High-throughput preparation of alkyl 4-aryl substituted-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates under microwave irradiation

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Abstract

An efficient high-throughput synthesis of 4-aryl substituted 1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylates **5a-p** was developed by using Lawesson's reagent, a very effective thionating reagent for carbonyl compounds, under conventional conditions and microwave irradiation. In order to gain a better understanding of the structure of the heterocycles obtained, theoretical calculations at the *ab initio* level were carried out.

Keywords: Microwave irradiation, Lawesson's reagent, thiopyridones, theoretical calculation, heterocycles

Introduction

The importance of sulfur-containing heterocyclic compounds for biomedical[1] and material science applications[2] has led to an increase in the number of synthetic methods available for the preparation of this type of heterocyclic compounds.[3,4] In particular, thioxo derivatives of 1,4-dihydropyridines have attracted attention as reactive compounds with cardiovascular activity.[5] Also 2-alkylthio-1,4-dihydropyridine derivatives present hepatoprotective[6] and anti-oxidant activity.[7]

The preparation of the 3,4-dihydropyridine-2(1*H*)-thione ring is a challenge in organic synthesis. The usual procedure for the synthesis of these derivatives is a modification of

Hantzsch route; however, this approach has several serious drawbacks, such as low catalyst life cycle, side reactions, unsatisfactory yield, high temperatures, and long reaction times.[3,8]Therefore, we searched for milder, more convenient and efficient methods for the preparation of these heterocyclic derivatives.

In this regard, we took advantage of new technologies for high-throughput synthesis, which have been promoted by the demand for structurally diverse compound libraries for screening in lead discovery.[9] One of these high-speed techniques is microwave-assisted organic synthesis, which has attracted a substantial amount of attention in recent years since the first reports by Gedye[10] and Giguere[11] in 1986. The main benefits of performing reactions under microwave irradiation conditions are the significant rate-enhancements and the higher product yields.[12] Not surprisingly, these features have recently attracted the interest in drug discovery and medical chemistry communities,[13,14] for which reaction efficiency and speed is of maximum importance. Although the exact reasons why microwave irradiation is able to enhance chemical processes are still unknown, many research works have been recently contribute, to obtain a definitive answer about the existence or nonexistence of the "specific effects" of microwave irradiation in a chemical reaction. [15]

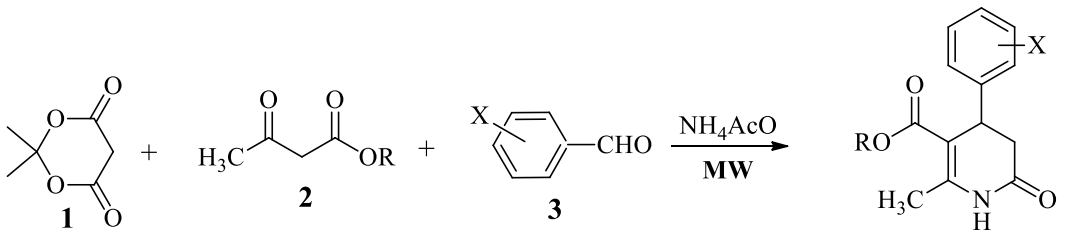
As part of our studies addressing the synthesis of 1,4-dihydropyridine derivatives with substitution patterns required for a biological chemical programme,[14] and in order to improve the methods to obtain them, we synthesized a new series of 4-aryl substituted 1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylates **5a-p** from 4-aryl substituted 1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylates **4a-p** by using Lawesson's reagent (LR= 2,4-bis (4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide) under microwave irradiation. These results were compared with those obtained by conventional heating.

Lawesson's reagent has been widely used as a powerful, mild, and versatile reagent for transforming carbonyl into thiocarbonyl groups.[16] The key issue here is the chemoselectivity of LR observed when a nucleophilic centre, other than a carbonyl group, is present in the molecule.[17] The functionalized molecules **5** are building blocks of interest for further chemical transformations.

Results and Discussion

The synthesis of 4-aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5a-p** was performed in a one-step procedure by thionation of the alkyl 2-methyl 6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates **4a-p**. The intermediates **4a-p** were prepared following a procedure previously reported by our group.[18] Thus, equimolecular amounts of starting compounds **1**, **2** and **3** in ammonium acetate (see Scheme 1) were placed in a microwave monomode reactor (CEM *Discover*) in a cylindrical Pyrex vessel and irradiated at a controlled temperature (100 ºC) for 10 min. When the irradiation was stopped, the solids were treated with ethyl acetate and filtered to give the pure products **4a-p** in good yields (83 – 95 %).

Since it has been reported that LR decomposes over 60-70 ºC,[19] the conventional thionation of compounds **4a-p** using the LR was accomplished by heating in dry toluene at 60 ºC (Method **A,** see Scheme 1). 4-Aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5a-p**, were obtained as yellow crystals in moderate yields, after purification from ethanol. Table 1 shows the main data for the synthesis of compounds **5a-p**. An increase in the reaction temperature leads to the formation of side products reducing the yield by about 10%.



a) R = CH_3 X = H
b) R = CH_3 X = 2-Cl
c) R = CH_3 X = 2,4-diCl
d) R = CH_3 X = 2-NO_2
e) R = CH_3 X = 3-OCH_3
f) R = CH_3 X = 4-$COOCH_3$
g) R = CH_2CH_3 X = H
h) R = CH_2CH_3 X = 2-Cl
i) R = CH_2CH_3 X = 2,4-diCl
j) R = CH_2CH_3 X = 2-NO_2
k) R = CH_2CH_3 X = 3-NO_2
l) R = CH_2CH_3 X = 4-NO_2
m) R = CH_2CH_3 X = 3-OCH_3
n) R = CH_2CH_3 X = 4-OCH_3
o) R = CH_2CH_3 X = 4-$COOCH_3$
p) R = CH_2CH_3 X = F_5

Scheme 1. Synthesis of compounds **5a-p**. Method **A**: conventional heating (60-70ºC), toluene, 4 hr; Method **B**: MW (60ºC, 250W), without solvent, 8 min; Method **C**: MW (60ºC, 250W), xylene (2mL), 10 min.

