Microwave-Assisted High-Speed Parallel Synthesis of 4-Aryl-3,4-dihydropyrimidin-2(1*H*)-ones using a Solventless Biginelli Condensation Protocol[1]

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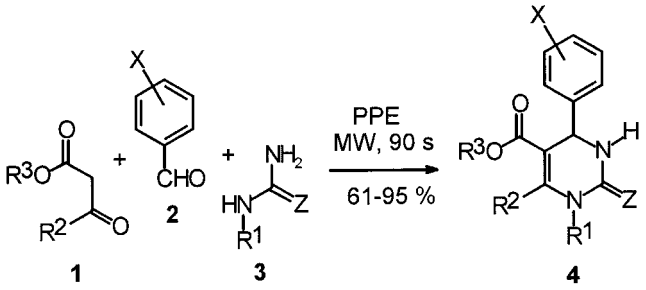
Abstract: 4-Aryl-3,4-dihydropyrimidin-2-(1*H*)-ones **4a-o** are synthesized by a microwave-promoted, solvent-free modification of the Biginelli three-component cyclocondensation reaction. The novel method employs neat mixtures of ß-ketoesters, aryl aldehydes, and urea derivatives with polyphosphate ester (PPE) being used as a reaction mediator. Irradiation of these mixtures for 90 s in an unmodified household microwave oven provides DHPMs **4a-o** in 61-95% yield after aqueous workup. This safe and environmentally benign protocol was performed on a 1-50 mmol scale and can furthermore be extended towards the parallel synthesis of DHPMs compound libraries.

Key words: synthetic methods, microwave-enhanced chemistry, heterocycles, combinatorial chemistry, cyclizations

4-Aryl-3,4-dihydro-2(1*H*)-pyrimidone esters of type **4** ("Biginelli compounds", DHPMs) represent a heterocyclic system of remarkable pharmacological efficiency.[2-6] In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives.[2] More recently, appropriately functionalized DHPMs have emerged as potent calcium channel blockers,[3] antihypertensive agents,[4] α_{1a}-adrenergic antagonists,[5] and neuropeptide Y (NPY) antagonists.[6] The most straightforward protocol to synthesize DHPMs **4** involves the one-pot condensation of a ß-keto ester **1**, with an aryl aldehyde **2**, and urea or thiourea derivative **3** under strongly acidic conditions (Biginelli condensation, see Scheme 1).[2,7] Unfortunately, this one-pot, one-step protocol often provides only low to moderate yields of the desired target molecules **4**, in particular when substituted aromatic aldehydes or thioureas are employed.[2,8-10] This has led to the recent disclosure of several improved reaction protocols for the synthesis of DHPMs, either by modification of the classical one-pot Biginelli approach itself,[8] or by the development of novel, but more complex multistep strategies.[9] In addition, several combinatorial approaches towards DHPMs **4** have been advanced,[10] using e.g. solid phase,[10a,b] or fluorous phase[10c,d] reaction conditions.

We herein report a method that allows the rapid and parallel synthesis of DHPMs **4** that does not rely on polymer-supported building blocks and therefore does not require the development of solid phase linking/cleaving chemistry. Instead, our procedure involves a microwave-promoted, solvent-free variation of the classical Biginelli condensation. The application of microwave (MW) irradiation in organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology.[11] The salient features of the microwave approach are the rapid reaction rates, cleaner reaction conditions and ease of manipulation.[11] Reactions in "dry media" or under solvent-free conditions are especially appealing as they provide an opportunity to work with open vessels, thus avoiding the risk of high pressure development and with the possibility of upscaling the reactions to larger scale.[11]

