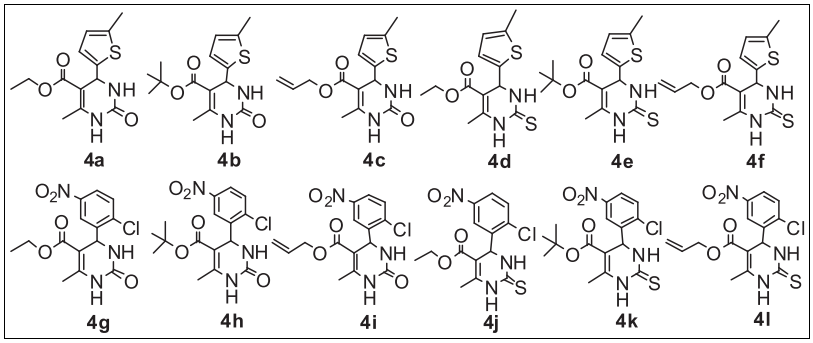
Magnesium Bromide and Magnesium Chloride Hexahydrate Catalyzed One-Pot Synthesis of Dihydropyrimidines *via* Biginelli Reaction under Solvent-Free Conditions

Şirin Gülten*

Department of Chemistry, Faculty of Arts and Sciences, Çanakkale Onsekiz Mart University, Çanakkale 17020, Turkey
*E-mail: siringulten@hotmail.com

Received March 3, 2011
DOI 10.1002/jhet.980
Published online 4 April 2013 in Wiley Online Library (wileyonlinelibrary.com).



Biologically important 12 new important 3,4-dihydropyrimidin-2-(1*H*)-ones (-thiones) were synthesized with in one-pot three-component Biginelli reaction from the corresponding aromatic aldehydes (5-methyl-2-thiophenecarboxaldehyde and 2-chloro-5-nitrobenzaldehyde), β-keto esters (ethylacetoacetate, allylacetoacetate, and *t*-butylacetoacetate), and urea/thiourea in the presence of catalytic amount of magnesium bromide and magnesium chloride hexahydrate as nontoxic, inexpensive, and easily available catalysts under solvent-free conditions at 80 and 100°C. Compared with the catalyst-free three-component Biginelli reaction conditions, this method consistently has the advantage of short reaction time (45–100 min) and good to excellent yields (75–91%).

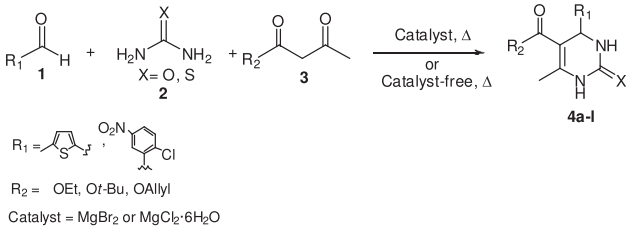
J. Heterocyclic Chem., **50**, 391 (2013).

INTRODUCTION

In recent years, 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) and thiones have attracted significant attention because of their wide range of biological activities such as antihypertensives (calcium channel modulators), neuropeptide Y antagonists, antifungal, antibacterial, antiviral, anticancer leads (mitotic kinesin Eg5 motor protein inhibitors and blood platelet aggregation inhibitors), antioxidative, anti-inflammatory, antistaphylococcal antibiotics, and their treating benign prostatic hyperplasia (α-1a-adrenergic receptor antagonists) [1–28]. In addition, several isolated marine alkaloids containing the 3,4-dihydropyrimidinone-5-carboxylate skeleton display interesting biological properties [29, 30]. Among them, the most notable are the batzelladine alkaloids A and B which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells which are potential compounds in AIDS therapy [31–33]. Structurally simple DHPM derivative Monastrol has emerged as a mitotic kinesin Eg 5 motor protein inhibitor for the development of anticancer drugs [34, 35]. Therefore, the synthesis of DHPM core scaffold is of much current importance.

