), 170.0 (C1), 137.9 (C1, Ph), 133.8 (C4, Ph), 130.2 (C3 and C5, Ph), 125.6 (C2 and C6, Ph), 117.4 (q, $^1J_{CF}$ 288 Hz, C7), 88.5 (C5), 51.9 (OMe), 31.4 (C2), 27.1 (C3), 20.9 (4-CH_3). MS (EI, 70 eV): *m/z* (%): 315 (M$^+$, 61), 284 (16), 228 (25), 214 (100), 186 (73), 158 (34), 144 (41), 91 (59).

3f: Yield 74 %; mp 52-54 ºC; Anal. Calcd. for $C_{15}H_{16}F_3NO_4$ (331.29 g.mol^{-1}): C, 54.38; H, 4.87, N, 4.23. Found: C, 54.25; H, 4.93; N, 3.87. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (t, $^3J_{HH}$ 7.8 Hz, H2), 2.66 (t, $^3J_{HH}$ 7.8 Hz, H3), 5.50 (s, H5), 3.66 (s, OMe), 3.83 (s, 4-OMe), 6.93 (m, 2H, Ph), 7.11 (m, 2H, Ph), 12.4 (NH, br).^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (q, $^2J_{CF}$ 33 Hz, C6), 171.6 (C4), 170.5 (C1), 159.1 (C4, Ph), 129.2.(C1, Ph), 127.2 (C3 and C5, Ph), 117.4 (q, $^1J_{CF}$ 288 Hz, C7), 114.8 (C2 and C6, Ph), 88.4 (C5), 55.5 (4-OMe), 51.9 (OMe), 31.5 (C2), 27.2 (C3). MS (EI, 70 eV): *m/z* (%): 331 (M$^+$, 100), 300 (15), 272 (24), 230 (78), 202 (38), 160 (27), 132 (13), 92 (15).

3g: Yield 98 %; mp 81-83 ºC; Anal. Calcd. for $C_{14}H_{13}ClF_3NO_3$ (335.71 g.mol^{-1}): C, 50.09; H, 3.90, N, 4.71. Found: C, 50.18; H, 3.91; N, 4.97. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (t, $^3J_{HH}$ 7.2 Hz, H2), 2.70 (t, $^3J_{HH}$ 7.2 Hz, H3), 5.55 (s, H5), 3.66 (s, OMe), 7.16 (m, 2H, Ph), 7.40 (m, 2H, Ph), 12.5 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (q, $^2J_{CF}$ 33 Hz, C6), 171.4 (C4), 169.8 (C1), 135.0 (C1, Ph), 133.5 (C4, Ph), 129.7 (C3 and C5, Ph), 127.0 (C2 and C6, Ph), 117.2 (q, $^1J_{CF}$ 288 Hz, C7), 88.9 (C5), 51.8 (OMe), 31.3 (C2), 26.9 (C3). MS (EI, 70 eV): *m/z* (%): 335 (M$^+$, 31), 304 (14), 276 (18), 234 (100), 206 (96), 178 (60), 143 (39), 111 (81), 75 (82).

3h: Yield 95 %; mp 77-79 ºC; Anal. Calcd. for $C_{14}H_{13}BrF_3NO_3$ (380.16 g.mol^{-1}): C, 44.23; H, 3.45, N, 3.68. Found: C, 44.37; H, 3.44; N, 3.57. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.54 (t, $^3J_{HH}$ = 7.2 Hz, H2), 2.70 (t, $^3J_{HH}$ = 7.2 Hz, H3), 5.55 (s, H5), 3.67 (s, OMe), 7.10 (m, 2H, Ph), 7.56 (m, 2H, Ph), 12.5 (NH, br).^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (q, $^2J_{CF}$ 34 Hz, C6), 171.4 (C4), 169.7 (C1), 135.4 (C1, Ph), 132.7 (C3 and C5, Ph), 127.3 (C2 and C6, Ph), 121.4 (C4, Ph), 117.1 (q, $^1J_{CF}$ 288 Hz, C7), 88.9 (C5), 51.9 (OMe), 31.2 (C2), 26.9 (C3). MS (EI, 70 eV): *m/z* (%): 380 (M$^+$, 69), 348 (21), 310 (34), 278 (100), 250 (52), 231 (57), 199 (61), 172 (70), 143 (86), 76 (77).

3i: Yield 95 %; mp 68-70 ºC; Anal. Calcd. for $C_{12}H_{13}F_3N_2O_4$ (306.24 g.mol^{-1}): C, 47.06; H, 4.28, N, 9.15. Found: C, 46.97; H, 4.19; N, 8.98. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (t, $^3J_{HH}$ 7.6 Hz, H2), 3.13 (t, $^3J_{HH}$ 7.6 Hz, H3), 5.68 (s, H5), 3.70 (s, OMe), 2.43 (s, 3-CH_3, isox), 5.98 (s, H5, isox), 12.4 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5 (q, $^2J_{CF}$ 34 Hz, C6), 171.6 (C4), 170.7 (C1), 168.3 (C5, isox), 157.6 (C3, isox), 116.6 (q, $^1J_{CF}$ 288 Hz, C7), 96.7 (C4, isox), 92.2 (C5), 51.5 (OMe), 31.3 (C2), 29.4 (C3), 11.9 (3-Me, isox). MS (EI, 70 eV): *m/z* (%): 306 (M$^+$, 9), 275 (18), 237 (100), 278 (100), 205 (60), 149 (43), 135 (47), 119 (46), 68 (58).

