An Efficient Protocol for the Liquid-Phase Synthesis of Methyl 3,4-Dihydropyrimidin-2(1*H*)-one-5-carboxylate Derivatives

Min Xia,*[a] Yan-guang Wang[b]

[a] Department of Applied Chemistry, Zhejiang Institute of Science and Technology, Hangzhou 310033, P. R. China
Fax 0086(0571)88802212; E-mail: chchxm@21cn.com

[b] Department of Chemistry, Zhejiang University, Hangzhou, 310027, P. R. China

Received 19 August 2002; revised 30 October 2002

Abstract: Methyl 3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate derivatives **7** were effectively synthesized on the soluble polymer of polyethylene glycol (PEG) 4000 by heating or solvent-free microwave irradiation through the Biginelli three-component cyclocondensation. Compared with the classical solution-phase Biginelli reactions, the yields could be considerably improved and the reaction time could be shortened dramatically under microwave promotion in a liquid-phase protocol. Moreover, the polymer-supported synthesis provided the target compounds in high purity.

Key words: Biginelli reaction, condensation, polymers, cyclizations, heterocycles, liquid-phase synthesis, polyethylene glycol, microwave irradiation

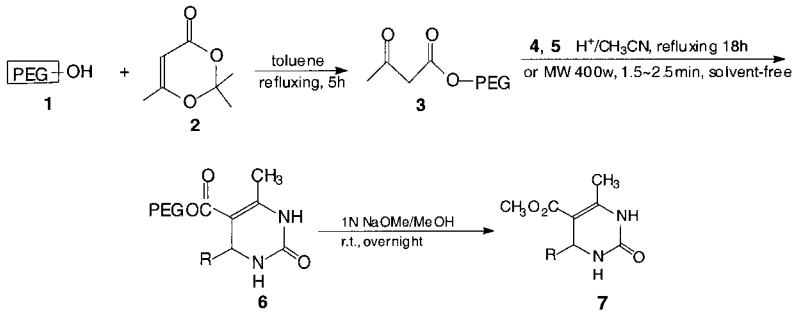
3,4-Dihydropyrimidin-2(1*H*)-one derivatives **7** (named as Biginelli compounds, DHPMs) represent a heterocyclic system of remarkable pharmacological efficacy.[1] Recently, appropriately functionalized DHPMs have emerged as potent calcium channel blockers,[2] antihypertensive agents,[3] α_{1a} adrenergic antagonists[4] and neuropeptide Y antagonists.[5] The most straightforward protocol to synthesize DHPMs **7** involves the one-pot and one-step condensation of a β-keto ester, an aldehyde and urea under strongly acidic conditions, termed as Biginelli cyclocondensation.[6] Unfortunately, one major drawback of this protocol lies in the fact that it often provides only low to moderate yields (20–50%) of the desired target products, in particular when substituted aromatic aldehydes are employed. Generally, in order to drive the reaction to completion, an excess of two of the three components has to be used for solution-phase synthesis. So far, problems with the workup, recrystallization or chromatography steps are inevitable, and the resultant loss of products cannot be neglected in some cases. Although the solid-phase strategy on insoluble polymers has appeared to solve the problem of separation and purification,[7] their drawbacks of long-step modification and linkage on resins, high cost, and complicated cleavage-and-analysis techniques hinder their further developments in combinatorial and parallel synthesis.

Recently, organic synthesis of small molecular compounds on soluble polymers, i.e. liquid-phase chemistry, has increasingly become the attractive field.[8] It couples the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without the cleavage-and-check procedure) with those of solid-phase chemistry (use of excessive reagents and easy isolation and purification of products). Moreover, owing to the homogeneity of liquid-phase reactions, the reaction conditions can be readily shifted from solution-phase systems without large changes, and the amount of the excessive reagents is less than that in solid-phase reactions. Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising. In connection with our work on the synthesis of small molecular compounds on soluble polymer,[9] we herein developed the Biginelli reaction on PEG 4000 (**1**) that offers the desired products i.e. 3,4-dihydropyrimidinone derivatives **7** in good to excellent yields and high purity after the direct cleavage from PEG, maintaining the simplicity of the one-pot procedure (Scheme1). To our knowledge, this is the first report of a liquid-phase synthesis of Biginelli compounds.