It has been reported that LR gives an efficient conversion of carbonyl functionalities into their thio analogues, mixing the carbonyl substrates with Lawesson's reagent followed by exposure to microwave irradiation under no-solvent conditions.[20] Following this methodology, equimolecular amounts of starting compound **4** and LR were placed in a microwave monomode reactor (CEM Discover) in a cylindrical Pyrex vessel and were irradiated, under temperature control protocol at 60 ºC and a maximum power of 250W (Method **B**. See Scheme 1 and Table 1). Unexpectedly, when the reaction was carried out under solvent-free conditions (Method **B**), **5** were obtained in low or moderate yields.

Table 1. Comparison between the conventional procedure (Method **A**) and microwave irradiation Methods **B** and **C**) for the synthesis of compounds **5a-o**

Comp.	R	X	Method	Solvent	Reaction time	Temperature	Yield
5a	CH_3	H	A	Toluene	240	60	70
			B	None	8	60	35
			C	**Xylene**	**10**	**60**	**82**
5b	CH_3	2-Cl	A	Toluene	240	60	72
			B	None	8	60	38
			C	**Xylene**	**10**	**60**	**90**
5c	CH_3	2,4-diCl	A	Toluene	240	60	58
5d	CH_3	2-NO_2	A	Toluene	240	60	74
			B	None	8	60	42
			C	**Xylene**	**10**	**60**	**91**
5e	CH_3	3-OCH_3	A	Toluene	240	60	78
5f	CH_3	4-$COOCH_3$	A	Toluene	240	60	81
			B	None	8	60	39
			C	**Xylene**	**10**	**60**	**92**
5g	CH_2CH_3	H	A	Toluene	240	60	68
			B	None	8	60	30
			C	**Xylene**	**10**	**60**	**87**
5h	CH_2CH_3	2-Cl	A	Toluene	240	60	75
			B	None	8	60	29
			C	**Xylene**	**10**	**60**	**89**
5i	CH_2CH_3	2,4-diCl	A	Toluene	240	60	77
5j	CH_2CH_3	2-NO_2	A	Toluene	240	60	72
5k	CH_2CH_3	3-NO_2	A	Toluene	240	60	72
			B	None	8	60	32
			C	**Xylene**	**10**	**60**	**91**
5l	CH_2CH_3	4-NO_2	A	Toluene	240	60	82
			B	None	8	60	36
			C	**Xylene**	**10**	**60**	**93**
5m	CH_2CH_3	3-OCH_3	A	Toluene	240	60	81
			B	None	8	60	39
			C	**Xylene**	**10**	**60**	**90**
5n	CH_2CH_3	4-OCH_3	A	Toluene	240	60	76
5o	CH_2CH_3	4-$COOCH_3$	A	Toluene	240	60	74
			B	None	8	60	39
			C	**Xylene**	**10**	**60**	**88**
5p	CH_2CH_3	F_5	A	Toluene	240	60	64
			B	None	8	60	35
			C	**Xylene**	**10**	**60**	**87**

Taking into account that to increase the efficiency of the MW assisted synthesis the reaction requires, preferably, at least one liquid phase in the heterogeneous media to produce an interfacial reaction, these results can be attributed to the poor homogeneity of the reaction medium, since derivatives **4** have melting points above 100 ºC and the reaction must occur at 60 ºC to avoid decomposition of LR.

In order to increase the efficiency of the thionation reaction, the reactions were carried out in the same conditions but by using xylene (2 mL) as solvent (Method **C**). The mixtures were irradiated with the same MW protocol at 60 ºC under continuous stirring for 10 minutes. In these conditions the 6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5** were obtained in excellent yields (see Table 1). Xylene is a non-polar solvent widely used to observe some MW effects provided that it is transparent to MW and, consequently, it allows specific interactions with reaction partners. Also when the reaction is carried out in the presence of small amount of xylene, dissociation of LR into dithiophosphine **6** (see Scheme 2) is favored, which could explain the high yield of the products.

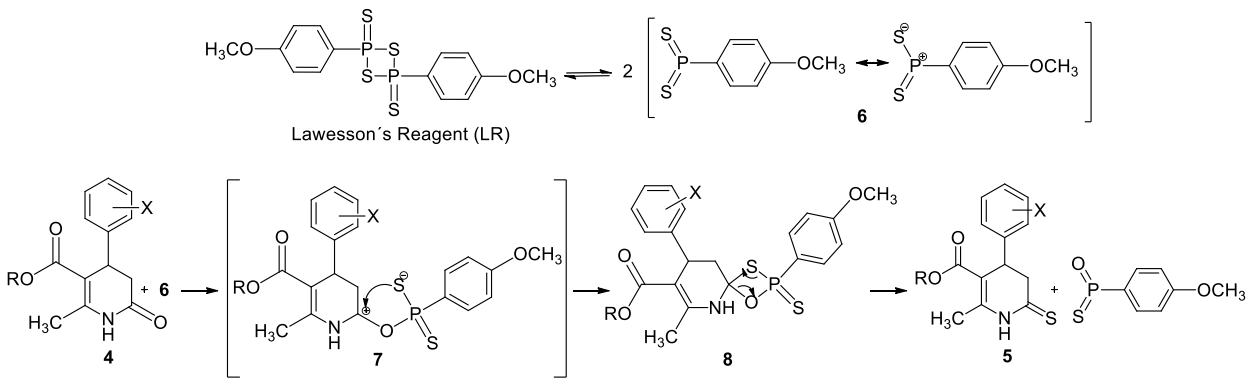
All reactions were monitored by TLC and the experiments were replicated in order to ensure reproducibility. A maximum power setting of 250 W was found to be the best balance between efficiency and safety.