3j: Yield 95 %; mp 65-68 ºC; Anal. Calcd. for $C_{13}H_{13}F_3N_2O_3$ (302.26 g.mol^{-1}): C, 51.66; H, 4.34, N, 9.27. Found: C, 51.41; H, 4.18; N, 9.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (t, $^3J_{HH}$ 7.2 Hz, H2), 3.33 (t, $^3J_{HH}$ 7.2 Hz, H3), 5.61 (s, H5), 3.70 (s, OMe), 7.0, 7.1, 7.7, 8.4 (2-pyridyl), 12.9 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (q, $^2J_{CF}$ 34 Hz, C6), 172.1 (C4), 168.7 (C1), 151.1 (C2, pyr), 148.3 (C6, pyr), 138.4 (C4, pyr),

120.2 (C3, pyr), 115.5 (C5, pyr), 117.0 (q, $^1J_{CF}$ 288 Hz, C7), 92.5 (C5), 51.1 (OMe), 32.3 (C2), 29.5 (C3). MS (EI, 70 eV): *m/z* (%): 271 (M^+-OMe, 34), 233 (21), 205 (100), 173 (98), 131 (88), 96 (18), 78 (97), 51 (38).

3k: Yield 95 %; mp 65-68 ºC; Anal. Calcd. for $C_{14}H_{15}F_3N_2O_3$ (316.28 g.mol^{-1}): C, 53.17; H, 4.78, N, 8.86. Found: C, 55.00; H, 5.28; N, 9.90. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (t, $^3J_{HH}$ 7.5 Hz, H2), 2.66 (t, $^3J_{HH}$ 7.5 Hz, H3), 5.47 (s, H5), 3.66 (s, OMe), 6.68 (m, 2H, Ph), 6.96 (m, 2H, Ph), 13.2 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (q, $^2J_{CF}$ 34 Hz, C6), 171.7 (C4), 170.8 (C1), 146.3 (C4, Ph), 126.9 (C3, C4 and C5, Ph), 115.4 (C2 and C6, Ph), 88.2 (C5), 31.5 (C2), 27.2 (C3). MS (EI, 70 eV): *m/z* (%): 316 (M^+, 100), 285 (10), 257 (15), 215 (36), 187 (33), 173 (32), 92 (19).

*Methyl 7,7,7-trichloro-4-alkylamino-6-oxo-4-heptenoates (***4a** *and* **4c***)*

To a stirred solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-3-heptenoate **2** (5 mmol, 1.52 g) in $CHCl_3$ (5 mL), kept at 25 ºC, was added n-propylamine (Aldrich, 18570-1, 5.1 mmol, 0.42 mL) or phenethylamine (Aldrich, 24095-8, 5.1 mmol, 0.62 mL) in $CHCl_3$ (5 mL). The mixture was stirred for 2 h. Then the solvent was evaporated and solid residue was dried under vacuum. The enaminones **4a** and **4c** were purified on silica-gel chromatographic column using chloroform-hexane (2:1) as eluent, yield refers to purified product.

4a: Yield 94 %; Oil; Anal. Calcd. for $C_{11}H_{16}Cl_3NO_3$ (316.61 g.mol^{-1}): C, 41.73; H, 5.09, N, 4.42. Found: C, 41.39; H, 4.95; N, 4.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (m, H2 and H3), 5.67 (s, H5), 3.73 (s, OMe), 3.36 (t, CH_2), 1.72 (q, CH_2), 1.05 (t, CH_3), 12.8 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1 (C6), 171.6 (C4), 170.3 (C1), 96.9 (C7), 84.2 (C5) 51.8 (OMe), 44.9 (NCH_2-), 31.2 (C2), 27.0 (C3), 22.7 (-CH_2-), 11.1 (Me). MS (EI, 70 eV): *m/z* (%): 318 (M^++ 2, 10), 316 (M^+, 10), 252 (39), 198 (100), 166 (36).