The microwave-expedited Biginelli reaction described herein[12] is based on our recent finding that polyphosphate ester (PPE) serves as an excellent reaction mediator in the three-component Biginelli reaction.[8b] Using THF/PPE mixtures (reflux, 24 h) instead of the traditional protic solvent/mineral acid reaction media (e.g. EtOH/HCl),[13] improved yields of DHPMs are obtainable.[8b] The success of this PPE-mediated method may be due to a specific interaction of PPE with the proposed *N*-acyliminium ion intermediate formed from the aldehyde **2** and urea **3** component in the initial reaction step.[14]



Scheme 1

In order to be able to carry out such Biginelli condensations in a faster and more efficient way - eliminating the use of a solvent and reflux conditions - we investigated the influence of MW irradiation on a neat mixture of ß-keto ester **1**, aryl aldehyde **2**, (thio)urea derivative **3**, and PPE. After some experimentation with respect to the molar ra-

tios of reagents, and the irradiation time and power level of the MW set-up we have found a set of conditions that generally provides DHPMs in good to excellent yields (Table 1). These conditions employed a 1.1:1.0:3.0 ratio of ß-keto ester **1**, aryl aldehyde **2**, and (thio)urea derivative **3**, using 150 mg of PPE as reaction mediator. The amount of PPE does not appear to be critical as we have run successful experiments with 20-200 mg of PPE per mmol of aldehyde. However, the presence of about 150 mg of liquid, non-volatile PPE ensures the homogeneity of the reaction mixture in particular when solid aldehydes are employed. Similarily, in most cases the molar ratio of the (thio)urea component could be reduced to 1.5 equiv without lowering the yield of DHPMs significantly. In a typical experiment the four reaction components are simply mixed in a glass beaker and irradiated in an unmodified household MW oven for a total of 90 s (see the Experimental Section). During MW irradiation the reaction vessel is placed inside a larger container filled with alumina, which acts as a heat sink. After cooling, water was added to the reaction mixture which hydrolyzed PPE, dissolved excess (thio)urea and precipitated the solid DHPMs. For the majority of cases, the products obtained using this microwave/PPE-mediated Biginelli protocol had at least 95% purity (^{1}H NMR, 200 MHz). Only in a few instances (entries **4k** and **4n**, see Table 1) the purity of the crude products was relatively lower (85-90%) and purification by chromatography or recrystallization had to be carried out. For comparison purposes, literature yields obtained for DHPMs **4a-o** using the traditional Biginelli reaction conditions (EtOH/catalytic HCl or H_2SO_4) are also given in Table 1. In the majority of cases a very significant increase (20-50%) in yield using the MW-induced protocol can be achieved. At the same time, the reaction time is reduced from typically 4-8 hours reflux (traditional heating)[2] to a few minutes (MW irradiation).

Table 1 Microwave/PPE-Mediated Synthesis of DHPMs

DHPM	X	Z	R^1	R^2	R^3	yield (%)	
						a	b
4a	H	O	H	Me	Et	85	79
4b	3-NO_2	O	H	Me	Et	93	51
4c	2-Cl	O	H	Me	Et	95	51
4d	2-CF_3	O	H	Me	Et	76	15
4e	2,3-$(Cl)_2$	O	H	Me	Et	91	59
4f	3,4-$(F)_2$	O	H	Me	Et	87	66
4g	2-Me	O	H	Me	Me	86	68
4h	4-NO_2	O	H	Me	Me	86	41
4i	3-NO_2	O	H	Me	*i*-Pr	94	–
4j	H	O	H	Me	*t*-Bu	81	55
4k	3,4-$(F)_2$	O	H	Et	Me	65[c]	55
4l	H	O	Me	Me	Et	89	60
4m	H	S	H	Me	Et	82	42
4n	3-NO_2	S	H	Me	Et	71[c]	24
4o	H	S	Me	Me	Et	78	48

[a] Microwave/PPE-mediated reaction conditions, for details see the Experimental Section.
[b] Literature yields based on classical Biginelli conditions (cat. H^+/EtOH), for individual references see the Experimental Section.
[c] After chromatographic workup.

