

# Synthesis of fluorinated ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one/thione-5-carboxylates under microwave irradiation

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## Abstract

Microwaves have been found to greatly accelerate the Biginelli synthesis of fluorine containing ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one/thione-5-carboxylates in unsealed vessels using ethanol as energy transfer medium. Results were compared with those obtained following the classical method. The advantages obtained by the use of microwave irradiation were demonstrated. All synthesized compounds have been characterized on the basis of elemental analyses, IR,  $^1\text{H}$  NMR and  $^{19}\text{F}$  NMR spectral studies. © 1998 Elsevier Science S.A. All rights reserved.

*Keywords:* Microwave irradiation; Tetrahydropyrimidin-2-one/thione-5-carboxylates; Biginelli compounds

## 1. Introduction

Research on ethyl 4-aryltetrahydropyrimidin-5-carboxylates, known as Biginelli compounds is of current interest due to their exceptional activities as calcium antagonists and antihypertensive agents [1–9]. This is not surprising since the dihydropyrimidines can be regarded as aza analogs of dihydropyridines of the nifedipine type, which have served as important tools for the study of calcium channel structure and function [10]. Pyrimidin-5-carboxamides have been reported to possess anti carcinogenic activity [11,12]. A number of derivatives have shown anti-inflammatory [13], analgesic and blood platelet aggregation inhibitory activity [14]. 1,4-Dihydropyrimidine is useful as a platelet activating factor antagonist [15,16]. Other Biginelli compounds were shown to inhibit the uptake of adenosine by thrombocytes [17,18].

Dihydropyrimidine and some of its analogs were screened as antitumor agents [19,20]. Although the Biginelli synthesis is 100 years old, the cardiovascular activity of Biginelli compounds, namely  $\beta$ -aminoethyl esters, was first discovered by Khanna et al. in 1978 [21] and since 1986, the number of publications and patents dealing with the cardiovascular activity of dihydropyrimidines has grown rapidly.

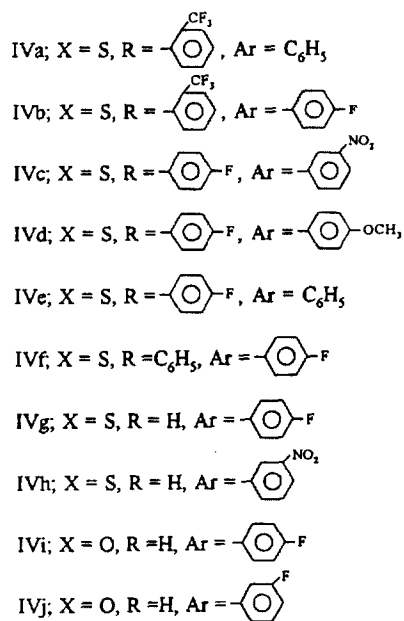
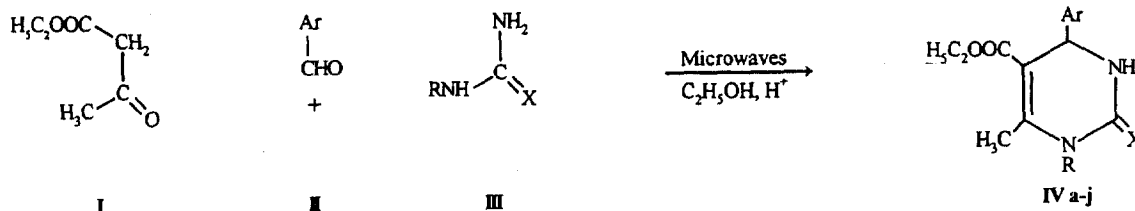
Simple modifications of the aromatic ring present at the 4-position are reported [22,23] to give various substances with moderate cardiovascular activity, but there is only one report [24] in the literature regarding the presence of a phenyl ring at the 1-position of the pyrimidine nucleus.

A comprehensive review article on the '100 Years of the Biginelli Dihydropyrimidine Synthesis' was published in 1993 by Kappe [21], in which most of the references are patents. A perusal of the literature has revealed scanty information on the fluorinated derivatives of Biginelli compounds [24–26]. Only three reports indicated the presence of a fluorinated aryl group at the 4-position of the pyrimidine nucleus, and no report mentions fluorine incorporation at the 1-position in these heterocycles.