Classical Biginelli reaction suffers from the harsh reaction conditions, lengthy reaction time and relatively low reaction yields of products because of the side reaction, in particular, when substituted aromatic aldehydes or thioureas are used. Recently, many improved synthetic procedures using different types of catalysts and conditions were reported for the synthesis of DHPMs either by the modification of classical Biginelli condensation or by the development of novel but more complex multistage strategies [36–63]. However, despite their potential utility, some of these procedures require expensive reagents, strong acidic conditions, prolonged reaction time, high temperature, stoichiometric amounts of catalyst, toxic reagents, large amount of solvents, unsatisfactory yields, and inconvenient purification techniques. Therefore, the discovery of a novel and inexpensive catalyst, which can be easily separated and environmentally benign procedure for the preparation of DHPMs under mild conditions is of main importance. Recently, magnesium bromide and magnesium chloride have had considerable attention as a powerful reaction medium for effecting various transformations [54–64]. Herein, we report an efficient, economic, and practical route for the one-pot synthesis of DHPMs by Biginelli cyclocondensation reaction using either magnesium bromide or magnesium chloride hexahydrate as mild catalysts under solvent-free conditions (Scheme 1).

Scheme 1. General procedure for the synthesis of DHPMs.

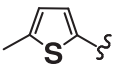
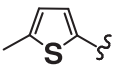
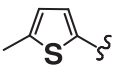
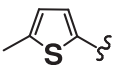
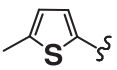
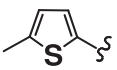
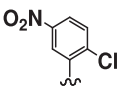
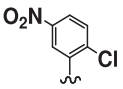
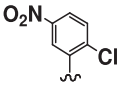
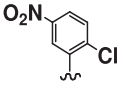
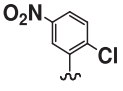
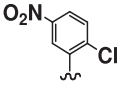


RESULTS AND DISCUSSION

We studied the Biginelli condensation using anhydrous and hydrous salts as catalysts under solvent-free conditions. Inexpensive and easily available $MgBr_2$ and $MgCl_2{\cdot}6H_2O$ as catalysts were selected to the three-component Biginelli condensation under solvent-free conditions. Twelve **4a-l** variously substituted DHPMs were synthesized, and the results obtained exhibited in Table 1.

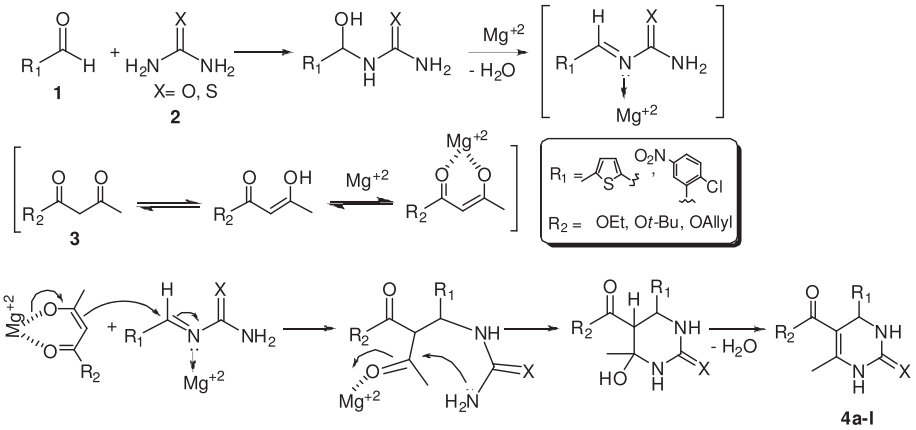
Table 1

Magnesium bromide and magnesium chloride hexahydrate catalyzed one-pot synthesis of DHPMs under solvent-free conditions versus catalyst-free conditions.

Entries	R_1	R_2	X	Product	Time (min)	Yield (%)	Mp (found) (°C)/(lit.) (°C)
1		OEt	O	**4a**	45[a] 90[b], 200[c]	88[a], 85[b], 55[c]	232–234/–
2		O*t*-Bu	O	**4b**	90[a], 100[b], 210[c]	78[a], 75[b], 44[c]	226–227/–
3		OAllyl	O	**4c**	45[a], 100[b], 210[c]	85[a], 82[b], 50[c]	206–208/–
4		OEt	S	**4d**	95[a], 90[b], 210[c]	91[a], 89[b], 52[c]	209–210/–
5		O*t*-Bu	S	**4e**	60[a], 90[b], 220[c]	77[a], 75[b], 43[c]	191–193/–
6		OAllyl	S	**4f**	45[a], 100[b], 220[c]	81[a], 80[b], 49[c]	193–195/–
7		OEt	O	**4g**	60[a], 90[b], 130[c]	91[a], 88[b], 58[c]	254–256/–
8		O*t*-Bu	O	**4h**	45[a], 60[b], 130[c]	86[a], 83[b], 45[c]	238–239/–
9		OAllyl	O	**4i**	60[a], 90[b], 130[c]	86[a], 82[b], 47[c]	215–217/–
10		OEt	S	**4j**	80[a], 90[b], 160[c]	90[a], 85[b], 55[c]	193–195/–
11		O*t*-Bu	S	**4k**	60[a], 90[b], 140[c]	85[a], 81[b], 44[c]	208–210/–
12		OAllyl	S	**4l**	90[a], 120[b], 150[c]	84[a], 80[b], 46[c]	158–160/–