The yields given in Table 1 refer to reaction runs at 2.0 mmol scale. For DHPM **4a** a scale-up to 50 mmol (ca 13 g of product) was performed without any difficulties furnishing the desired DHPM in 88% yield after recrystallization (see Experimental Section). It appears that in upscaling the reaction the amount of PPE has not to be proportionally increased. In our optimization studies with 50 mmol scale reactions we have experimented with varying amounts of PPE (1-5 g) and found that reproducible results are obtained in each case employing a total irradiation (50% power level) time of 2 min (successive irradiations of 30 s each with cooling intervals of 1 min, the bulk bath temperature being 95 °C). In view of the relatively exothermic reaction with large excess of PPE, 1 g of PPE appears to be optimal for completion of the reaction; with lower amounts the reaction remains incomplete with concomitant formation of side products. Vigorous reaction ensues during the initial 30 s of exposure to microwave irradiation when the alumina bath temperature reaches 55 °C. The intermittent MW heating not only promotes the selective interaction of substrates and avoids their evaporation but also results in the formation of a cleaner product especially in large scale runs. The selective coupling of microwaves to the ensuing water molecules and their rapid removal from the reaction mixture may be responsible for the faster assembly of the DHPMs.

Apart from its simplicity and speed an important feature of the microwave-induced protocol is the ability to tolerate variations in all of the three building blocks. The aryl aldehyde **2** for example can be varied to a large extent and many of the pharmaceutically relevant[3-6] substitution patterns on the 4-aryl ring (i.e., entries **4b-f**) can be introduced in excellent yield. Similarily, a variety of ß-keto esters **1** (i.e., entries **4g-k**) and different (thio)urea derivatives **3** can be employed (i.e., entries **4l-o**). Thus, all five variable substituents around the DHPM scaffold **4** (R^1-R^3, X, Z) can be modified, increasing the structural diversity of DHPM analogs that can be synthesized expeditiously.

We have therefore extendend the scope of this microwave/PPE-mediated Biginelli procedure and have carried out the synthesis of a number of DHPM analogs (i.e., **4a-j**) in a parallel fashion in a single microwave irradiation experiment. For this purpose 10 reaction vessels containing the appropriate mixtures of ß-keto esters **1**, aldehydes **2**, urea **3**, and PPE were placed inside an alumina bath and subsequently irradiated in the microwave oven (see Experimental Section). After the usual aqueous workup the individual DHPMs **4a-j** were obtained in yields identical to the ones obtained in the conventional MW experiment (Table 1). This strategy is therefore clearly applicable to the parallel synthesis of single compound DHPM libraries. In view of the large number of commercially available or readily accessible aromatic aldehydes, ß-keto esters, and urea derivatives large collections of DHPMs can potentially be prepared, applying the recently developed automated, high throughput robotic technologies for

performing microwave-assisted combinatorial synthesis.[15]

In conclusion, we have described a novel and highly efficient microwave-induced modification of the Biginelli multicomponent reaction that allows the rapid assembly of structurally diverse DHPM derivatives. The advantages of this environmentally benign and safe protocol include a simple reaction set-up not requiring specialized equipment, high product yields, short reaction times, and the elimination of solvents or solid supports. Furthermore, the present procedure is readily amenable to parellel synthesis and the generation of combinatorial DHPM libraries.

Melting points were determined on a Gallenkamp melting point apparatus Mod. MFB-595 and are uncorrected. ^{1}H NMR spectra were obtained on a Varian XL-200 Gemini instrument at 200 MHz. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer. Elemental analyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Reactions were monitored by thin layer chromatography on 0.2 mm silica gel F-252 (Merck) plates. All ß-keto esters **1**, aldehydes **2**, and urea derivatives **3** were obtained from Aldrich Chemical Co. and used without further purification, with the exception of benzaldehyde which was distilled in vacuo prior to use. PPE was prepared according to literature procedures.[16] All solid components were employed as grained powders.