4c: Yield 98 %; Oil; Anal. Calcd. for $C_{16}H_{18}Cl_3NO_3$ (378.69 g.mol^{-1}): C, 50.75; H, 4.79, N, 3.70. Found: C, 52.0; H, 4.97; N, 4.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.53 (t, $^3J_{HH}$ 7.2 Hz, H2), 2.95 (t, $^3J_{HH}$ 7.2 Hz, H3), 5.64 (s, H5), 3.69 (s, OMe), 2.53 (CH_2), 3.61 (CH_2), 7.2 - 7.33 (Ph), 12.8 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3 (C6), 171.6 (C4), 170.2 (C1), 137.3 (C1, Ph), 128.6 (C3 and C5, Ph), 128.5 (C4, Ph), 126.8 (C2 and C6, Ph), 96.9 (C7), 84.5 (C5), 51.9 (OMe), 45.0 (NCH_2-), 36.1 (-CH_2Ph), 31.2 (C2), 26.8 (C3). MS (EI, 70 eV): *m/z* (%): 381 (M^++ 2, 13), 379 (M^+, 10), 314 (44), 286 (50), 260 (100), 228 (23), 105 (100), 77 (50).

*Methyl 7,7,7-trichloro-4-arylamino-6-oxo-4-heptenoates (***4d-4i***)*

To a stirred solution of methyl 7,7,7-trichloro-4-methoxy-6-oxo-3-heptenoate **2** (5 mmol, 1.52 g) in MeCN (5 mL), kept at 25 ºC, was added appropriate arylamine (Aldrich, 5.1 mmol) in MeCN (5 mL). The mixture was refluxed for 2 to 6 h. The solvent was evaporated and the solid residue was dried under reduced pressure. The enaminones **4d-i, 4k** were recrystallised from hexane: $CHCl_3$ (2:1), yield refers to purified product.

4d: Yield 73 %; mp 79-82 ºC; Anal. Calcd. for $C_{14}H_{14}Cl_3NO_3$ (350.63 g.mol^{-1}): C, 47.96; H, 4.02, N, 3.99. Found: C, 48.0; H, 4.50; N, 3.90. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, $^3J_{HH}$ 7.0 Hz, H2), 2.75 (t, $^3J_{HH}$ 7.0 Hz, H3), 5.88 (s, H5), 3.66 (s, OMe), 7.2 - 7.44 (Ph), 13.8 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4 (C6), 171.6 (C4), 168.8 (C1), 136.8 (C1, Ph), 129.6 (C3 and C5, Ph), 127.5 (C4, Ph), 125.7 (C2 and C6, Ph), 96.9 (C7), 86.5 (C5), 51.9 (OMe), 31.6 (C2), 27.5 (C3). MS (EI, 70 eV): *m/z* (%): 352 (M^++ 2, <5), 350 (M^+, 10), 232 (85), 200 (100), 172 (61), 144 (27), 77 (60).

4e: Yield 76 %; mp 53-55 ºC; Anal. Calcd. for $C_{14}H_{14}Cl_3NO_3$ (364.66 g.mol^{-1}): C, 49.41; H, 4.42, N, 3.84. Found: C, 49.90; H, 5.0; N, 3.55. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, $^3J_{HH}$ 7.7 Hz, H2), 2.73 (t, $^3J_{HH}$ 7.5 Hz, H3), 5.86 (s, H5), 3.65 (s, OMe), 2.37 (4-Me), 7.1 (3H, Ph), 7.3 (2H, Ph), 13.6 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2 (C6), 171.7 (C4), 169.2 (C1), 137.6 (C1, Ph), 134.1 (C3 and C5, Ph), 130.1 (C4, Ph), 125.5 (C2 and C6, Ph), 96.9 (C7), 86.2 (C5) 51.9 (OMe), 31.7 (C2), 27.5 (C3), 20.9 (4-Me). MS (EI, 70 eV): *m/z* (%): 367 (M^++2, 7), 365 (M^+, 7), 246 (70), 214 (100), 186 (47), 158 (14), 91 (39).

4f: Yield 70 %; mp 79-81 ºC; Anal. Calcd. for $C_{15}H_{16}Cl_3NO_4$ (380.66 g.mol^{-1}): C, 47.33; H, 4.24, N, 3.68. Found: C, 47.10; H, 4.20; N, 4.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, $^3J_{HH}$ 7.5 Hz, H2), 2.70 (t, $^3J_{HH}$ 7.5 Hz, H3), 5.86 (s, H5), 3.66 (s, OMe), 3.84 (4-OMe), 6.9 (3H, Ph), 7.13 (2H, Ph), 13.6 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2 (C6), 171.7 (C4), 169.5 (C1), 158.9 (C4, Ph), 129.2 (C1, Ph), 127.2 (C3 and C5, Ph), 114.7 (C2 and C6, Ph), 97.0 (C7), 86.0 (C5), 55.4 (4-OMe), 51.9 (OMe), 31.7 (C2), 27.5 (C3). MS (EI, 70 eV): *m/z* (%): 381 (M^++2, 15), 379 (M^+, 14), 262 (75), 230 (100), 202 (28), 174 (10), 77 (16).