The Biginelli reaction conditions:
[a]Method I: $MgBr_2$ (0.2 mmol), solvent-free, 100°C.
[b]Method II: $MgCl_2{\cdot}6H_2O$ (0.4 mmol), solvent-free, 80°C.
[c]Method III: catalyst-free, EtOH (2 mL), 100°C.

Scheme 2. The plausible mechanism for $MgBr_2$ and $MgCl_2{\cdot}6H_2O$ catalyzed Biginelli reaction.



For comparison purposes, DHPMs were prepared using three different procedures (Scheme 1). Our initial attempts focused on the catalyzed Biginelli reaction which involves condensation of β-keto ester, aldehyde and urea/thiourea under solvent-free conditions. In the case of $MgBr_2$ as a catalyst, we found that its isolated yield was higher than when $MgCl_2{\cdot}6H_2O$ was used as a catalyst. Magnesium chloride hexahydrate was very much moisture sensitive. Therefore, we determined that $MgBr_2$ as the best catalyst for the Biginelli reaction. In the course of our work, we utilized the same synthetic procedure of Salehi [61–63] and Zhang [64]. All the synthesized DHPMs were new and not reported elsewhere.

In the final experimental procedure, a mixture of β-keto ester, aldehyde and urea/thiourea was heated at 100°C in a little amount of EtOH without catalyst [65]. For all the cases, the catalyzed methods (methods I and II) produced significantly shorter reaction time (45–120 min) and better reaction yields (75–91%) than the catalyst-free Biginelli reaction [65]. This indicates the special advantage of the solventless and catalyzed Biginelli reaction.

The results indicated that steric hindrance and the long chain of the R_2 (O*t*-Bu and OAllyl) on the 1,3-dicarbonyl compound reduced the reaction yield (Table 1).

The plausible mechanism is given in Scheme 2. In this mechanism, the first step of the reaction between aldehyde **1** and urea/thiourea **2** includes the formation of the acyl imine intermediate like the Schiff's base (a conjugated imino-ketone as a Michael acceptor) which is stabilized by the magnesium ion followed by β-carbonyl carbon of the β-carbonyl enolate attack on the imine carbon produces an open-chain ureide which subsequently cyclizes to six-member heterocyclic compound. Dehydration leads to the DHPMs **4**.

EXPERIMENTAL

The melting points were measured on an Electrothermal 9100 melting point apparatus and are uncorrected. The IR spectra were recorded on a One FTIR ATR PerkinElmer spectrometer. The ^{1}H- and ^{13}C-NMR spectra were taken with a Bruker 400 Ultra Shield spectrometer and chemical shifts were recorded as ppm downfield from internal tetramethylsilane. The mass spectra were taken on a Waters ZQ Micromass LC/MS spectrometer. Elemental analyses were performed on a Leco 932 CHNS instrument. Reaction progress was monitored by TLC on precoated aluminum-backed plates (Merck SIL G/UV_{254}) and chromophoric compounds were visualized by UV light and subsequent staining with alkaline potassium permanganate solution or iodine.

General procedure for the one-pot synthesis of 3, 4-dihydropyrimidinones under solvent-free conditions. ***Method I (catalyst: $MgBr_2$).*** The mixture of aldehyde (2 mmol), β-keto ester (2 mmol), urea/thiourea (3 mmol), and $MgBr_2$ (0.2 mmol, 10% mol) was heated at 100°C with stirring until the mixture turned to solid mass. After the completion of the reaction (monitored by TLC), the solid was cooled to room temperature and poured onto crushed ice (20 g) and stirred for 10 min. The crude product was filtered, washed with cold water (2 × 10 mL), and then recrystallized from either ethanol or ethyl acetate/hexane to afford pure products.