To show the advantages of the microwave heating mode and to check the possibility of intervening with the specific non-purely thermal effects of microwaves, the reactions were performed by heating in a thermostated oil bath under the same experimental conditions used for microwave irradiation (time: 8 min. without solvent and 10 min. with xylene; temperature 60 ºC, profiles of rise in temperature, vessels). In all cases, no reaction was detected by tlc, thus again supporting that the effect of microwave irradiation is not solely thermal.

The experimental findings suggest that the improvement achieved with Method **C** [MW (Temperature control: 60 ºC/Max. Power: 250 W)/xylene (2 mL)] was due to a strong MW effect, related to the reaction mechanism and to the evolution of polarity during the course of the reaction.

Taking into account previous reports using different substrates,[17b,17c] Scheme 2 shows the proposed mechanism for obtaining compound **5**. LR is in equilibrium with a highly reactive dithiophosphine ylide **6** that reacts with **4** to form the thiaoxaphosphetane derivatives **8**, which decompose as in a Wittig-analogue reaction[21] to the corresponding 6-thioxo-1,4,5,6-tetrahydropyridine derivatives **5**.

In the proposed mechanism, we can observe that the polarity of the system is enhanced during the course of the reaction since, for example, one of the intermediates **7** is charged. We should expect a decrease in the energy of activation under microwave irradiation as a result of greater electrostatic stabilization of the transition state compared to the ground state.[22]



Scheme 2. Plausible mechanism for the formation of thiopyridones **5a-p.**

6-Thioxo-1,4,5,6-tetrahydropyridine compounds **5** were fully characterized by their analytical and spectroscopical data. NMR experiments confirmed the formation of these derivatives. Their spectroscopic data were very similar to those of the previously reported pyridone ring intermediates **4**.[23]

The ^{1}H NMR spectra at 400 MHz show, in general, the presence of the NH group as a singlet at 8.9-9.2 ppm; the ABX system corresponding to the three protons of the thiopyridone ring, H4, H5a and H5b appear at 4.18-4.68 ppm, 3.02-3.37 ppm, and 2.76-3.19 ppm, respectively. In all cases, the methyl group on C-2 appeared as a singlet at δ 2.5 ppm. The ^{13}C NMR spectra for the thiopyridone ring showed two quaternary carbon signals C-2 and C-3 at δ 150 ppm and δ 110 ppm respectively, one tertiary carbon signal C-4 at δ 37 ppm, and one secondary carbon signal C-5 at δ 45 ppm. The carbonyl groups on C-3 appeared at 165.2-167.0 ppm. The main difference between **5** and its oxo-analogous **4** was found in the ^{13}C NMR spectra for the signals of C-5 and C-6 atoms. The methylene signal corresponding to C-5 for derivatives **4** appeared at 36-39 ppm, whereas this signal appeared at 43-46 ppm for the thioxo derivates **5** as a result of the deshielding effect of the thiocarbonyl group present in the ring. The C=O signal corresponding to the C-6 of the 6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate **4** appeared at δ 169 ppm, and the C=S signal of the thioxopyridine derivatives **5** appeared at a higher δ value (δ 200 ppm).

We have previously reported the mass spectra of pyridones **4** under EI conditions,[24] and found that the base peaks are formed by the loss of the alkoxycarbonyl group. Thioxopyridone derivatives **5** underwent the same main fragmentation, thereby revealing that the sulfur atom does not induce changes in the fragmentation pattern.

In order to gain a better understanding of the novel compounds and to analyze the influence that the change of a carbonyl group to a thiocarbonyl group has on the molecular geometry of the heterocyclic ring, we carried out *ab-initio* quantum chemical calculations at MP2/6-31G** level for compounds **4g** and **5g**. The geometrical features predicted are listed in Table 2, which shows the most relevant bond distances, valence angles, and dihedral angles.

For both molecules, MP2 predicted that the heterocyclic ring presents a twisted boat conformation with the phenyl group in a pseudoaxial position and nearly orthogonal to the mean

plane of the heterocycle (See dihedral angles C2´-C1´-C4-C3 and C2´-C1´-C4-C5). This result is consistent with the X-ray structure of **4a** previously reported.[25] However, it is important to note some differences between compounds **4g** and **5g**. As expected, the bond distance C6-X increased in going from the carbonyl group (C6=O = 1.2261 Å) to the thiocarbonyl (C6=S = 1.638 Å), which caused the bond distances C2-N1 and C6-N1 in **5g** to be smaller.

The main difference between the two structures is the dihedral angle C4-C5-C6-X; in **4g**, it has a negative value (-174.11°) and in **5g** a positive value (140.99°), thereby indicating distinct orientations with respect to the plane that defines C4-C5-C6.

A relevant factor related to the pharmacological activity of the biologically active 1,4-dihydropyridines and related compounds is the geometry and orientation of the carbonyl group in the alkoxycarbonyl substituent on C3.[26] In previous papers, we reported that the ester group on C3 in compounds **4** is coplanar with the endocyclic double bond, with a carbonyl group in a *cis* disposition. Theoretical calculations showed the same behavior for the novel compound **5g,** with only minimal deviation of the dihedral angle C2-C3-C7-O7 (11.15°).