The PEG 4000 linked acetoacetate **3** was prepared by reacting of PEG 4000 (**1**) with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**2**) (i.e. diketene acetone adduct, TKD)[10] in anhydrous toluene under reflux for 5 hours. The conversion of the terminal hydroxyl groups on PEG 4000 was determined by ^{1}H NMR to be quantitative. The liquid-phase synthesis of DHPMs **7** was achieved as follows: the PEG 4000 linked acetoacetate **3**, urea **4** and corresponding aldehyde **5** were mixed in the ratio of 1:4:4 in MeCN with 2–3 drops of concd hydrochloric acid as the catalyst. The resulting mixture was refluxed for 18 hours and the solvent was removed. The residue was dissolved in a small volume of CH_2Cl_2 and Et_2O was poured with stirring to precipitate the solid, which was washed several times with Et_2O and EtOAc. The target compounds **7** were obtained by cleavage from the PEG support under the treatment of the polymer bound products **6** with NaOMe (1 N) in MeOH. Complete cleavage of the products was determined by the observation of the downfield shift of the α-methylene protons at the polymer attached site from δ = 4.4 to 3.6 in the ^{1}H NMR. If the peak of the α-methylene protons was still present after NMR checking, the recovered PEG bound products could be resubmitted to the same reaction conditions until a completed scission was reached. Normally, it was enough for complete cleavage in NaOMe (1 N)–MeOH overnight.

Synthesis 2003, No. 2, Print: 31 01 03.
Art Id.1437-210X,E;2003,0,02,0262,0266,ftx,en;F06502SS.pdf.

ISSN 0039-7881



Scheme 1

The results are indicated in Table 1. It can be seen from Table 1 that the yields were much improved over those in classical solution-phase Biginelli reactions, due to the ability to use excess of reagents to drive the reaction in liquid-phase strategy. Also, thanks to the adoption of polymer-supported synthesis, the complicated separation was simplified and the excessive reagents could be removed by ready washing and filtration before the deprotection step to provide the crude products in high purity (>91%, determined by HPLC).[26] More importantly, crude products of high purity obtained from the liquid-phase protocol were especially valuable since libraries were usually not purified before pharmaceutical screening. It was worthy to note that, in contrast to the various restrictions on the analysis of reaction developed in the solid-phase synthesis, the liquid-phase protocol allowed routine analytical instruments (UV, NMR, TLC, etc.) to monitor reaction progress without following the cleavage-and-check procedure.

Table 1 Liquid-Phase Synthesis of DHPM Derivatives on a PEG Support

Entry	ArCHO	Yield (%)		Purity (%)[c]
		A[a]	B[b]	
7a	PhCHO	91	42[21]	99.37
7b	*p*-HOC_6H_4CHO	82	67[22,d]	99.80
7c	*p*-$CH_3OC_6H_4CHO$	88	28[21]	99.17
7d	*o*-ClC_6H_4CHO	85	51[23,d]	91.85
7e	*m*-$O_2NC_6H_4CHO$	94	51[24,d]	99.52
7f	PhCH=CHCHO	89	–	98.12
7g	*o*-HOC_6H_4CHO	70	19[22,d]	95.27
7h	(2-Furyl)CHO	72	36[22,d]	91.60
7i	*p*-$NO_2C_6H_4CHO$	83	41[21]	93.47

[a] Method A: PEG supported liquid-phase reaction (concd aq HCl, reflux 18 h) with yield relating to product isolated and purified after cleavage from polymer.
[b] Method B: classical solution-phase reaction (concd aq HCl or concd H_2SO_4, reflux 18 h).
[c] Determined on HPLC analysis of crude products before purification.
[d] Yield referred to ethyl 3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate.