As a part of our extensive research programme for developing new fluorinated bioactive heterocycles [27–36], we have now investigated synthesis of fluorine-containing tetrahydropyrimidines by both thermal methods and under microwave irradiation. This is the first report of the synthesis of fluorine-containing tetrahydropyrimidines. Also, some non-fluorinated compounds have been synthesized under similar conditions, to compare the bioactivity and role of substituents.

The introduction of a fluorine atom or  $\text{CF}_3$  group into an organic molecule frequently provides compounds of pharmacological interest as compared to their non-fluorinated

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Scheme 1.

analogues [37]. The substituents attached to the benzene ring of benzaldehyde may facilitate or retard the condensation through their electronic effects. Stereo effects of the substituents which seem to hinder the condensations were observed in these compounds.

Microwave-induced reaction rate enhancement is just a decade old [38–40] but has emerged as an important method of reaction activation [41,42]. In 1986, it was first reported that organic reactions could be accelerated in domestic microwave ovens [39,40]. Most of the reported reactions [39–42] have been carried out either in sealed vessels or in the solid phase, though a few reports of the use of unmodified domestic microwave ovens have appeared for carrying out organic synthesis in open vessels [43,44] using organic solvents such as ethanol, *N,N*-dimethylformamide (DMF), *o*-dichlorobenzene, 1,2-dichloroethane (DCE), etc. as energy transfer media [45–47]. The rapid and efficient syntheses of fluorine-containing ethyl 4-aryl-6-methyl-tetra-hydropyrimidin-2-one/thione-5-carboxylates under microwave irradiation using ethanol as energy transfer medium are described.

The results obtained demonstrate the versatility of the process as considerable reaction rate enhancement has been observed, bringing down the reaction time from hours to minutes with improved yields. The identity of the products synthesized by conventional and microwave-induced method

was established by their melting points, elemental analyses and spectral data.

## 2. Results and discussion

The concept of microwave-induced organic reactions activation has been utilized for rapid and efficient syntheses of a series of new fluorine-containing Biginelli compounds. The ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidine-2-one/thione-5-carboxylates (**IV**) have been synthesized by the acid catalyzed condensation of fluorinated aromatic aldehydes (**I**) with ethyl acetoacetate (**II**) and urea/fluorinated phenylthiourea (**III**) in open borosilicate glass vessels using ethanol as energy transfer medium (Scheme 1).

The compounds (**IV**) were characterized by <sup>1</sup>H NMR signals at δ 5.3–5.6 (s, 1H, CH), 4.0–4.28 (q, 2H, CH<sub>2</sub> CH<sub>3</sub>), 1.09–1.25 (t, 3H, CH<sub>2</sub>–CH<sub>3</sub>), 7.0–8.0 (m, aromatic protons) and 7.6–8.0 (s, 1H, NH) ppm. The position of the NH proton was confirmed on deuteration. Apart from these, a singlet at δ 2.2–2.38 ppm was also observed for methyl protons attached to a benzene ring at the 6-position, which further confirms the formation of the desired compounds.

The IR spectra of compounds (**IVa–j**) displayed absorption bands at 3200–3350 (>NH) and at 1715–1730 cm<sup>-1</sup> for

(>C=O stretching of ester). The compounds (IVi) and (IVj) showed an additional band at  $1680\text{ cm}^{-1}$  for the carbonyl group. Along with these, characteristic bands were observed at  $1230\text{ cm}^{-1}$  (>C=S) and  $1570\text{ cm}^{-1}$  for phenyl (C=C) stretching. In  $^{19}\text{F}$  NMR spectra of (IV) single fluorine attached to aryl ring was observed at  $\delta - 111.26$  ppm while the  $\text{CF}_3$  group was observed at  $\delta - 63.248$  ppm. In the mass spectrum, a weak molecular ion peak  $M^+$  at  $m/z$  420 (IVa), corresponds to the molecular mass.