These results indicate that the geometrical features of compounds **5** are quite similar to structurally related 1,4-dihydropyridines and, therefore, they exhibit appropriate structural features to act as potential calcium channel modulators.[27]

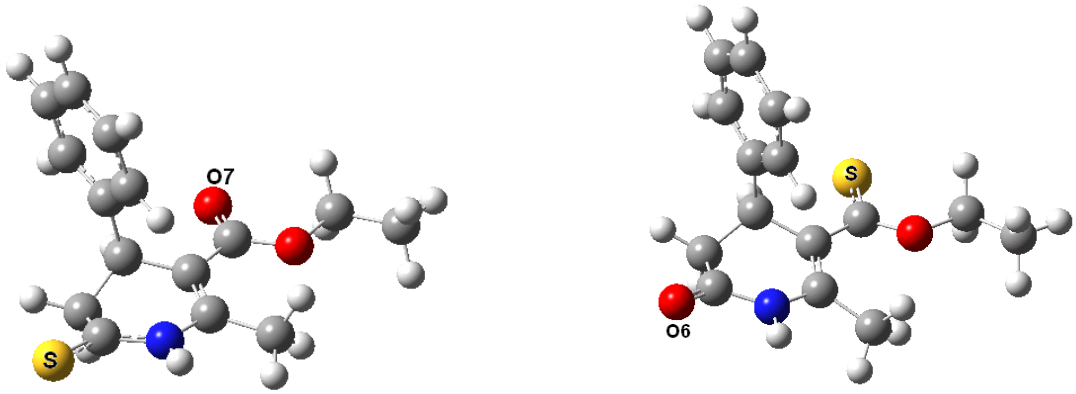
Table 2. Most relevant bond distances, bond angles and dihedral angles for the most stable conformation of compounds **4g** and **5g**. Distances are given in Å and angles in degrees

	4g	**5g**
Bond distances (Å)		
N1-C2	1.397	1.361
C2-C3	1.361	1.361
C3-C4	1.513	1.511
C4-C5	1.535	1.535
C5-C6	1.506	1.502
C6-N1	1.387	1.368
C4-C1´	1.516	1.514
C6-X[a]	1.226	1.638
Bond angles (degrees)		
C2-N1-C6	126.23	126.50
C3-C4-C5	110.30	109.85
C5-C4-C1´	112.08	112.49
Dihedral angles (degrees)		
C4-C3-C2-N1	2.89	1.88
C4-C5-C6-N1	-39.63	-42.54
C2-N1-C6-C5	10.57	13.08
C6-N1-C2-C3	8.98	8.41
C3-C4-C5-C6	49.14	50.64

Table 2. Continued

	4g	5g
C5-C4-C3-C2	-31.26	-30.62
C1´-C4-C3-C2	94.44	95.24
C1´-C4-C5-C6	-76.60	-75.03
C2-N1-C6-X	-173.36	-170.33
C4-C5-C6-X	-174.11	140.99
C2-C3-C7-O7	11.99	11.15
C2´-C1´-C4-C3	137.24	135.37
C2´-C1´-C4-C5	-98.04	-100.00

To explain the selectivity of the thionation reaction, we analyzed the data obtained from the quantum-chemical calculations at MP2/6-31G** level. The reaction of **4** with dithiophosphine ylide **6** could take place either on O6 and/or O7. Figure 1 shows the most stable conformations calculated for compounds **5g**, and **9** where the reaction occurs on O7.



5g **9**

Figure 1. Ab initio (MP2/6-31G**) optimized geometry for compounds **5g** and **9**.

The experimental results showed that the attack occurs solely on O6 of the 4-aryl substituted 1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylates **4**, and no reaction is observed on O7. The regioselectivity of this reaction could be influenced by the following: i) the different charge of the oxygen atoms; ii) the geometrical accessibility of the reactive dithiophosphine ylide **6** to the oxygen atoms of molecule **4**; and iii) the energy of the two possible products **5** and **9**.

The charges of the two oxygens atoms, O6 and O7, in compound **4** are very similar, -0.57 and -0.61, respectively. In addition, although O6 is less sterically hindered than O7, because of the size and shape of **6** the reagent can access both sites. However, the energy of the two possible products **5** and **9** is very near: 741 917.03 and 741 910.76 kcal/mol, the first one is 6.27 kcal/mol

more stable than the second one. This finding could explain that only compounds **5** are obtained in the thionation reaction.

Conclusions

In summary, here we have carried out a practical and efficient high-throughput synthesis of novel 4-aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5a-p** from the readily available 4-aryl substituted alkyl 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates **4a-p** using LR, a very effective thionating reagent for carbonyl compounds, under a microwave-assisted optimized conditions. The best results were obtained under microwave conditions using xylene (2 mL) as solvent (Method **C**, 78-92%) to achieve a new, environmentally clean procedure (decrease in reaction time and amount of solvent used) for the synthesis of potential biologically active 6-thioxopyridines-3-carboxylate derivatives **5**. These compounds are of interest as useful building blocks and as pharmacological compounds because they present the conformational features established as calcium channel modulators.