Method II (catalyst: $MgCl_2{\cdot}6H_2O$). The mixture of aldehyde (2 mmol), β-keto ester (2 mmol), urea/thiourea (3 mmol), and $MgCl_2{\cdot}6H_2O$ (0.4 mmol, 20% mol) was heated at 80°C with stirring until the mixture turned to solid mass. After the completion of the reaction (monitored by TLC), the solid was cooled to room temperature and poured onto crushed ice (20 g) and stirred for 10 min. The crude product was filtered, washed with cold water (2 × 10 mL), and then recrystallized from either ethanol or ethyl acetate/hexane to afford pure products.

Method III (without catalyst). The solution of aldehyde (2 mmol), β-keto ester (2 mmol), and urea/thiourea (3 mmol) in EtOH (2 mL) was heated at 100°C with stirring. After the reaction completion (monitored by TLC), the resulting mixture was then poured onto crushed ice (20 g), and solid product separated was filtered and recrystallization from ethanol provides the pure products.

5-Ethoxycarbonyl-6-methyl-4-(5-methylthiophen-2-yl)-3,4-dihydropyrimidin-2(1H)-one (4a). White crystals. R_f = 0.23 (50% ethyl acetate/hexane). IR (ATR, neat): 3233, 3110, 2971, 1723, 1702, 1650 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.27 (s, 1H, NH), 7.83 (s, 1H, NH), 6.65 (d, 1H, J = 3.4 Hz, H_{ar}), 6.60 (m, 1H, H_{ar}), 5.31 (d, 1H, J = 3.5 Hz, CH), 4.07 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 2.36 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 1.18 (t, 3H, J = 7.1 Hz, OCH_2CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 165.5, 152.72, 148.95, 146.67, 138.41, 125.10, 123.69, 100.24, 59.79, 49.91, 18.12, 15.42, 14.64. MS (ES+): *m/z* (%) = 344.41

(M^+ + Na + CH_3CN, 71), 332.38 (M^+ + 1 + CH_3CN, 73), 281.37 (M^+ + 1, 100). Anal. Calcd. for ($C_{13}H_{16}N_2O_3S$): C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.73; H, 5.65; N, 10.08; S, 11.42.

5-tert-Butoxycarbonyl-6-methyl-4-(5-methylthiophen-2-yl)-3,4-dihydropyrimidin-2(1H)-one (4b) Pale yellow crystals. R_f = 0.25 (50% ethyl acetate/hexane). IR (ATR, neat): 3233, 3110, 2976, 1718, 1699, 1645 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.15 (s, 1H, NH), 7.76 (s, 1H, NH), 6.64–6.61 (m, 2H, H_{ar}), 5.25 (d, 1H, J = 3.2 Hz, CH), 2.37 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 1.39 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR (100 MHz, DMSO-d_6): 165.0, 152.8, 148, 146.82, 138.3, 125.0, 123.5, 101.6, 79.8, 50.13, 28.4, 18.1, 15.4. MS (ES+): m/z (%) = 372.51 (M^+ + Na + CH_3CN, 93), 350.42 (M^+ + 1 + CH_3CN, 83), 309.46 (M^+ + 1, 100). Anal. Calcd. for ($C_{15}H_{20}N_2O_3S$): C, 58.42; H, 6.54; N, 9.08; S, 10.40. Found: C, 58.68; H, 6.18; N, 9.20; S, 10.46.

5-Allyloxycarbonyl-6-methyl-4-(5-methylthiophen-2-yl)-3,4-dihydropyrimidin-2(1H)-one (4c). White solid. R_f = 0.28 (50% ethyl acetate/hexane). IR (ATR, neat): 3413, 3245, 3114, 2946, 1723, 1708, 1654 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.34 (s, 1H, NH), 7.85 (s, 1H, NH), 6.65 (d, 1H, J = 3.3 Hz, H_{ar}), 6.61–6.60 (m, 1H, H_{ar}), 5.86–5.94 (m, 1H, CH_2═C*H*), 5.34 (d, 1H, J = 3.4 Hz, CH_2═CH), 5.24 (m, 1H, CH_2═CH), 5.16 (s, 1H, CH), 4.55 (d, 2H, J = 5.2 Hz, CH_2O), 2.36 (s, 3H, CH_3), 2.23 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 165.1, 152.6, 149.6, 146.6, 138.5, 133.5, 125.2, 123.8, 117.6, 99.9, 64.3, 49.8, 18.21, 15.4. MS (ES+): m/z (%) = 356.33 (M^+ + Na + CH_3CN, 47), 334.38 (M^+ + 1 + CH_3CN, 75), 293.45 (M^+ + 1, 100). Anal. Calcd. for ($C_{14}H_{16}N_2O_3S$): C, 57.52; H, 5.52; N, 9.58; S, 10.97. Found: C, 57.33; H, 5.32; N, 9.45; S, 10.74.