In order to study the possible existence of a specific microwave effect as compared with the conventional heating mode, we have studied two reactions both under microwave irradiation and by the thermal method, but in the latter case, lower yield was observed even after heating for 10 h, which indicates that the effect of microwave irradiation is not purely

thermal. Short reaction times along with enhanced yields and easy work up are the main advantages observed.

### 3. Experimental

Melting points were determined in open glass capillary and were uncorrected, IR spectra were recorded on a Perkin-Elmer (model-577) in KBr pellets.  $^1\text{H}$  and  $^{19}\text{F}$  NMR were recorded on Jeol (model-FX 90 Q) using  $\text{CDCl}_3$  as solvent at 89.55 and 84.25 MHz, respectively. TMS was used as internal reference for  $^1\text{H}$  NMR and hexafluorobenzene as external reference for  $^{19}\text{F}$  NMR. Mass spectra were recorded on a Kratos 30 and 50 mass spectrometers. All compounds were found homogeneous on TLC in various solvent systems.

Table 1  
Microwave-induced Biginelli condensations: analytical data of the new compounds prepared

| Compound no. | X | R                                    | Ar                                    | Reaction time (min) | m.p. ( $^{\circ}\text{C}$ ) | Yield (%) | Molecular formula  | Elemental analysis (calcd./found) |           |             |
|--------------|---|--------------------------------------|---------------------------------------|---------------------|-----------------------------|-----------|--|-----------------------------------|-----------|-------------|
|              |   |                                      |                                       |                     |                             |           |  | C                                 | H         | N           |
| IVa          | S | 2- $\text{CF}_3\text{C}_6\text{H}_4$ | $\text{C}_6\text{H}_5$                | 11                  | 177                         | 86.4      | $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2\text{S}$ | 60.00/59.97                       | 4.52/4.50 | 6.67/6.64   |
| IVb          | S | 2- $\text{CF}_3\text{C}_6\text{H}_4$ | 4- $\text{FC}_6\text{H}_4$            | 10                  | 192                         | 65        | $\text{C}_{21}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_2\text{S}$ | 57.53/57.49                       | 4.11/4.09 | 6.39/6.37   |
| IVc          | S | 4- $\text{FC}_6\text{H}_4$           | 3- $\text{NO}_2\text{C}_6\text{H}_4$  | 7                   | 284                         | 70.2      | $\text{C}_{20}\text{H}_{18}\text{FN}_3\text{O}_4\text{S}$          | 57.83/57.79                       | 4.34/4.30 | 10.12/10.09 |
| IVd          | S | 4- $\text{FC}_6\text{H}_4$           | 4- $\text{OCH}_3\text{C}_6\text{H}_4$ | 6                   | 302                         | 75.2      | $\text{C}_{21}\text{H}_{21}\text{FN}_2\text{O}_3\text{S}$          | 63.00/62.92                       | 5.25/5.22 | 7.00/6.96   |
| IVe          | S | 4- $\text{FC}_6\text{H}_4$           | $\text{C}_6\text{H}_5$                | 6                   | 230                         | 82.4      | $\text{C}_{20}\text{H}_{19}\text{FN}_2\text{O}_2\text{S}$          | 64.86/64.85                       | 5.14/5.13 | 7.57/7.55   |
| IVf          | S | $\text{C}_6\text{H}_5$               | 4- $\text{FC}_6\text{H}_4$            | 6                   | 110                         | 87.9      | $\text{C}_{20}\text{H}_{19}\text{FN}_2\text{O}_2\text{S}$          | 64.86/64.83                       | 5.14/5.12 | 7.57/7.53   |
| IVg          | S | H                                    | 4- $\text{FC}_6\text{H}_4$            | 4                   | 184                         | 81        | $\text{C}_{14}\text{H}_{14}\text{FN}_2\text{O}_2\text{S}$          | 57.34/57.27                       | 4.78/4.77 | 9.56/9.53   |
| IVh          | S | H                                    | 3- $\text{NO}_2\text{C}_6\text{H}_4$  | 4                   | 188                         | 78.4      | $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$           | 52.34/52.28                       | 4.67/4.64 | 13.08/13.01 |
| IVi          | O | H                                    | 4- $\text{FC}_6\text{H}_4$            | 6                   | 173                         | 86        | $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}_3$                  | 60.43/60.40                       | 5.39/5.37 | 10.07/10.04 |
| IVj          | O | H                                    | 3- $\text{FC}_6\text{H}_4$            | 6                   | 202                         | 80        | $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}_3$                  | 60.43/60.39                       | 5.39/5.38 | 10.07/10.05 |