Experimental Section

General. Reagents and solvents were purchased from Fluka or Aldrich. 4-aryl substituted 1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylates **4** were synthesized according to a method reported in the literature [21] but using a domestic microwave oven (700 W, generating 2450 MHz frequency) at a power of 280 W for 10 min at 72 ºC. The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck $60F_{250}$) using dichloromethane:methanol (8:2) as eluent. Melting points were determined in capillary tubes in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Mercury 400 spectrometer [400 MHz (^{1}H) and 75.4 (^{13}C)]. Chemical shifts are given as δ values against tetramethylsilane as the internal standard and *J* values are given in Hz. Mass spectra were obtained in a LC/MSD-TOF(2006) Instrument (Agilent technologies). Microanalysis was performed in a Perkin-Elmer 2400 CHN. *Ab initio* calculations were carried out with the GAUSSIAN 98 program. Full geometry optimization and orbital analysis of compounds **4**, **6** and the two possible products of the reaction **5** and **9** were performed at MP2 level using the 6/31G** basis set.[28]

General procedure for the microwave-assisted synthesis of 4-aryl substituted alkyl 1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylates (4)

4-aryl substituted alkyl 1,4,5,6-tetrahydro-2-methyl-6-oxopyridine-3-carboxylates **4a-p** were prepared following the procedure previously reported by us.[21] In this case the MW irradiation was provided by a CEM Discover LabMate Focused Single Mode MW Synthesis Reactor, which

produced continuous stirring and irradiation with control of pressure and temperature. All these compounds were characterized by determination of physical constants and by NMR spectroscopy, which coincided with those previously reported for these compounds.[17, 23]

General procedure for the conventional synthesis of 4-aryl substituted alkyl 1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylates (5). (Method A)

A mixture of appropriate 4-aryl substituted alkyl 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates **4** (5 mmol) and LR (5mmol) in dry toluene was stirred and heated at controlled temperature (60-70 ºC). After 4 h, the reaction mixture was cooled to room temperature and filtered to remove white solid crystals. The toluene was removed *in vacuo* and the residue was precipitated by adding cool ether and filtered to afford the 4-aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5** as yellow crystals. In some cases, further purification was accomplished by recrystalization from ethanol.

General procedure for the microwave-assisted synthesis of 4-aryl substituted alkyl 1,4,5,6-tetrahydro-2-methyl-6-thioxopyridine-3-carboxylates (5). (Method B and C)

Method B. An equimolar mixture of the appropriate alkyl 4-aryl substituted-2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates **4** (5 mmol) and LR (5mmol) were mixed thoroughly and irradiated in a CEM Discover LabMate Focused Single Mode MW Synthesis reactor at 250 W for 8 min. The product was extracted with $CHCl_3$. Excess solvent was removed *in vacuo* and the residue was precipitated by adding cool ether and filtered to afford the 4-aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5**.

Method C. An equimolar mixture of the appropriate 4-aryl substituted alkyl 2-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylates **4** (5 mmol) and LR (5mmol) were dissolved in a minimum amount of xylene (2 mL) and irradiated in the CEM Discover reactor at 250 W for 10 min. The reaction mixture was then cooled, the xylene was removed *in vacuo* and the residue was precipitated by adding cool ether and filtered to afford the 4-aryl substituted alkyl 2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylates **5**.

Methyl 2-methyl-4-phenyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5a). Yield 70% (Method **A**); 35% (Method **B**) and 82% (Method **C**); yellowish solid; mp 139-140 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 3.10 (d, *J* = 16.2 Hz, B part of ABX, 1H, H5b), 3.38 (dd, *J* = 16.2 Hz, *J* = 7.2 Hz, A part of ABX 1H, H5a), 3.68 (s, 3H, OCH_3), 4.18 (d, *J*=7.2 Hz, X part of ABX, 1H, H4), 7.06-7.26 (m, 5H, Ph), 8.84 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 19.2 (CH_3-C2), 37.5 (C4), 46.0 (C5), 61.0 (OCH_3), 110.1 (C3), 126.4 (C4´), 128.2 (C3´), 126.8 (C2´, C6´), 128.6 (C5´), 140.8 (C1´), 151.1 (C2), 166.4 (CO), 200.5 (C6); MS (*m/z*): 261 (M^+), 229, 200, 199. Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.41; H, 5.72; N, 5.30.

Methyl 4-(2'-chlorophenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5b). Yield 72% (Method **A**); 38% (Method **B**) and 90% (Method **C**); pale yellow solid; mp 110-111 °C; ^{1}H NMR (DMSO-d_6) δ 8.94 (br s, 1H, NH), 7.49 (m, 1H, H3´), 7.28 (m, 2H, H4´, H5´), 6.92 (m, 1H, H6´), 4.68 (d, *J* = 7.7 Hz, X part of ABX, 1H, H4), 4.01 (s, 3H, OCH_3), 3.32 (dd,

16.3 Hz, *J* = 7.7 Hz, A part of ABX, 1H, H5a), 3.18 (d, *J* = 16.3 Hz, B part of ABX, 1H, H5b), 2.36 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6) δ 18.5 (CH_3-C2), 34.6 (C4), 44.8 (C5), 60.8 (OCH_3), 110.1 (C3), 131.8 (C5´), 133.1 (C4´), 134.2 (C6´), 135.7 (C3´), 136.9 (C2´), 142.8 (C1´), 149.9 (C2), 166.6 (CO), 200.9 (C6); MS (*m/z*): 295 (M^+), 260. Anal. Calcd for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.74. Found: C, 56.80; H, 4.81; N, 4.70.

Methyl 4-(2',4'-dichlorophenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5c). Yield 58% (Method A); pale yellow solid; mp 175-176 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H, CH_3), 2.92 (d, *J* = 16.3 Hz, B part of ABX, 1H, H5b), 3.20 (dd, *J* = 16.3 Hz, *J* = 7.7 Hz, A part of ABX, 1H, H5a), 3.49 (s, 3H, OCH_3), 4.43 (d, *J* = 7.7 Hz, X part of ABX, 1H, H4), 7.02 (m, 1H, H6´), 7.30 (m, 1H, H5´), 7.69 (m, 1H, H3´), 8.38 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_3-C2), 34.5 (C4), 43.1 (C5), 59.2 (OCH_3), 102.9 (C3), 127.8 (C5´), 129.7 (C6´), 131.2 (C3´), 134.2 (C4´), 136.5 (C2´), 141.6 (C1´), 150.2 (C2), 166.5 (CO), 200.3 (C6); MS (*m/z*): 329 (M^+), 294. Anal. Calcd for $C_{14}H_{13}Cl_2NO_2S$: C, 50.92; H, 3.97; N, 4.24. Found: C, 50.87; H, 3.94; N, 4.20.