4g: Yield 88 %; mp 105-107 ºC; Anal. Calcd. for $C_{14}H_{13}Cl_4NO_3$ (385.08 g.mol^{-1}): C, 43.67; H, 3.40, N, 3.64. Found: C, 44.87; H, 4.10; N, 3.90. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (t, $^3J_{HH}$ 7.8 Hz, H2), 2.73 (t, $^3J_{HH}$ 7.6 Hz, H3), 5.89 (s, H5), 3.66 (s, OMe), 7.15 (3H, Ph), 7.40 (2H, Ph), 13.4 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7

(C6), 171.5 (C4), 168.6 (C1), 135.4 (C1, Ph), 133.3 (C3 and C5, Ph), 129.8 (C4, Ph), 127.0 (C2 and C6, Ph), 96.8 (C7), 86.9 (C5), 52.0 (OMe), 31.6 (C2), 27.4 (C3). MS (EI, 70 eV): *m/z* (%): 385 (M^++2, 10), 383 (M^+, 6), 266 (70), 234 (100), 206 (40), 178 (10), 111 (10).

4h: Yield 85 %; mp 97-100 ºC; Anal. Calcd. for $C_{14}H_{13}BrCl_3NO_3$ (429.53 g.mol^{-1}): C, 39.15; H, 3.05, N, 3.26. Found: C, 39.17; H, 3.10; N, 3.50. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (t, $^3J_{HH}$ 7.5 Hz, H2), 2.74 (t, $^3J_{HH}$ 7.6 Hz, H3), 5.89 (s, H5), 3.67 (s, OMe), 7.1 (3H, Ph), 7.56 (2H, Ph), 13.0 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6 (C6), 171.5 (C4), 168.4 (C1), 135.4 (C1, Ph), 133.3 (C3 and C5, Ph), 129.8 (C4, Ph), 127.0 (C2 and C6, Ph), 96.7 (C7), 86.9 (C5), 52.0 (OMe), 31.5 (C2), 27.4 (C3). MS (EI, 70 eV): *m/z* (%): 430 (M^++2, 16), 428 (M^+, 10), 310 (86), 278 (100), 250 (30), 231 (70).

4k: Yield 90 %; mp 114-116 ºC; Anal. Calcd. for $C_{14}H_{15}Cl_3N_2O_3$ (366.65 g.mol^{-1}): C, 45.99; H, 4.13, N, 7.66. Found: C, 47.17; H, 4.83; N, 8.20.^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (t, $^3J_{HH}$ 7.0 Hz, H2), 2.74 (t, $^3J_{HH}$ 7.2 Hz, H3), 5.85 (s, H5), 3.60 (s, OMe), 6.75 (3H, Ph), 7.0 (2H, Ph), 13.8 (NH, br). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7 (C6), 173.3 (C4), 172.3 (C1), 149.6 (C4, Ph), 128.6 (C3 and C5, Ph), 127.5 (C1, Ph), 116.4 (C2 and C6, Ph), 99.1 (C7), 86.6 (C5), 52.9 (OMe), 33.0 (C2), 29.0 (C3). MS (EI, 70 eV): *m/z* (%): 366 (M^++2, 16), 364 (M^+, 15), 247 (46), 215 (100), 187 (38), 173 (50), 159 (12), 92 (16).

1-[Alkyl(aryl)]-5-(3,3,3-trifluoro[chloro]-2-oxopropylidene)pyrrolidin-2-ones **(5, 6)**

To a stirred solution of appropriate methyl 7,7,7-trihalo-4-alkyl(aryl)amino-6-oxo-3-heptenoate (**3** or **4,** 2 mmol) in MeCN (5 mL), kept at 25 °C, was added Et_3N (2 mmol, 0.3 mL) in MeCN (1 mL). The mixture was refluxed for 1 to 24 h and the solvent was removed under reduced pressure. The residue was crystallised from hexane, yield refers to purified product.

5b: Yield 69 %; mp 96-98 ºC; Anal. Calcd. for $C_{14}H_{12}F_3NO_2$ (283.25 g.mol^{-1}): C, 59.37; H, 4.27, N, 4.94. Found: C, 60.10; H, 4.01; N, 5.03. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (m, H3), 3.33 (m, H4), 5.89 (s, CH), 4.79 (s, CH_2), 7.23 (3H, Ph), 7.4 (2H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 ($^2J_{CF}$ 34 Hz, C2, propylidene), 177.1 (C5, pyrrolidin-2-one), 167.8 (C2, pyrrolidin-2-one), 133.9 (C1, Ph), 128.9 (C4, Ph), 128.1 (C2 and C6, Ph), 127.3 (C3 and C5, Ph), 116.3 ($^1J_{CF}$ 292 Hz, C3, propylidene), 92.0 (C1, propylidene), 44.5 (-CH_2-), 27.2 (C4, pyrrolidin-2-one), 26.6 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 283 (M^+, 5), 214 (28), 186 (17), 91 (100), 65 (22).