It appeared that there was no apparent electronic effect on the Biginelli reaction in that aryl aldehydes with electron-withdrawing or electron-donating groups offered good yields. In addition to aryl aldehydes, heterocyclic and α,β-unsaturated aldehydes were both effective substrates.

Another shortcoming of the classical Biginelli reactions was the long time (18–36 h) they took for completion. Although there have been some modifications to reduce the reaction time to within several hours using Lewis acids, such as $FeCl_3$,[11] $Yb(OTf)_3$,[12] $InCl_3$,[13] $LaCl_3$,[14] etc., these condition could not be transferred to the PEG supported reaction system, since the Lewis acids would become ineffective due to the strong coordination between Lewis acids and the oxygen atoms on the PEG chain. In recent years, the application of microwave (MW) irradiation in organic synthesis has been the focus of considerable attention and is becoming an increasingly popular technology.[15] The prominent features of the microwave approach are the rapid reaction rates, clean reaction conditions and ease of manipulation. 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. Recently, we have reported that PEG 4000 could be utilized as a polymeric support and solvent as well under microwave-assisted reaction.[16] Herein we described the microwave-induced Biginelli cyclocondensation on PEG 4000 support.

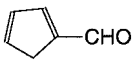
Stefani et al. has reported[17] that DHPMs **7** could be synthesized with methyl acetoacetate, urea and corresponding aldehyde under MW heating. However, due to the absence of acidic catalyst, this protocol could only offer low to moderate yields. It appeared that in order to obtain good yields, acidic catalyst was indispensable in spite of the MW promotion. Considering several protonic acids, such as HCl, H_2SO_4, CF_3CO_2H, CF_3SO_3H, etc., we chose the non-volatile, high boiling point and non-oxidant polyphosphoric acid (PPA) as the catalyst. Kappe et al. reported[18] that PPA was an effective catalyst in solution-phase Biginelli reactions because it favored the formation of an *N*-acyliminium ion intermediate, which was the key intermediate in the one-pot synthesis according to its

mechanism.[19] We put the PEG 4000 bound acetoacetate **3**, urea (**4**) and corresponding aldehyde **5** together and dispersed them completely. Then the reaction vessel was placed inside a large container filled with alumina, which acted as a heat sink. After cooling, a small volume of dichloromethane was added to the reaction mixture and the filtrate was poured into diethyl ether to precipitate the solid, which was washed several times with Et_2O and EtOAc. The target compounds **7** were obtained by cleavage from the PEG polymer in NaOMe (1 N)–MeOH solution. After a series of experiments, we found 400 W irradiation power was the most suitable energy for the MW assisted reaction on the PEG support and the time needed was varied according to the property of the corresponding aldehyde. During MW heating the PEG linked acetoacetate **3** was melted into a liquid, in which substrates were ensured to react with each other in homogeneity, especially in the cases that solid aldehydes were used. As we knew that PEG with low molecular weight has received attention as solvent in a wide range of reactions,[20] PEG 4000 in our case acted simultaneously as a polymeric support and as a solvent under MW irradiation, transporting energy and making the reaction system homogenous. The results are shown in Table 2. It indicates that the MW-induced protocol could achieve significantly improved yields over those under traditional Biginelli reaction conditions. At the same time, the reaction time was decreased from several hours to a few minutes.

Based on the MS data, we proposed a possible mechanism of fragmentation in Scheme 2.

In conclusion, we herein described a novel and efficient liquid-phase method of Biginelli multicomponent reaction on soluble polymer. All three reactions involved (linker attachment, cyclocondensation and resin cleavage) allowed the synthesis of DHPM derivatives in high purity and improved yields over those in classical solution-phase reaction, simplifying the procedure of isolation and purification. Furthermore, the MW-promoted protocol provided a rapid and solvent-free preparation of DHPMs in an environmentally benign and safe way. These versatile methods produce compounds with known pharmacophoric scaffolds and are thus suitable for the generation of a combinatorial library. Further applications of liquid-phase multicomponent synthesis of heterocycles will be reported in due course.