Methyl 2-methyl-4-(2'-nitrophenyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5d). Yield 74% (Method **A**), 42% (Method **B**) and 91% (Method **C**); yellow solid; mp 159-160 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 2.78 (d, *J* = 16.6 Hz, B part of ABX, 1H, H5b), 3.22 (dd, *J* = 16.6 Hz, *J* = 8.5 Hz, A part of ABX, 1H, H5a), 3.98 (3H, s, OCH_3), 4.47 (1H, d, H4, *J* = 8.5 Hz, X part of ABX), 7.35 (dt, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H, H4´), 7.26 (1H, dd, H6´, *J* = 7.9 Hz, *J* = 1.2 Hz), 7.48 (dt, *J* = 7.9 Hz, *J* = 1.2 Hz, H5´, 1H), 7.59 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H, H3´), 8.88 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3-C2), 35.6 (C4), 42.6 (C5), 58.5 (OCH_3), 108.7 (C3), 128.2 (C3´), 129.0 (C4´), 131.2 (C6´), 134.5 (C5´), 139.7 (C1´), 143.8 (C2´), 150.3 (C2), 167.6 (CO), 201.6 (C6); MS (*m/z*): 306 (M^+), 289. Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14. Found: C, 54.83; H, 4.66; N, 9.19.

Methyl 4-(3'-methoxyphenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5e). Yield 78% (Method A); yellow solid; mp 165-166 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H, CH_3), 3.19 (d, *J* = 16.5 Hz, B part of ABX 1H, H5b), 3.37 (dd, *J* = 16.5 Hz, *J* = 8.3 Hz, A part of ABX 1H, H5a), 3.72 (s, 3H, OCH_3), 4.18 (d, *J* = 8.3 Hz, X part of ABX, 1H, H4), 7.10 (m, 2H, H5´, H6'), 7.18 (br s, 1H, H2´), 7.29 (dt, *J* = 6.3 Hz, *J* = 2.7 Hz, 1H, H4´), 8.65 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 18.6 (CH_3-C2), 37.2 (C4), 45.7 (C5), 54.8 (OCH_3), 60.5 (OCH_3), 112.7 (C3), 119.8 (C4´), 121.1 (C2´), 124.2 (C5´), δ 129.7 (C6´), 142.9 (C1´), 143.6 (C3´), 159.9 (C2), 166.5 (CO), 201.4 (C6); MS (*m/z*): 291 (M^+), 259, 229. Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.79; H, 5.92; N, 4.78.

Methyl 4-[4'-(methoxycarbonyl)phenyl]-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5f). Yield 81% (Method **A**), 39% (Method **B**) and 92% (Method **C**); yellow solid; mp 139-141 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (3H, s, CH_3), 2.76 (d, *J* = 16.5 Hz, B part of ABX, 1H, H5b), 3.02 (dd, *J* = 16.5 Hz, *J* = 8.3 Hz, A part of ABX, 1H, H5a), 3.62 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.32 (d, *J* = 8.3 Hz, X part of ABX, 1H, H4), 7.37 (d, *J* = 8.3 Hz, 2H, H2´, H6´), 7.89 (d, *J* = 8.3 Hz, 2H, H3´, H5´), 8.92 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 19.3 (CH_3-C2), 36.8 (C4), 45.6 (C5), 52.4 (OCH_3), 58.5 (OCH_3), 110.7 (C3), 126.5 (C2´, C6´), 128.9 (C4´),

130.3 (C3′, C5′),147.5 (C1′), 149.8 (C2), 166.1 (CO**),** 167.8 (CO), 201.0 (C6); MS (*m/z*): 319 (M^+), 260, 191. Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 69.17; H, 5.37; N, 4.39. Found: C, 69.22; H, 5.41; N, 4.32.

Ethyl 2-methyl-4-phenyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5g). Yield 68% (Method **A**), 30% (Method **B**) and 87% (Method **C**); yellowish solid; mp 149-150 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H, CH_3), 3.09 (d, *J* = 16.2 Hz, B part of ABX, 1H, H5b), 3.34 (dd, 16.2 Hz, *J* = 7.2 Hz, A part of ABX, 1H, H5a), 3.70 (s, 3H, OCH_3), 4.15 (d, *J*.2 Hz, X part of ABX, 1H, H4), 7.02-7.22 (m, 5H, Ph), 8.93 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3CH_2), 18.9 (CH_3-C2), 37.5 (C4), 45.3 (C5), 59.7 (OCH_2), 110.3 (C3), 126.4 (C4′), 126.9 (C2′, C6′), 128.2 (C5′), 128.8 (C3′), 140.8 (C1′), 150.9 (C2), 166.8 (CO), 200.3 (C6), MS (*m/z*): 275 (M^+), 229, 200. Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.48; H, 6.18; N, 5.04.