Table 2  
Spectral data of the compounds

| Compound no. | IR ( $\text{cm}^{-1}$ )  | $^1\text{H}$ NMR ( $\delta$ ppm) |                                 |                                 |                 |             |             |                  |
|--------------|--|----------------------------------|---------------------------------|---------------------------------|-----------------|-------------|-------------|------------------|
|              |  | - $\text{CH}_3$                  | $\text{CH}_3$ - $\text{CH}_2$ - | $\text{CH}_3$ - $\text{CH}_2$ - | - $\text{CH}$ - | Ar-H        | NH          | - $\text{OCH}_3$ |
| IVa          | 3350–3300, 1715, 1600, 1570, 1450, 1340, 1230, 1130, 1015, 860, 750, 640 | 2.2 (s)                          | 1.1–1.13 (t)                    | 4.0–4.03 (q)                    | 5.3 (s)         | 7.0–7.3 (m) | 7.7 (br,s)  | –                |
| IVb          | 3340–3220, 1720, 1610, 1580, 1450, 1330, 1240, 1120, 1000, 870, 740, 630 | 2.24 (s)                         | 1.09–1.12 (t)                   | 4.1–4.14 (q)                    | 5.35 (s)        | 7.1–7.6 (m) | 7.75 (br,s) | –                |
| IVc          | 3350–3290, 1715, 1630, 1570, 1460, 1350, 1240, 1140, 1020, 860, 740, 630 | 2.26 (s)                         | 1.15–1.2 (t)                    | 4.25–4.28 (q)                   | 5.6 (s)         | 7.2–7.8 (m) | 8.0 (br,s)  | –                |
| IVd          | 3300–3240, 1730, 1610, 1560, 1440, 1350, 1230, 1110, 1010, 880, 750, 640 | 2.38 (s)                         | 1.2–1.25 (t)                    | 4.1–4.13 (q)                    | 5.4 (s)         | 7.3–8.0 (m) | 7.72 (br,s) | 3.8 (s)          |
| IVe          | 3330–3280, 1720, 1620, 1590, 1460, 1340, 1230, 1140, 1030, 870, 770, 650 | 2.3 (s)                          | 1.09–1.13 (t)                   | 4.2–4.24 (q)                    | 5.42 (s)        | 7.2–7.9 (m) | 7.9 (br,s)  | –                |
| IVf          | 3340–3300, 1715, 1600, 1580, 1450, 1340, 1240, 1120, 1015, 860, 760, 650 | 2.35 (s)                         | 1.2–1.24 (t)                    | 4.0–4.04 (q)                    | 5.35 (s)        | 7.4–8.0 (m) | 7.7 (br,s)  | –                |
| IVg          | 3320–3260, 1725, 1620, 1580, 1470, 1330, 1240, 1110, 1020, 860, 780, 640 | 2.32 (s)                         | 1.14–1.17 (t)                   | 4.19–4.23 (q)                   | 5.3 (s)         | 7.1–7.5 (m) | 7.7 (br,s)  | –                |
| IVh          | 3300–3250, 1720, 1610, 1570, 1460, 1340, 1230, 1140, 1020, 860, 770, 650 | 2.37 (s)                         | 1.20–1.25 (t)                   | 4.2–4.25 (q)                    | 5.5 (s)         | 7.1–7.6 (m) | 7.8 (br,s)  | –                |
| IVi          | 3340–3280, 1730, 1680, 1600, 1570, 1470, 1350, 1130, 1010, 850, 740, 670 | 2.1 (s)                          | 1.09–1.12 (t)                   | 4.2–4.23 (q)                    | 5.2 (s)         | 7.3–8.0 (m) | 7.7 (br,s)  | –                |
| IVj          | 3350–3300, 1715, 1690, 1620, 1560, 1480, 1340, 1120, 1000, 860, 750, 640 | 2.2 (s)                          | 1.1–1.14 (t)                    | 4.21–4.24 (q)                   | 5.25 (s)        | 7.2–7.6 (m) | 7.9 (br,s)  | –                |

The Induced Microwave convection system, manufactured by BPL Sanyo Utilities and Appliances (India) has been used, where microwaves are generated at a frequency of 2450 MHz. The oven has a range of microwave output energy up to 1200 W.

