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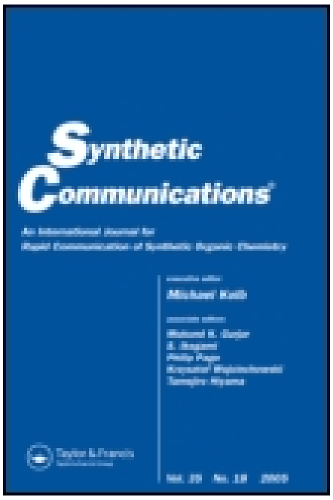

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A CONVENIENT FERRIC CHLORIDE CATALYZED SYNTHESIS OF 5-ALKOXYCARBONYL-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES UNDER MICROWAVE IRRADIATION

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A CONVENIENT FERRIC CHLORIDE CATALYZED SYNTHESIS OF 5-ALKOXYCARBONYL-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONES UNDER MICROWAVE IRRADIATION

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ABSTRACT

A series of ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one-5-carboxylates **4** were synthesized by the condensation of aromatic aldehydes, ethyl acetoacetate and urea in the presence of ferric chloride hexahydrate under microwave irradiation. The reactions were completed in 4–6 min with 87–92% yield.

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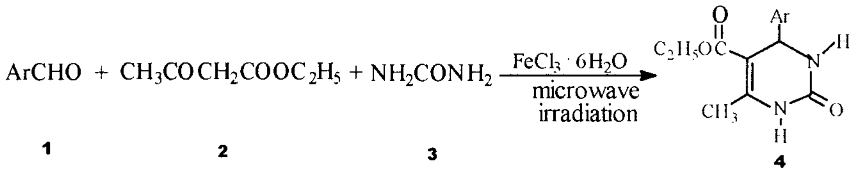
Since Biginelli[1] reported the synthesis of 3,4-dihydropyrimidin-2(1H)-ones in 1893, scientists have found these compounds to be useful as the calcium channel blockers, antihypertensive agents and α-1a-antagonists.[2] Consequently, the Biginelli reaction continues to attract the attention of researchers for the discovery of a milder and more practical route for the synthesis of dihydropyrimidin-2(1H)-ones. Several improved procedures for the preparation of DHPMs (Biginelli compounds) have been reported,[3–10] Hu[11] and Kappe[12] reported reagents involving the use of $BF_3{\cdot}OEt_2/CuCl$ and PPE (polyphosphate ester)-mediated variation of the Biginelli reaction giving high yields of dihydropyrimidinones of type (4). Then, Kappe[13] improved this reaction by employing microwave irradiation in the presence of PPE. Recently, Stefani and Gatti[14] have preparated Biginelli compounds (methyl ester) using methyl acetoacetate under microwave irradiation without catalyst and solvent free. However, in our laboratory, Hantzsch compounds have obtained (not Biginelli compounds) using ethyl acetoacetate at the same condition. But, Biginelli compounds (ethyl ester) have been successfully obtained when using ferric chloride hexahydrate as catalyst at above condition.

In this paper, we would like to report the synthesis of ethyl 4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidin-2-one-5-carboxylates (**4**) by one-pot condensation of aromatic aldehydes, ethyl acetoacetate and urea in the presence of ferric chloride hexahydrate using silica gel as carrier under microwave irradiation and solvent free. The reactions were completed in 4–6 min with 87–92% yields. All the products were confirmed by melting points, elemental analysis and spectral data.

The results are shown in the Table 1.



In this reaction, the ferric chloride hexahydrate is necessary, because diethyl 4-aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**5**) were obtained without ferric chloride hexahydrate. The results are shown in the Table 2.

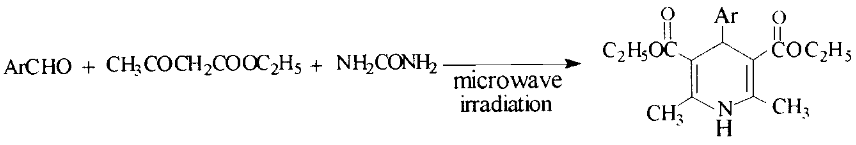
Table 1. Microwave-Induced and Iron (III)-Catalyzed Biginelli Condensations