Table 2 PEG Supported Biginelli Reaction Under MW Irradiation[a]

Entry	ArCHO	Time (min)	Yield (%)[b]	Purity (%)[c]
7a	PhCHO	1.5	85	99.23
7b	*p*-$CH_3OC_6H_4CHO$	1.5	82	98.89
7c	*m*-$O_2NC_6H_4CHO$	2.0	85	98.57
7d	*o*-ClC_6H_4CHO	2.0	77	94.13
7e	PhCH=CHCHO	1.5	85	96.55
7f		2.5	71	90.46

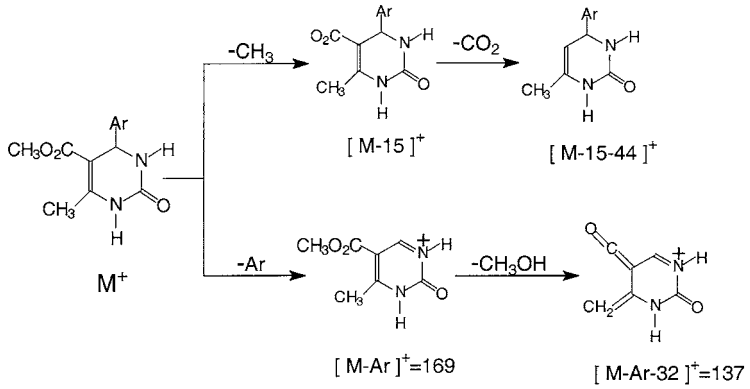
[a] PEG supported liquid-phase reaction without solvent.
[b] Yield referred to product isolated and purified after cleavage from PEG.
[c] Determined on HPLC analysis of crude products before purification.

Mps were determined on X_4 mp apparatus and the thermometer was uncorrected. ^{1}H NMR spectra were obtained on a Bruker Avance DMX 500MHz instrument. FT-IR spectra were recorded on Perkin–Elmer 298 spectrophotometer. MS data were recorded on HP5989B instrument. HPLC analysis was carried out on Agilent 1100 (250 × 4.6mm C_{18} Column, gradient elution 50% MeCN and 50% H_2O, 1 mL/min, UV detection at λ = 254 nm). MW experiments were performed on a Galaz WP800J-823 domestic microwave oven. All the chemicals were used without further purification.

PEG Bound Acetoacetate 3; General Procedure

Under a flow of nitrogen, PEG4000 (**1**) (4 g, 2 mmol terminal hydroxyl groups) and TKD (**2**) (5 mmol) were added to anhyd toluene (20 mL). The resulted mixture was refluxed under stirring for 5 h. After cooling, anhyd Et_2O (100 mL) was poured onto the mixture to precipitate the yellow solid, which was washed with Et_2O and EtOAc several times. After drying in vacuo, the solid was stored for the next step of the synthesis.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 3.49 (s, 2 H, $COCH_2CO$), 3.53–3.79 (m, PEG backbone, OCH_2CH_2O), 4.30 (t, 2 H, *J* = 5 Hz, PEG-OCH_2CH_2OCO).



Scheme 2

DHPMs 7; General Procedure

At r.t., PEG 4000 linked acetoacetate **3** (1 g, 0.5 mmol), urea (**4**) (2.0 mmol) and corresponding aldehyde **5** (2.0 mmol) were added to the MeCN (10 mL) containing 2–3 drops of concd aq HCl and the mixture was refluxed for 18 h. After cooling, the solvent was removed under reduced pressure and the residue was dissolved in a small volume of CH_2Cl_2 (3 mL), then Et_2O (20 mL) was added under stirring to precipitate the solid, which was washed with Et_2O (2 × 10 mL) and EtOAc (2 × 10 mL). After drying in vacuo, the solid was added to the NaOMe (1 N)–MeOH solution (15 mL) to cleave the products at r.t. overnight (checked by TLC). The target compounds **7** were obtained by extraction from the reaction mixture with EtOAc (2×10 mL), dilution with H_2O (30 mL) and then removal of the solvent. The samples were purified by recrystallization from EtOH.