5c: Yield 87 %; mp 103-105 ºC; Anal. Calcd. for $C_{15}H_{14}F_3NO_2$ (297.28 g.mol^{-1}): C, 60.61; H, 4.75, N, 4.71. Found: C, 60.41; H, 4.60; N, 4.57. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (m, H3, pyrrolidin-2-one), 3.29 (m, H4, pyrrolidin-2-one), 5.78 (s, H1, propylidene), 2.88 (CH_2), 3.82 (CH_2), 7.1 - 7.4 (Ph).^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 ($^2J_{CF}$ 34 Hz, C2, propylidene), 176.8 (C5, pyrrolidin-2-one), 168.2 (C2, pyrrolidin-2-one), 137.0 (C1, Ph), 128.7 (C3 and C5, Ph), 128.6 (C2 and C6, Ph), 127 (C4, Ph), 116.4 ($^1J_{CF}$ 292 Hz, C3, propylidene), 91.0 (C1, propylidene), 42.3 (NCH_2), 32.6 (CH_2Ph), 26.7 (C3, pyrrolidin-2-one), 27.1 (C4, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 297 (M^+, 5), 228 (24), 178 (10), 104 (100), 77 (13).

5d: Yield 77 %; mp 146-149 ºC; Anal. Calcd. for $C_{13}H_{10}F_3NO_2$ (269.23 g.mol^{-1}): C, 58.00; H, 3.74, N, 5.20. Found: C, 57.78; H, 3.81; N, 4.90. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (m, H3), 3.53 (m, H4), 5.66 (s, CH), 7.2 (3H, Ph), 7.5 (2H, Ph).^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2 ($^2J_{CF}$ 34 Hz, C2, propylidene), 176.5 (C5, pyrrolidin-2-one), 169.2 (C2, pyrrolidin-2-one), 133.2 (C1, Ph), 130.1 (C3 and C5, Ph), 129.8 (C2 and C5, Ph), 127.1 (C4, Ph), 116.4 ($^1J_{CF}$ 292 Hz, C3, propylidene), 92.7 (C1, propylidene), 27.8 (C4, pyrrolidin-2-one), 26.9 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 269 (M^+, 13), 200 (100), 172 (68), 144 (29), 77 (69), 51 (41).

5e: Yield 86 %; mp 129-131 ºC; Anal. Calcd. for $C_{14}H_{12}F_3NO_2$ (283.25 g.mol^{-1}): C, 59.37; H, 4.27, N, 4.94. Found: C, 59.28; H, 4.38; N, 4.79. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.80 (m, H3, pyrrolidin-2-one), 3.50 (m, H4, pyrrolidin-2-one), 5.67 (s, H1, propylidene), 2.43 (4-Me), 7.06 (3H, Ph), 7.34 (2H, Ph).^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0 ($^2J_{CF}$ 34 Hz, C2, propylidene), 176.7 (C5, pyrrolidin-2-one), 169.5 (C2, pyrrolidin-2-one), 139.9 (C1, Ph), 130.7 (C2 and C6, Ph), 130.4 (C4, Ph), 126.8 (C3 and C5, Ph), 116.2 ($^1J_{CF}$ 291 Hz, C3, propylidene), 92.6 (C1, propylidene), 27.7 (C4, pyrrolidin-2-one), 26.9 (C3, pyrrolidin-2-one), 21.1 (4-Me). MS (EI, 70 eV): *m/z* (%): 283 (M^+, 24), 214 (100), 186 (53), 158 (17), 91 (43).

5f: Yield 91 %; mp 88-90 ºC; Anal. Calcd. for $C_{14}H_{12}F_3NO_3$ (299.25 g.mol^{-1}): C, 56.19; H, 4.04, N, 4.68. Found: C, 55.91; H, 4.10; N, 4.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (m, H3), 3.50 (m, H4), 5.66 (s, CH), 3.87 (OMe), 7.05 (3H, Ph), 7.12 (2H, Ph). ^{13}C NMR (100 MHz, CDCl3) δ 178.9 ($^2J_{CF}$ 34 Hz, C2, propylidene), 176.6 (C5, pyrrolidin-2-one), 169.7 (C2, pyrrolidin-2-one), 160.3 (C4, Ph), 128.2 (C1, Ph), 125.6 (C3 and C5, Ph), 115.3 (C2 and C6, Ph), 116.3 ($^1J_{CF}$ 291 Hz, C3, propylidene), 92.4 (C1, propylidene), 55.4 (OMe), 27.6 (C4, pyrrolidin-2-one), 26.8 (C3, pyrrolidin2-one). MS (EI, 70 eV): *m/z* (%): 299 (M^+, 53), 230 (100), 202 (28), 188 (31), 159 (24), 131 (14), 77 (21).

5g: Yield 70 %; mp 163-165 ºC; Anal. Calcd. for $C_{13}H_9ClF_3NO_2$ (303.67 g.mol^{-1}): C, 56.19; H, 4.04, N, 4.68. Found: C, 55.91; H, 4.10; N, 4.51. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (m, H3), 3.52 (m, H4), 5.66 (s, CH), 7.16 (3H, Ph), 7.54 (2H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.7 (C2), 26.9 (C3), 27.7 (C4), 176.3 (C5), 92.7 (CH) 178.0 ($^2J_{CF}$ 35 Hz, C=O), 116.2 ($^1J_{CF}$ 291 Hz, CF_3), 128.5, 130.4, 131.5, 135.8 (Ph). MS (EI, 70 eV): *m/z* (%): 303 (M^+, 23), 234 (100), 206 (62), 178 (21), 143 (23), 111 (28), 75 (41).