Ethyl 4-(2'-chlorophenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5h). Yield 75% (Method **A**), 29% (Method **B**) and 89% (Method **C**); yellow solid; mp 119-120 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.15 (d, *J* = 16.3 Hz, B part of ABX, 1H, H5b), 3.32 (dd, *J* = 16.3 Hz, *J* = 7.7 Hz, A part of ABX, 1H, H5a), 4.12 (m, 2H, OCH_2), 4.66 (d, *J* = 7.7 Hz, X part of ABX, 1H, H4), 6.92 (m, 1H, H6′), 7.18 (m, 1H, H4′, H5′), 7.42 (m, 1H, H3′), 8.92 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 18.6 (CH_3-C2), 34.3 (C4), 44.4 (C5), 60.4 (OCH_2), 110.6 (C3), 127.0 (C6′), 127.2, 128.3 (C4′, C5′), 130.0 (C3′), 133.0 (C2′), 138.2 (C1′), 148.0 (C2), 166.1 (CO), 200.8 (C6); MS (*m/z*): 309 (M^+), 274, 236. Anal. Calcd for $C_{15}H_{16}ClNO_2S$: C, 58.15; H, 5.21; N 4.52. Found: C, 58.20; H, 5.18; N, 4.56.

Ethyl 4-(2',4'-dichlorophenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5i). Yield 77% (Method **A**); pale yellow solid; mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3H,CH_3), 2.51 (s, 3H, CH_3), 3.15 (d, *J* = 16.3 Hz, B part of ABX, 1H, H5b), 3.25 (dd, *J* = 16.3 Hz, *J* = 7.9 Hz, A part of ABX, 1H, H5a), 4.05 (m, 2H, OCH_2), 4.55 (d, *J* = 7.9 Hz, X part of ABX, 1H, H4), 6.91 (d, *J* = 8.4 Hz, 1H, H6′), 7.15 (dd, *J* = 8.4 Hz, *J* = 2.2 Hz 1H, H5′), 7.45 (d, *J* = 2.2 Hz, 1H, H3′), 8.91 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 18.6 (CH_3-C2), 34.0 (C4), 46.5 (C5), 60.7 (OCH_2), 109.8 (C3), 127.6 (C5′), 128.4 (C3′), 130.1 (C6′), 133.6 (C4′), 133.9 (C2′), 137.1 (C1′), 148.5 (C2), 166.2 (CO), 200.6 (C6); MS (*m/z*): 343 (M^+), 308, 270. Anal. Calcd for $C_{15}H_{15}Cl_2NO_2S$: C, 52.33; H, 4.39; N, 4.07. Found: C, 52.39; H, 4.43; N, 4.03.

Ethyl 2-methyl-4-(2'-nitrophenyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5j). Yield 72% (Method **A**); yellow solid; mp 150-151 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.19 (d, *J* = 16.6 Hz, B part of ABX, 1H, H5b), 3.35 (dd, *J* = 16.6 Hz, *J* = 8.6 Hz, A part of ABX, 1H, H5a), 4.16 (m, 2H, OCH_2), 4.25 (d, *J* = 8.6 Hz, X part of ABX, 1H, H4), 7.25 (m, 1H, H6′), 7.52 (td, *J* = 7.9 Hz, *J* = 0.9 Hz, 1H, H4′), 8.02 (m, 1H, H5′), 8.11 (dd, *J* = 7.9, *J* = 0.9 Hz, 1H, H3′), 9.00 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3); 19.2 (CH_3-C2), 37.4 (C4), 45.9 (C5), 61.0 (OCH_2), 110.3 (C3), 122.5 (C3′), 127.5 (C6′), 128.3 (C4′), 130.4 (C5′), 133.2 (C1′), 140.2 (C2′), 148.1 (C2), 166.4 (CO), 200.5 (C6), MS (*m/z*): 320 (M^+), 247. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03, N 8.74. Found: C, 56.20; H, 5.07; N, 8.71.

Ethyl 2-methyl-4-(3'-nitrophenyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5k). Yield 72% (Method **A**), 32% (Method **B**) and 91% (Method **C**); yellow solid; mp 160-161 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, *J* = 7.1 Hz, 3H, CH_3); 2.33 (s, 3H, CH_3), 2.85 (d, *J* = 16.5 Hz, B part of ABX, 1H, H5b),3.14 (dd, *J* = 16.5 Hz, *J* = 7.1 Hz, A part of ABX, 1H, H5a), 3.89 (m, 2H, OCH_2), 4.25 (d, *J* = 7.1 Hz, X part of ABX 1H, H4), 6.99 (m, 2H, H6′, H5′), 7.24 (br s, 1H, H2′), 7.65 (dt, *J* = 6.5 Hz, *J* = 2.4 Hz, 1H, H4′), 9.02 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_3), 19.1 (CH_3-C2), 37.4 (C4), 44.8 (C5), 60.3 (OCH_2), 111.9 (C3), 124.8 (C4′), 125.1 (C2′), 127.2 (C5′), 130.7 (C6′), 143.5 (C1′), 144.5 (C3′), 150.9 (C2), 166.6 (CO), 200.8 (C6); MS (*m/z*): 320 (M^+), 303, 247. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.19; H, 4.99; N, 8.70.

Ethyl 2-methyl-4-(4'-nitrophenyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5l). Yield 82% (Method **A**), 36% (Method **B**) and 93% (Method **C**); yellow solid; mp 153-154 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, *J* = 7.1 Hz, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.85 (d, *J* = 16.5 Hz, B part of ABX, 1H, H5b), 3.14 (dd, *J* = 16.5 Hz, *J* = 7.1 Hz, A part of ABX, 1H, H5a), 3.89 (m, 2H, OCH_2), 4.25 (d, *J* = 7.1 Hz, X part of ABX 1H, H4), 7.24 (d, *J* = 8.7 Hz, 2H, H2′, H6′), 7.75 (d, *J*=8.7 Hz, 2H, H3′, H5′), 8.89 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_3), 19.1 (CH_3-C2), 37.2 (C4), 45.8 (C5), 60.3 (OCH_2), 110.9 (C3), 124.8 (C4′), 125.1 (C2′), 127.2 (C5′), 130.7 (C6′), 143.5 (C1′), 144.5 (C3′), 149.9 (C2), 166.6 (CO), 200.8 (C6); MS (*m/z*): 320 (M^+), 303, 247. Anal. Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.21; H, 5.06; N, 8.72.