For the microwave irradiation experiments described below a conventional (unmodified) houesehold microwave oven equipped with a turntable was used (Panasonic NN-3356/3306, 2450 MHz, 800 W; a similar MW oven with 900 W power was used for the large scale experiments).

Microwave/PPE-Mediated Synthesis of Dihydropyrimidinones 4a-o; General Procedure

a) Single-Compound Method

The appropriate ß-keto ester (2.2 mmol), aldehyde (2.0 mmol), urea derivative (6.0 mmol) and PPE (300 mg) was placed (in that order) in a 20 mL glass beaker. After the mixture had been stirred for 10-20 s with a spatula the reaction container was inserted into a 400 mL pyrex beaker filled with neutral alumina (150 g, 100-290 mesh). This set-up was irradiated in the MW oven 3 times at the 50% power level for 30 s (25% power level for entries **4l** and **4o**, 5 times 50% power level for entry **4k**) with a 1 min and 2 min cooling period after the 1st and 2nd irradiation cycle, respectively. After the addition of H_2O (5 mL) the mixture was stirred at r.t. for 1-2 h. The solid products were filtered, washed with H_2O and subsequently dried. ^{1}H NMR (200 MHz) measurements of these products confirmed their purity to be >95%.

b) Preparation of DHPM 4a on a 50 mmol Scale

A mixture of benzaldehyde (5.3 g, 50 mmol), urea (6.0 g, 100 mmol), ethyl acetoacetata (6.5 g, 50 mmol) and PPE (1 g) was taken in a 100 mL beaker and placed inside in a pyrex crystallization dish (12.5 cm diameter) filled with alumina (400 g). The mixture was exposed to microwaves at 50% power level for four successive irradiations of 30 s each with cooling and mixing interval of 1 min. The mixture was allowed to cool and the ensuing solid contents were stirred with H_2O (300 mL) at r.t. for 3 h. The white solid product was filtered, washed with H_2O and dried to yield 12.0 g (92%) of crude product. A sample of analytical purity was obtained in 88% yield by recrystallization from EtOH.

c) Parallel Synthesis of DHPMs 4a-j

The appropriate (see Table 1) ß-keto esters 1 (1.1 mmol), aldehydes 2 (1.0 mmol), urea 3 (3.0 mmol) and PPE (150 mg) were placed in 10 individual 10 mL glass beakers immersed in a crystallization dish (13.5 cm diameter) filled with alumina (400 g). This set-up was irradiated on the turntable in the MW oven 3 times at the 50% power level for 40 s with a 1 min and 2 min cooling period after the 1st and 2nd irradiation cycle, respectively. Aqueous workup as above provided DHPMs **4a-j** in yields given in Table 1.

Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

85% yield, mp 206–207 °C (EtOH) (lit.[13] mp 202.4 °C, 79% yield);

IR (KBr): ν = 3240, 3110, 1725, 1700, 1645 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.12 (t, 3H, *J* = 7.5 Hz, CH_3), 2.28 (s, 3H, CH_3), 4.03 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.17 (d, 1H, *J* = 3.0 Hz, H-4), 7.22-7.41 (m, 5H, H_{arom}), 7.78 (br s, 1H, NH), 9.22 (br s, 1H, NH).

Ethyl 6-Methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

93% yield, mp 228 °C (HOAc) (lit.[13] mp 226–227.5, 51% yield).

IR (KBr): ν = 3300, 3120, 1710, 1690, 1630 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.11 (t, 3H, *J* = 7.5 Hz, CH_3), 2.29 (s, 3H, CH_3), 4.02 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.31 (d, 1H, *J* = 3.0 Hz, H-4), 7.65-7.75 (m, 2H, H_{arom}), 7.95 (br s, 1H, NH), 8.09-8.20 (m, 2H, H_{arom}), 9.34 (br s, 1H, NH).