5h: Yield 95 %; mp 151-153 ºC; Anal. Calcd. for $C_{13}H_9BrF_3NO_2$ (348.12 g.mol^{-1}): C, 44.85; H, 2.61, N, 4.02. Found: C, 44.75; H, 2.63; N, 3.95. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (m, H3), 3.52 (m, H4), 5.66 (s, CH), 7.1 (3H, Ph), 7.7 (2H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.5 (C2), 26.9 (C3), 27.8 (C4), 176.2 (C5), 92.9 (CH) 179.2 ($^2J_{CF}$ 35 Hz, C=O), 116.2 ($^1J_{CF}$ 291 Hz, CF_3), 124.0, 128.8, 132.1, 133.5 (Ph). MS (EI, 70 eV): *m/z* (%): 348 (M^+, 29), 278 (100), 250 (29), 222 (14), 199 (37), 143 (39), 76 (41).

5j: Yield 73 %; mp 165-167 ºC; Anal. Calcd. for $C_{12}H_9F_3N_2O_2$ (270.21 g.mol^{-1}): C, 53.34; H, 3.36, N, 10.37. Found: C, 53.30; H, 3.50; N, 10.60. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (m, H3), 3.54 (m, H4), 5.94 (s, CH), 7.36 (1H, Py), 7.46 (1H, Py), 7.95 (1H, Py), 8.69 (1H, Py). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.1 (C2), 26.9 (C3), 28.0 (C4), 176.3 (C5), 93.7 (CH) 179.2 ($^2J_{CF}$ 34 Hz, C=O), 116.2 ($^1J_{CF}$ 292 Hz, CF_3), 122.5, 124.5, 139.1, 147.2, 150.1 (Py). MS (EI, 70 eV): *m/z* (%): 201 (18), 173 (100), 145 (20), 131 (43), 78 (52), 69 (8).

5k: Yield 71 %; mp 256-258 ºC; Anal. Calcd. for $C_{20}H_{14}F_6N_2O_4$ (460.34 g.mol^{-1}): C, 52.18; H, 3.07, N, 6.09. Found: C, 52.80; H, 3.10; N, 6.50. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (m, H3), 3.57 (m, H4), 5.77 (s, CH), 7.4 (Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3 ($^2J_{CF}$ 35 Hz, C2, propylidene), 176.2 (C5, pyrrolidin-2-one), 168.2 (C2, pyrrolidin-2-one), 134.2 (2C, C1, Ph), 129.1 (4C, C2, C3, Ph), 116.2 ($^1J_{CF}$ 291 Hz, C3, propylidene), 93.0 (C1, propylidene), 27.8 (C4, pyrrolidin-2-one), 26.9 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 460 (M^+, 36), 391 (100), 363 (10), 161 (20), 143 (15), 69 (15), 55 (33).

6a: Yield 75 %; mp 78-80 ºC; Anal. Calcd. for $C_{10}H_{12}Cl_3NO_2$ (284.57 g.mol^{-1}): C, 42.21; H, 4.25, N, 4.92. Found: C, 42.80; H, 4.50; N, 5.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (m, H3), 3.35 (m, H4), 6.17 (s, CH), 3.6 (CH_2), 1.65 (CH_2), 0.95 (Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2 (C2, propylidene), 177.0 (C5, pyrrolidin-2-one), 167.2 (C2, pyrrolidin-2-one), 97.4 (C3, propylidene), , 90.3 (C1, propylidene), 42.5 (NCH_2), 27.5 (C4, pyrrolidin-2-one), 26.3 (C3, pyrrolidin-2-one), 19.9 (CH_2), 11.3 (Me). MS (EI, 70 eV): *m/z* (%): 285 (M^++2, 10), 283 (M^+, 10), 220 (22), 166 (100), 124 (73), 68 (61).

6c: Yield 87 %; mp 145-148 ºC; Anal. Calcd. for $C_{10}H_{12}Cl_3NO_2$ (346.64 g.mol^{-1}): C, 51.97; H, 4.07, N, 4.04. Found: C, 51.30; H, 3.80; N, 4.00. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (m, H3), 3.32 (m, H4), 6.18 (s, CH), 2.9 (CH_2), 3.85 (CH_2), 7.1- 7.4 (Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0 (C2, propylidene), 176.6 (C5, pyrrolidin-2-one), 166.8 (C2, pyrrolidin-2-one), 137 (C1, Ph), 128.7 (C3 and C5, Ph), 128,5 (C4, Ph), 126.9 (C2 and C6, Ph), 97.3 (C3, propylidene), 90.3 (C1, propylidene), 42.2 (NCH_2), 32.7 (CH_2Ph), 27.4 (C4, pyrrolidin-2-one), 26.2 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 347 (M^++2, 7), 345 (M^+, 7), 282 (20), 228 (100), 124 (35), 105 (90).