Ethyl 4-(3'-methoxyphenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5m). Yield 81% (Method **A**), 39% (Method **B**) and 90% (Method **C**); yellow solid; mp 157-158 °C; H^1 NMR ($CDCl_3$) δ 1.16 (t, *J* = 7.0 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.91 (d, *J* = 16.4 Hz, B part of ABX, 1H, H5b), 3.09 (dd, *J* = 16.4 Hz, *J* = 7.3 Hz, A part of ABX, 1H, H5a), 3.65 (s, 3H, CH_3O), 3.77 (m, 2H, OCH_2), 4.19 (d, *J* = 7.3 Hz, X part of ABX, 1H, H4), 6.69 (m, 1H, H2′), 6.77 (d, *J* = 7.7 Hz, 1H, H6′), 6.94 (dd, *J* = 7.7 Hz, *J* = 2.1 Hz, 1H, H4′), 7.34 (t, *J* = 7.7 Hz, 1H, H5′), 9.00 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 14.7 (CH_3), 19.2 (CH_3-C2), 37.6 (C4), 44.7 (C5), 53.9 (OCH_3), 59.8 (OCH_2), 111.4 (C4′), 112.0 (C3), 115.1 (C2′), 118.9 (C6′), 129.7 (C5′), 141.5 (C1′), 149.4 (C3′), 151.7 (C2), 166.7 (CO), 201.6 (C6); MS (*m/z*): 305 (M^+), 259, 231. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59. Found: C, 62.98; H, 6.30; N, 4.62.

Ethyl 4-(4'-methoxyphenyl)-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5n). Yield 76% (Method **A**); yellow solid; mp 146-147 °C; H^1 NMR ($CDCl_3$) δ 1.13 (t, *J* = 7.0 Hz, 3H, CH_3), 2.51 (s, 3H, CH_3), 2.89 (d, *J* = 16.3 Hz, B part of ABX, 1H, H5b), 3.19 (dd, *J* = 16.3 Hz, *J* = 7.1 Hz, A part of ABX, 1H, H5a), 3.70 (s, 3H, CH_3O), 3.92 (m, 2H, OCH_2), 4.21 (d, *J* = 7.1 Hz, X part of ABX, 1H, H4), 7.04 (d, *J* = 8.5 Hz, 2H, H2′, H6′), 7.74 (d, *J* = 8.5 Hz, 2H, H3′, H5′), 8.91 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 18.6 (CH_3-C2), 34.0 (C4), 44.5 (C5), 52.1 (OCH_3), 60.7 (OCH_2), 109.8 (C3), 127.6 (C3′, C5′), 128.4 (C1′), 130.1 (C2′, C6′), 137.1 (C4′), 144.5 (C2), 166.2 (CO), 200.6 (C6); MS (*m/z*): 305 (M^+), 259, 231. Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59. Found C, 62.88; H, 6.32; N, 4.64.

Ethyl 4-[4'-(methoxycarbonyl)phenyl]-2-methyl-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5o). Yield 74% (Method **A**), 39% (Method **B**) and 88% (Method **C**); yellow solid; mp 167-168 °C; H^1 NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.0 Hz, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.12 (d, *J* = 16.4 Hz, B part of ABX, 1H, H5b), 3.31 (dd, *J* = 16.4 Hz, *J* = 7.3 Hz, A part of ABX, 1H, H5a), 3.91 (s, 3H, CH_3O), 4.08 (m, 2H, OCH_2), 4.18 (d, *J* = 7.3 Hz, X part of ABX, 1H, H4), 7.20 (d, *J* = 8.3 Hz, 2H, H2´, H6´), 7.92 (d, *J* = 8.3 Hz, 2H, H3´, H5´), 9.18 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 18.7 (CH_3-C2), 37.4 (C4), 45.8 (C5), 52.0 (OCH_3), 60.5 (OCH_2), 110.4 (C3), 126.9 (C3´, C5´), 128.9 (C4´), 130.0 (C2´, C6´), 143.3 (C1´), 146.9 (C2), 166.3 (CO), 166.7 (CO), 200.7 (C6); MS (*m/z*): 333 (M^+), 287, 260, 228. Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.29; H, 5.77; N, 4.26.

Ethyl 2-methyl-4-(pentafluorophenyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carboxylate (5p). Yield 64% (Method **A**), 35% (Method **B**) and 87% (Method **C**); yellow pale solid; mp 132-133 °C; ^1H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.2 Hz, 3H, CH_3), 2.45 (3H, s, CH_3), 2.89 (d, *J* = 16.6 Hz, B part of ABX, 1H, H5b), 3.22 (dd, *J* = 16.6 Hz, *J* = 10.2 Hz, A part of ABX, 1H, H5a), 4.10 (m, 2H, OCH_2), 4.52 (d, *J* = 10.2 Hz, X part of ABX, 1H, H4), 8.82 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 19.0 (CH_3-C2), 27.9 (C4), 43.6 (C5), 60.33 (OCH_2), 116.2 (C3), 136.2 (C3´, C5´), 141.4 (C1´), 143.8 (C4´), 144.8 (C2´, C6´), 146.3 (C2), 166.9 (CO), 199.1 (C6), MS (*m/z*): 366 (M^+), 334, 207. Anal. Calcd for $C_{15}H_{12}F_5NO_2S$: C, 42.32; H, 3.31; N, 3.83. Found: C, 42.38; H, 3.35; N, 3.79.

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