Ethyl 4-(2-Chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

95% yield, mp 215–218 °C (EtOH) (lit.[17] mp 214 °C, yield 51%).

IR (KBr): ν = 3360, 3220, 3100, 1690, 1640 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.08 (t, 3H, *J* = 7.5 Hz, CH_3), 2.32 (s, 3H, CH_3), 3.91 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.67 (d, 1H, *J* = 2.5 Hz, H-4), 7.22-7.46 (m, 4H, H_{arom}), 7.72 (br s, 1H, NH), 9.30 (br s, 1H, NH).

Ethyl 6-Methyl-2-oxo-4-[2-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)

76% yield, mp 202-203 °C (EtOH) (lit.[9a] mp 198-200 °C, lit.[8a] yield 15%).

IR (KBr): ν = 3230, 3100, 1700, 1640 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.97 (t, 3H, *J* = 7.5 Hz, CH_3), 2.45 (s, 3H, CH_3), 3.97 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.37 (br s, 1H, H-4), 5.82 (br s, 1H, NH), 7.32-7.70 (m, 4H, H_{arom}), 8.46 (br s, 1H, NH).

Ethyl 4-(2,3-Dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

91% yield, mp 244–246 °C (MeOH) (lit.[9a] mp 212–214 °C, lit.[8a] yield 59%).

IR (KBr): ν = 3360, 3100, 1700, 1690sh, 1640 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 0.97 (t, 3H, *J* = 7.5 Hz, CH_3), 2.31 (s, 3H, CH_3), 3.89 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.69 (br s, 1H, H-4), 7.25-7.43 (m, 2H, H_{arom}), 7.50-7.61 (m, 1H, H_{arom}), 7.80 (br s, 1H, NH), 9.32 (br s, 1H, NH).

Ethyl 4-(3,4-Difluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)

87% yield, mp 188–189 °C (EtOH) (lit.[8b] mp 185–186 °C, 66% yield).

IR (KBr): ν = 3320, 1710, 1680, 1660, 1640 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.11 (t, 3H, *J* = 7.5 Hz, CH_3), 2.29 (s, 3H, CH_3), 4.02 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.17 (d, 1H, *J* = 3.0 Hz, H-4), 7.05-7.50 (m, 3H, H_{arom}), 7.80 (br s, 1H, NH), 9.28 (br s, 1H, NH).

Methyl 6-Methyl-4-(2-methylphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)

86% yield, mp 240–242 °C (EtOH) (lit.[18] mp 240–242 °C, 68% yield).

IR (KBr): ν = 3230, 3100, 1695, 1665 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.31 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.48 (s, 3H, OCH_3), 5.41 (d, 1H, *J* = 4.0 Hz, H-4), 7.11-7.22 (m, 4H, ArH), 7.62 (br s, 1H, NH), 9.19 (br s, 1H, NH).

Methyl 6-Methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)
86% yield, mp 246–248 °C (HOAc/EtOH) (lit.[8b] mp 235–237 °C, 41% yield).

IR (KBr): ν = 3360, 3240, 3120, 1720, 1695, 1630 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 3.56 (s, 3H, OCH_3), 5.30 (br s, 1H, H-4), 7.53 (d, 2H, *J* = 8.5 Hz, H_{arom}), 7.92 (br s, 1H, NH), 8.23 (d, 2H, *J* = 8.5 Hz, H_{arom}), 9.40 (br s, 1H, NH).

Isopropyl 6-Methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)
94% yield, mp 205–208 °C (EtOH) (lit.[4a] mp 183–184 °C).

IR (KBr): ν = 3240, 3110, 1715sh, 1705, 1650 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.00 and 1.18 (2 d, 6H, *J* = 6.0 Hz each, 2 CH_3), 2.28 (s, 3H, CH_3), 4.84 (m, 1H, CH), 5.31 (d, 1H, *J* = 3.0 Hz, H-4), 7.65-7.77 (m, 2H, H_{arom}), 7.91 (br s, 1H, NH), 8.09-8.19 (m, 2H, H_{arom}), 9.38 (br s, 1H, NH).

tert.-Butyl-6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)
81% yield, mp 216–217 °C (EtOH) (lit.[19] mp 209 °C, 55% yield).