6d: Yield 93 %; mp 158-160 ºC; Anal. Calcd. for $C_{13}H_9Cl_3NO_2$ (318.59 g.mol^{-1}): C, 49.01; H, 3.16, N, 4.40. Found: C, 50.05; H, 3.20; N, 3.80. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.82 (m, H3), 3.53 (m, H4), 5.97 (s, CH), 7.2 (2H, Ph), 7.56 (3H, Ph).^{13}C NMR (50 MHz, $CDCl_3$) δ 180.4 (C2, propylidene), 176.5 (C5, pyrrolidin-2-one), 167.9 (C2, pyrrolidin-2-one), 133.3 (C1, Ph), 130 (C3 and C5, Ph), 129.6 (C2 and C6, Ph) 127.1 (C4, Ph), 97 (C3, propylidene), 92 (C1, propylidene), 28 (C4, pyrrolidin-2-one), 26.4 (C3, pyrrolidin-2-one). MS (EI, 70 eV): *m/z* (%): 319 (M^++2, <5), 317 (M^+, <5), 256 (5), 254 (10), 202 (15), 200 (100), 172 (30), 77 (20).

6e: Yield 95 %; mp 175-178 ºC; Anal. Calcd. for $C_{14}H_{12}Cl_3NO_2$ (332.62 g.mol^{-1}): C, 50.56; H, 3.64, N, 4.21. Found: C, 50.30; H, 3.50; N, 4.60. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (m, H3), 3.52 (m, H4), 5.98 (s, CH), 2.43 (4-Me), 7.1 (2H, Ph), 7.35 (3H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.5 (C2, propylidene), 176.5 (C5, pyrrolidin-2-one), 168.2 (C2, pyrrolidin-2-one), 133.3 (C1, Ph), 130.0 (C3 and C5, Ph), 129.6 (C4, Ph), 127.1 (C2 and C6, Ph), 97.0 (C3, propylidene), 92.0 (C1, propylidene), 28.0 (C4, pyrrolidin-2-one), 26.4 (C3, pyrrolidin-2-one), 21.2 (4-Me). MS (EI, 70 eV): *m/z* (%): 333 (M^++2, < 5), 331 (M^+, < 5), 270 (7), 268 (10), 216 (15), 214 (100).

6f: Yield 95 %; mp 169-171 ºC; Anal. Calcd. for $C_{14}H_{12}Cl_3NO_3$ (348.62 g.mol^{-1}): C, 48.24; H, 3.47, N, 4.02. Found: C, 48.90; H, 4.0; N, 3.78. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.79 (m, H3), 3.50 (m, H4), 5.98 (s, CH), 3.86 (4-OMe), 7.05 (2H, Ph), 7.15 (3H, Ph).^{13}C NMR (50 MHz, $CDCl_3$) δ 168.4 (C2), 26.4 (C3), 27.9 (C4), 176.7 (C5), 92.0 (CH) 180.5 (C=O), 97.1 (CCl_3), 55.5 (4-Me), 115.3, 125.8, 128.3, 160.2 (Ph). MS (EI, 70 eV): *m/z* (%): 349 (M^++2, 15), 347 (M^+, 15), 284 (22), 230 (100), 188 (78), 159 (44).

6h: Yield 86 %; mp 167-170 ºC; Anal. Calcd. for $C_{13}H_9BrCl_3NO_2$ (397.49 g.mol^{-1}): C, 39.28; H, 2.28, N, 3.52. Found: C, 39.73; H, 2.5; N, 3.70. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (m, H3), 3.53 (m, H4), 5.98 (s, CH), 3.86 (4-OMe), 7.10 (2H, Ph), 7.69 (3H, Ph).^{13}C NMR (50

MHz, $CDCl_3$) δ 167.2 (C2), 26.4 (C3), 27.9 (C4), 176.2 (C5), 92.2 (CH) 180.3 (C=O), 96.9 (CCl_3), 123.6, 128.8, 132.3, 133.3 (Ph). MS (EI, 70 eV): *m/z* (%): 398 (M^++2, < 5), 396 (M^+, < 5), 280 (100), 278 (100), 252 (10), 250 (10), 199 (15).

6l: Yield 85 %; mp > 300 ºC; Anal. Calcd. for $C_{16}H_{14}Cl_6N_2O_4$ (511.02 $g.mol^{-1}$): C, 37.61; H, 2.76, N, 5.48. Found: C, 37.41; H, 2.90; N, 5.70. ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (m, H3), 3.17 (m, H4), 6.22 (s, CH), 3.83 (CH_2).^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (C2), 26.7 (C3), 28.0 (C4), 177.6 (C5), 88.0 (CH) 179.3 (C=O), 97.1 (CCl_3), 37.2 (CH_2). MS (EI, 70 eV): *m/z* (%): 359 (70), 357 (100), 236 (20), 234 (35), 150 (32).