Entry	Ar	Time (min)	M.P. (°C)	Yield (%)
4a	C_6H_5	6	202–4 (202.4)[15]	90
4b	3,4-$(OCH_2O)C_6H_3$	5	185–7 (187–8)[15]	94
4c	3,4-$(CH_3O)_2C_6H_3$	5	175–7 (178–8.5)[15]	91
4d	4-ClC_6H_4	4	208–211 (213–5)[11]	94
4e	3-$O_2NC_6H_4$	5	224–6 (226–7.5)[13]	89
4f	4-HOC_6H_4	4	228–9 (227–9)[15]	87
4g	4-$CH_3OC_6H_4$	6	199–200 (201–2)[15]	95
4h	4-HO-3-$CH_3OC_6H_3$	5	229–230 (232–3)[15]	92

Table 2. The Reaction Results in Absence of Ferric Chloride Hexahydrate

Ar	M.P. (°C)	Lit. M.P. (°C)	Yield (%)
C_6H_5	152–4	158–60[16]	68
4-HOC_6H_4	220–3	227–8[17]	70
4-HO-3-$CH_3OC_6H_3$	158–60	163–4[17]	75
3,4-$(CH_3O)_2C_6H_3$	138–40	142–5[17]	77

The synthetic route is shown as following:



5

The structure of **5a** is confirmed by X-ray diffraction studies on a monocrystal of **5a** (Figure 1).[18]

EXPERIMENTAL

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a Nicolet FI-IR50DX instrument. ^{1}H NMR spectra were measured on a Bruker DPX 300 MHz spectrometer using TMS as internal standard. Elemental analysis were determined by using

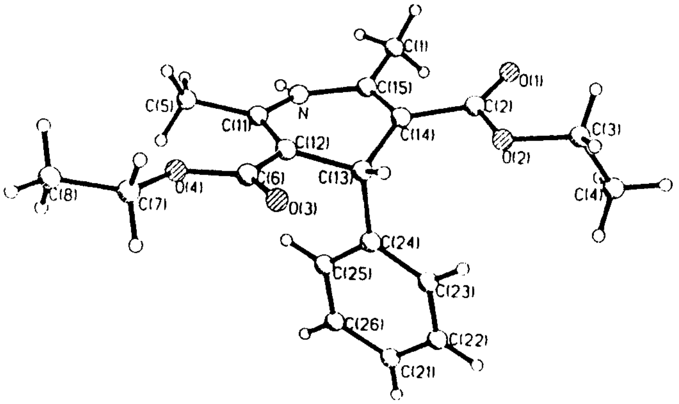


Figure 1. X-ray crystal structure of **5a**.

Perkin-Elmer 240 C elemental analyzer. X-ray diffraction were measured on an Enraf-Nonius CCD4 diffractometer. Microwave irradiation was carried out with a modified commercial microwave oven (2450 MHz, 650 W) under atmospheric pressure.

General Procedure

Aromatic aldehyde (**1**, 10 mmol), ethyl acetoacetate (**2**, 1.43 g, 11 mmol), urea (**3**, 1.8 g, 30 mmol) and $FeCl_3 \cdot 6H_2O$ (1.35 g, 5 mmol) were thoroughly mixed with silica gel (5.0 g, 70–230 mesh, 60 Å) in an agate mortar. The resulting fine powder was transferred to a flask (50 mL) connected with refluxing equipment. After microwave irradiation of several minutes, the reaction mixture was allowed to cool to room temperature. The inorganic support was separated by filtration after extracting the product with chloroform. The filtrate was evaporated to give the crude product (**4**), which was purified by recrystallization from ethanol.

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18. X-ray analysis of **5a**: Empirical formula $C_{19}H_{23}NO_4$, monoclinic, space group $P2_1/c$, $a = 9.745(2)\,\text{Å}$, $b = 7.388(2)\,\text{Å}$, $c = 24.354(5)\,\text{Å}$, $\alpha = 90^\circ$, $\beta = 92.60(3)^\circ$, $\gamma = 90^\circ$, $V = 1751.6(6)\,\text{Å}^3$, $Z = 4$ $W_r = 329.38$, $\text{Dc} = 1.249\,\text{Mg/cm}^3$, $\lambda(\text{M}_\text{o}\text{K}_\alpha) = 0{,}71073\,\text{Å}$, $\mu = 0.087\,\text{mm}^{-1}$, $F(000) = 704$, $1.67^\circ < \theta < 24.97^\circ$, $R = 0.0416$, $R_\text{w} = 0.1175$.

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