IR (KBr): ν = 3240, 3090, 1715sh, 1705, 1680, 1650 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.30 (s, 9H, *t*-Bu), 2.24 (s, 3H, CH_3), 5.12 (d, 1H, *J* = 3.0 Hz, H-4), 7.20-7.39 (m, 5H, H_{arom}), 7.69 (br s, 1H, NH), 9.09 (br s, 1H, NH).

Methyl 4-(3,4-Difluorophenyl)-6-ethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k)
65% yield after flash silica gel chromatography ($CHCl_3$/acetone 7:2) of the crude material, mp 187–189 °C (EtOH) (lit.[8b] mp 182–185 °C, 55% yield).

IR (KBr): ν = 3310, 3140, 1710, 1665, 1640 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.13 (t, 3H, *J* = 7.5 Hz, CH_3), 2.69 (m, 2H, CH_2), 3.57 (s, 3H, OCH_3), 5.18 (d, 1H, *J* = 3.0 Hz, H-4), 7.03-7.49 (m, 3H, H_{arom}), 7.82 (br s, 1H, NH), 9.32 (br s, 1H, NH).

Ethyl 1,6-Dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l)
89% yield, mp 180 °C (EtOH) (lit.[20] mp 176–178 °C, 60% yield).

IR (KBr): ν = 3220, 3100, 1710, 1680, 1620 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.14 (t, 3H, *J* = 7.5 Hz, CH_3), 2.51 (s, 3H, CH_3), 3.11 (s, 3H, NCH_3), 4.04 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.19 (d, 1H, *J* = 3.0 Hz, H-4), 7.21-7.39 (m, 5H, H_{arom}), 7.99 (br s, 1H, NH).

Ethyl 6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)
82% yield, mp 205–207 °C (EtOH) (lit.[20] mp 207–208 °C, 42% yield).

IR (KBr): ν = 3340, 3180, 3100, 1670, 1580 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.12 (t, 3H, *J* = 7.5 Hz, CH_3), 2.31 (s, 3H, CH_3), 4.02 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.20 (d, 1H, *J* = 3.0 Hz, H-4), 7.20-7.41 (m, 5H, H_{arom}), 9.68 (br s, 1H, NH), 10.31 (br s, 1H, NH).

Ethyl 6-Methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n)
71% yield after flash silica gel chromatography ($CHCl_3$/acetone 7:2) of the crude material, mp 208–209 °C (EtOH) (lit.[9b] mp 206–207, 24% yield).

IR (KBr): ν = 3180, 1715, 1660, 1595, 1530 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.12 (t, 3H, *J* = 7.5 Hz, CH_3), 2.33 (s, 3H, CH_3), 4.05 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.35 (br s, 1H, H-4), 7.65-7.73 (m, 2H, H_{arom}), 8.08-8.27 (m, 2H, H_{arom}), 9.80 (br s, 1H, NH), 10.55 (br s, 1H, NH).

Ethyl 1,6-Dimethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o)
78%, mp 146–147 °C (EtOH) (lit.[21] mp 146–147 °C, 48% yield).

IR (KBr): ν = 3210, 1710, 1640, 1540, 1500 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 1.18 (t, 3H, *J* = 7.5 Hz, CH_3), 2.55 (s, 3H, CH_3), 3.51 (s, 3H, NCH_3), 4.12 (q, 2H, *J* = 7.5 Hz, OCH_2), 5.22 (d, 1H, *J* = 3.5 Hz, H-4), 7.18-7.41 (m, 5H, H_{arom}), 9.88 (d, 1H, *J* = 3.5 Hz, NH).

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