DHPMs 7 by MW Irradiation; General Procedure

At r.t., PPA (2–3 drops) was added to the completely ground powders of PEG 4000 linked acetoacetate **3** (1 g, 0.5 mmol), urea (**4**) (1.0 mmol) and corresponding aldehyde **5** (1.0 mmol). The resulting mixture was added into an open vessel and stirred with a spatular for 30 s, and then the vessel was placed inside a large container filled with alumina at the center of the domestic microwave oven. After irradiated at 400 W for the necessary time, the mixture was cooled to r.t. and a small volume of CH_2Cl_2 (5 mL) was added into it. After filtration, Et_2O (20 mL) was poured under stirring to precipitate the solid, which was washed several times with Et_2O (2 × 10 mL) and EtOAc (2 × 10 mL). The cleavage step was performed according to the above procedure. The samples were purified by recrystallization from EtOH.

Methyl 6-Methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7a)

White, crystalline solid; mp 213–214 ºC (lit.[21] 209–212 ºC).

FT-IR (KBr): 3334,3222, 3105, 2950, 1699, 1667, 1639, 1433, 1342, 1238, 11092, 937, 793, 755, 698 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.25 (s, 3 H), 3.52 (s, 3 H), 5.13 (d, *J* = 3 Hz, 1 H), 7.22–7.25 (m, 3 H), 7.30–7.33 (m, 2 H), 7.76 (s, 1 H), 9.23 (s, 1 H).

MS: *m*/*z* (%) = 246 (M^+, 13.51), 231 (25.55), 214 (17.42), 187 (25.24), 169 (100.00), 137 (62.14), 77 (24.98), 42 (36.99).

Methyl 6-Methyl-4-(4-hydroxylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7b)

White, crystalline solid; mp 231–233 ºC.

FT-IR (KBr): 3588, 3371, 3270, 3119, 2955, 1702, 1681, 1639, 1431, 1318, 1230, 1088, 759, 658 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.23 (s, 3 H), 3.52 (s, 3 H), 5.03 (s, 1 H), 6.67 (d, *J* = 7.5 Hz, 2 H), 7.02 (d, *J* = 7.5 Hz, 2 H), 7.65 (s, 1 H), 9.15 (s, 1 H), 9.35 (s, 1 H).

MS: *m*/*z* (%) = 262 (M^+, 22.71), 247 (56.99), 230 (20.07), 203 (58.91), 169 (100.00), 137 (99.38), 110 (30.48), 65 (35.70), 42 (76.78).

Methyl 6-Methyl-4-(4-methyoxylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7c)

White, crystalline solid; mp 193–194 ºC (lit.[21] 192–194 ºC).

FT-IR (KBr): 3245, 3116, 2951, 1699, 1649, 1511, 1435, 1241, 196, 794 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.24 (s, 3 H), 3.52 (s, 3 H), 3.71 (s, 3 H), 5.08 (d, *J* = 2.5 Hz, 1 H), 6.86 (d, *J* = 8.5 Hz, 2 H), 7.15 (d, *J* = 8.5 Hz, 2 H), 7.70 (s, 1 H), 9.19 (s, 1 H).

MS: *m*/*z* (%) = 276 (M^+, 33.43), 261 (82.43), 244 (37.73), 217 (87.29), 169 (100.00), 137 (90.42), 110 (37.21), 77 (31.42), 42 (60.59).

Methyl 6-Methyl-4-(2-chlorophenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7d)

White, crystalline solid; mp 224–225 ºC.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.29 (s, 3 H), 3.45 (s, 3 H), 5.61 (s, 1 H), 7.31–7.39(m, 4 H), 7.71 (s, 1 H), 9.31 (s, 1 H).