### 3.1. Ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one/thione-5-carboxylates (IV)

Compounds **IVa** and **IVi** were prepared by two methods viz: (i) thermal and (ii) microwave irradiation. The percentage yields varied in each case.

#### 3.1.1. **IVa** (thermal)

A mixture of benzaldehyde (0.01 mol), ethyl acetoacetate (0.015 mol), 2-trifluoromethylphenyl thiourea (0.01 mol) and conc. HCl (1–2 drops) in absolute ethanol (20 ml) was refluxed for 10 h. Progress of reaction was monitored by TLC. On cooling, a solid compound separated out which was filtered and recrystallized from ethanol, m.p. 177°C, yield 64%; IR (KBr): 3350 (NH), 1715 (>C=O ester), 1570 (C=C), 1240 (C=S); PMR (CDCl<sub>3</sub>): 5.3 (s, 1H, CH), 4.0 (q, 2H, CH<sub>2</sub>-CH<sub>3</sub>), 1.1 (t, 3H, CH<sub>2</sub>-CH<sub>3</sub>), 2.2 (s, 3H, CH<sub>3</sub>), 7.0–7.3 (m, 9H, ArH), 7.7 (s, 1H, NH); MS *m/z* (%): 420 (10.2) 351 (24.9) 319 (30.4) 275 (52.6) 198 (60.5) 169 (64.6) 154 (72.2) 125 (80.4).

#### 3.1.2. **IVa** (microwave irradiation)

A mixture of **I** (0.015 mol), **II** (0.01 mol), **III** (0.01 mol) and conc. HCl (1–2 drops) in absolute ethanol (20 ml) was irradiated inside a microwave oven for 1 min (at 360 W, i.e., 30% microwave power). After this heating, an interval of 30 s was allowed in order to avoid excessive evaporation of the solvent. This protocol was repeated until reaching an overall heating time of 11 min.

Progress of reaction was monitored by TLC. The reaction mixture was then allowed to stand at room temperature and the product separated, was filtered, washed with ethanol, dried and recrystallized from ethanol, m.p. 177°C, yield 86.4%. The authenticity of the product was established by melting point, elemental analysis and spectral data.

### 3.2. **IVi** (thermal)

A mixture of 4-fluorobenzaldehyde (0.01 mol), ethylacetoacetate (0.015 mol), urea (0.01 mol) and conc. HCl (1–2 drops) in absolute ethanol (20 ml) was refluxed for 7 h. Progress of the reaction was monitored by TLC. On cooling, a solid compound separated out which was filtered and recrystallized from ethanol, m.p. 173°C, Yield 70%; IR (KBr): 3400 (NH), 1715 (CO ester), 1650 (CO ketone), 1570 (C=C); PMR (CDCl<sub>3</sub>): δ 5.2 (s, 1H, CH), 4.2 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.0 (t, 3H, CH<sub>2</sub>-CH<sub>3</sub>), 2.1 (s, 3H, CH<sub>3</sub>), 7.1–7.5 (m, 5H, Ar-H), 7.6–7.8 (s, 1H, NH).

### 3.3. **IVi** (microwave irradiation)

A mixture of **I** (0.015 mol), **II** (0.01 mol) and **III** (0.01 mol) in absolute ethanol (20 ml) was irradiated inside the microwave oven for 6 min (at 360 W, i.e., 30% microwave power), with short interruptions of 30 s to avoid excessive evaporation of the solvent. Progress of reaction was monitored by TLC. The reaction mixture was then allowed to stand at room temperature and the product separated, was filtered, washed with ethanol, dried and recrystallized from hot ethanol, m.p. 173°C; yield 86%.

The other compounds listed in (Tables 1 and 2) were synthesized by microwave irradiation, as considerable reaction rate enhancement along with 70.2–87.9% improved yields have been observed.

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