Supplementary Information

Supplementary data shown in Tables S1 and S2, ^1H, ^{13}C NMR and mass spectra are available free of charge as PDF file at http://jbcs.sbq.org.br

Acknowledgments

Thanks are due to financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de Amparo à Pesquisa do Rio Grande do Sul (FAPERGS). The Bruker X-ray diffractometer was funded by infrastructure grant from the Financiadora de Estudos e Projetos (CT-INFRA/FINEP). Students thank CNPq for fellowships.

References

1. Bonacorso, H. G.; Martins, M. A. P., Bittencourt, S. R. T.; Lourega, R. V.; Zanatta, N.; Flores, A. F. C.; *J. Fluorine Chem.* **1999,** *99*, 177 and references cited therein.
2. Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G.; *Tetrahedron* **2007**, *63*, 7753.
3. Martins, M. A. P.; Cunico, W.; Pereira, C. M. P.; Sinhorin, A. P.; Flores, A. F. C.; Bonacorso, H.; Zanatta, N.; *Curr. Org. Chem.* **2004**, *1*, 391.
4. 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.
5. Godoy, M. C.; Fighera, M. R.; Souza, F. R.; Flores, A. E.; Rubin, M. A.; Oliveira, M. R.; Zanatta, N.; Martins, M. A. P.; Bonacorso, H. G.; Mello, C. F.; *Eur. J. Pharmacol.* **2004**, *496*, 93.
6. Zanatta, N.; Flores, D. C.; Madruga, C. C.; Flores, A. F. C. ; Bonacorso, H. G.; Martins, M. A. P. *Tetrahedron Lett.* **2006**, *47*, 573.
7. Timokhin, B. V.; Baransky, V. A.; Eliseeva, G. D.; *Russ. Chem. Rev.* **1999**, *68*, 73.
8. Oliveira, G.; *Master Dissertation* **2005**, Universidade Federal de Santa Maria, Brazil. Precursors **1** and **2** were identified from mass spectrometric and ^1H /^{13}C NMR data.
9. Shorvon, S.; *The Lancet* **2001**, *358*, 1885.
10. Van der Schyf, C. Geldenhuys, W. J.; Youdim, M. B. H.; *J. Neurochem.* **2006**, *99*, 1033.
11. Nomura, T.; Nishizaki, T.; *Brain Res.* **2000**, *870*, 157.
12. Gorbunova, M. G.; Gerus, I. I.; Kukhar, V. P. *Synthesis* **2000**, 738, and references therein.
13. Gesser, J. C.; Zucco, C.; Nome, F. *J. Phys. Org. Chem.* **1995**, *8*, 97.
14. Vdovenko, S. I.; Gerus, I. I.; Wójcik, J.; *J. Phys. Org. Chem.* **2001**, *14*, 533.
15. Data for methyl 3-(2-methyl-7-(trifluoromethyl)pyrazolo-[1,5-*a*]-pyrimidin-5-yl)propanoate (**7**) yield 94 %**,** mp 124-125 ºC, anal. calcd for $C_{12}H_{12}F_3N_3O_2$: C, 50.18; H, 4.21; N, 14.63, found C, 50.35; H, 4.02; N, 13.83, ^1H NMR (400 MHz, $CDCl_3$): δ 2.55 (s, Me), 2.91 (t, $^3J_{HH}$ 7.5 Hz, CH_2), 3.20 (t, $^3J_{HH}$ 7.5 Hz, CH_2), 3.7 (s, OMe), 6.51 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.7 (Me), 31.2 (CH_2), 32.4 (CH_2), 51.8 (OMe), 96.9 (Pyrim), 105.7 (Pyr), 119.4 (q, $^1J_{CF}$ 285 Hz, CF_3), 133.3 (q, $^1J_{CF}$ 32 Hz, C7), 156.4 (C2), 159.1 (C5), 150.5 (C3a) 172.9 (COOR) and 3-(2-methyl-7-(trichloromethyl)pyrazolo-[1,5-*a*]-pyrimidin-5-yl)propanoate (**8**) yield 84 %**,** mp 191-193 ºC, anal. calcd for $C_{12}H_{12}Cl_3N_3O_2$: C, 42.82; H, 3.59; N, 12.48, found C, 42.55; H, 4.00; N, 12.20, ^1H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, Me), 2.72 (t, $^3J_{HH}$ 7.2 Hz, CH_2), 2.99 (t, $^3J_{HH}$ 7.2 Hz, CH_2), 3.57 (s, OMe), 5.59 (s, 1H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (Me), 28.0 (CH_2), 32.1 (CH_2), 51.9 (OMe), 89.6 (CCl_3), 94.6 (Pyrim), 102.1(Pyr), 142.2 (C7), 152.8 (C3a), 153.4 (C2), 157.9 (C5), 172.3 (COOR). For experimental details see Martins, M. A. P.; Cunico, W.; Scapin, E.; Emerich, D. J.; Fiss, G. F.; Rosa, F. A.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C.; *Lett. Org. Chem.* **2006**, *3*, 358.

Received: June 26, 2007
Published on the web: January 31, 2008