FT-IR (KBr): 3227, 3098, 2955, 1699, 1645, 1427, 1221, 1087, 760 cm^{-1}.

MS: *m*/*z* (%) = 280 (M^+, 4.07), 265 (11.68), 245 (59.21), 221 (24.50), 169 (100.00), 137 (62.35), 102 (13.98), 75 (25.33), 42 (42.07).

Methyl 6-Methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7e)

Pale yellow, crystalline solid; mp 278–279 ºC.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.28 (s, 3 H), 3.54 (s, 3 H), 5.30 (d, *J* = 3 Hz, 1 H), 7.65–7.68 (m, 2 H), 7.93 (s, 1 H), 8.09 (s, 1 H), 8.13 (d, *J* = 8 Hz, 1 H), 9.41 (s, 1 H).

FT-IR (KBr): 3357, 3221, 3103, 2957, 1700, 1642, 1535, 1435, 1348, 1230, 1098, 824, 693 cm^{-1}.

MS: *m*/*z* (%) = 291 (M^+, 43.67), 276 (58.99), 232 (86.13), 186 (20.06), 169 (100.00), 137 (78.76), 110 (17.33), 76 (34.55), 42 (61.32).

Methyl 6-Methyl-4-styryl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7f)

Pale yellow, crystalline solid; mp 216 ºC (decomp.).

FT-IR (KBr): 3245, 3114, 2952, 1722, 1684, 1645, 1433, 1319,1248, 1099, 976, 777, 757, 693 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.19 (s, 3 H), 3.63 (s, 3 H), 4.72 (t, *J* = 4 Hz, 1 H), 6.19 (dd, *J* = 5.5, 6 Hz, 1 H), 6.34 (d, *J* = 16 Hz, 1 H), 7.23 (t, *J* = 7 Hz, 1 H), 7.31 (t, *J* = 8 Hz, 2 H), 7.39 (d, *J* = 7.5 Hz, 2 H), 7.56 (s, 1 H), 9.17 (s, 1 H).

MS: *m*/*z* (%) = 272 (M^+, 100.00), 257 (48.07), 240 (37.64), 213 (87.63), 195 (19.96), 169 (70.70), 137 (91.10), 128 (24.69), 110 (42.93), 103 (20.85), 91 (23.60), 77 (55.82), 51 (37.01), 42 (97.74).

Methyl 6-Methyl-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7g)

White, crystalline solid; mp 243–244 ºC.

FT-IR (KBr): 3415, 3224, 3110, 2952, 1749, 1682, 1644, 1604, 1459, 1229, 1090, 755 cm**–1**.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3 H), 3.47 (s, 3 H), 5.44 (s, 1 H), 6.71–7.18 (m, 4 H), 7.61 (s, 1 H), 9.14 (s, 1 H), 9.63 (s, 1 H).

MS: *m*/*z* (%) = 262 (M^+, 42.77), 247 (45.66), 230 (82.87), 203 (47.15), 185 (18.32), 169 (100.00), 137 (55.98), 110 (17.83), 65 (33.20), 59 (30.74), 42 (94.88).

Methyl 6-Methyl-4-(2-furyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7h)

Pale red, crystalline solid; mp 196–198 ºC.

FT-IR (KBr): 3316, 3118, 2954, 1708, 1673, 1638, 1433, 1341, 1239, 1088, 762 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 2.23 (s, 3 H), 3.56 (s, 3 H), 5.19 (d, *J* = 3 Hz, 1 H), 6.09 (d, *J* = 3 Hz, 1 H), 6.34 (m, 1 H), 7.55 (d, *J* = 1 Hz, 1 H), 7.78 (s, 1 H), 9.27 (s, 1 H).

MS: *m*/*z* (%) = 236 (M^+, 30.24), 219 (23.12), 208 (14.79), 193 (13.47), 182 (12.80), 177 (60.89), 137 (18.81), 124 (18.61), 110 (12.23), 94 (18.91), 77 (14.76), 66 (24.34), 59 (20.62), 52 (29.52), 42 (100.00)

Methyl 6-Methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (7i)
Pale yellow, crystalline solid; mp 250–251 ºC (lit.[25] 246–248 ºC).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.27 (s, 3 H), 3.54 (s, 3 H), 5.28 (s, 1 H), 7.50 (d, *J* = 7.5 Hz, 2 H), 7.93 (s, 1 H), 8.21(d, *J* = 7.5 Hz, 2 H), 9.40 (s,1 H).

FT-IR (KBr): 3367, 3223, 3115, 2950, 2834, 1717, 1688, 1636, 1517, 1434, 1354, 1228, 1095, 803 cm^{-1}.

MS: *m*/*z* (%) = 291 (M^+, 8.08), 276 (25.66), 232 (13.34), 186 (15.95), 169 (100.00), 137 (76.74), 110 (11.34), 76 (12.96), 50 (13.00), 42 (48.89).

References

(1) (a) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937. (b) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043. (c) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879. (d) Lu, J.; Yang, B. Q.; Bai, Y. J. *Chin. J. Org. Chem.* **2001**, *21*, 640.
(2) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, D. J.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.
(3) Grover, G. J.; Dzwomczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289.
(4) Silder, D. R.; Larsen, R. D.; Chartrain, M.; Ikemote, N.; Roberge, C. M.; Taylor, C. S.; Li, W.; Bills, G. F. PCT Int. WO 99 07695, **1999**.
(5) Bruce, M. A.; Pointdexter, G. S.; Johnson, G. PCT Int. Appl. WO 98 33791, **1998**.
(6) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(7) (a) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819. (b) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917. (c) Kappe, C. O. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 49.
(8) (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (b) Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (c) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.
(9) Shang, Y. J.; Wang, Y. G. *Tetrahedron Lett.* **2002**, *43*, 2247.
(10) Birney, D. M.; Xu, X. L.; Ham, S. *J. Org. Chem.* **1997**, *62*, 7114.
(11) Lu, J.; Ma, H. *Synlett* **2000**, 63.
(12) Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
(13) Ranu, B. C.; Hajra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270.
(14) Lu, J.; Bai, Y. J.; Wang, Z. J.; Yang, B. Q.; Ma, H. R. *Tetrahedron Lett.* **2000**, *41*, 9075.
(15) (a) Varma, R. S. *Green Chem.* **1999**, 43. (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213.
(16) Xia, M.; Wang, Y. G. *J. Chem. Res.* **2002**, 173.
(17) Stefani, H. A.; Gatti, D. M. *Synth. Commun.* **2000**, *30*, 2165.
(18) Kappe, C. O.; Falsone, S. F. *Synlett* **1998**, 718.
(19) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201.
(20) (a) Totten, G. E.; Clinton, N. A. *J. M. S. Rev. Macromol. Chem. Phys.* **1988**, *C28*, 293. (b) Totten, G. E.; Clinton, N. A. *J. M. S. Rev. Macromol. Chem. Phys.* **1998**, *C38*, 77.
(21) Hu, E. H.; Sidler, D.; Dolling, U. H. *J. Org. Chem.* **1998**, *63*, 3454.
(22) Folkers, K.; Johnson, T. B. *J. Am. Chem. Soc.* **1933**, *55*, 2886.
(23) McKinstry, D. W.; Reading, E. H. *J. Franklin Inst.* **1944**, *237*, 203.
(24) Folkers, K.; Harwood, H. J.; Johnson, T. B. *J. Am. Chem. Soc.* **1932**, *54*, 3751.
(25) Kappe, C. O.; Kumar, D.; Varma, R. S. *Synthesis* **1999**, 1799.
(26) The purity was determined by HPLC analysis on Agilent 1100 (250 × 4.6 mm C_{18} Column, gradient elution 50% MeCN and 50% H_2O, 1 mL/min, UV detection at λ = 254 nm).