5-Ethoxycarbonyl-6-methyl-4-(5-methylthiophen-2-yl)-3,4-dihydropyrimidin-2(1H)-thione (4d). Pale yellow crystals. R_f = 0.72 (50% ethyl acetate/hexane). IR (ATR, neat): 3318, 3168, 3102, 1698, 1667, 1646, 1574 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.44 (s, 1H, NH), 9.72 (s, 1H, NH), 6.66 (d, 1H, J = 3.4 Hz, H_{ar}), 6.63 (m, 1H, H_{ar}), 5.32 (d, 1H, J = 3.3 Hz, CH), 4.08 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 1.17 (t, 3H, J = 7.1 Hz, OCH_2CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 175.04, 165.29 145.66, 144.90, 139.23, 125.30, 124.42, 101.64, 60.18, 49.88, 17.50, 15.43, 14.56. MS (ES+): m/z (%) = 297.40 (M^+ + 1, 100). Anal. Calcd. for ($C_{13}H_{16}N_2O_2S_2$·0.15H_2O): C, 52.20; H, 5.49; N, 9.36; S, 21.43. Found: C, 51.93; H, 5.60; N, 9.43; S, 21.22.

5-tert-Butoxycarbonyl-6-methyl-4-(5-methylthiophen-2-yl)-3,4-dihydropyrimidin-2(1H)-thione (4e). Pale yellow crystals. R_f = 0.76 (50% ethyl acetate/hexane), IR (ATR, neat): 3154, 3120, 2979, 1702, 1678, 1650, 1587 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.33 (s, 1H, NH), 9.64 (s, 1H, NH), 6.65 (m, 2H, H_{ar}), 5.26 (d, 1H, J = 3.3 Hz, CH), 2.38 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.39 (s, 9H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 175.05, 164.67 145.03, 144.84, 139.11, 125.20, 124.23, 102.97, 80.46, 50.10, 28.32, 17.48, 15.45. MS (ES+): m/z (%) = 325.41 (M^+ + 1, 100).

5-Allyloxycarbonyl-6-methyl-4-(5-methylthiophen-2-yl)-3,4-dihydropyrimidin-2(1H)-thione (4f). Pale yellow crystals. R_f = 0.69 (50% ethyl acetate/hexane). IR (ATR, neat): 3315, 3173, 3106, 2998, 1738, 1723, 1578, 1663 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.48 (br s, 1H, NH), 9.74 (br s, 1H, NH), 6.67 (d, 1H, J = 3.5 Hz, H_{ar}), 6.64 (m, 1H, H_{ar}), 5.90 (m, 1H, CH_2═C*H*), 5.35 (s, 1H, CH), 5.20 (m, 2H, CH_2═CH), 4.58 (d, 2H, J = 5.2 Hz, OCH_2), 2.37 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 174.96, 164.90 146.25, 144.85, 139.30, 133.24, 125.37, 124.53, 117.78, 101.25, 64.62, 49.80, 17.59, 15.44. MS (ES+): m/z (%) = 309.36 (M^+ + 1, 100). Anal. Calcd. for ($C_{14}H_{16}N_2O_2S_2$·0.38H_2O): C, 53.34; H, 5.36; N, 8.88; S, 20.34. Found: C, 53.41; H, 5.07; N, 8.68; S, 19.95.

4-(2-Chloro-5-nitrophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4g). White solid. R_f = 0.31 (50% ethyl acetate/hexane). IR (ATR, neat): 3339, 3228, 3113, 2976, 1701, 1642, 1575, 1524 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.45 (br s, 1H, NH), 8.14 (dd, 1H, J = 6.9, 1.8 Hz, H_{ar}), 8.07 (d, 1H, J = 1.7 Hz, H_{ar}), 7.90 (br s, 1H, NH), 7.76 (d, 1H, J = 8.7 Hz, H_{ar}), 5.72 (s, 1H, CH), 3.89 (q, 2H, J = 6.9 Hz, OCH_2CH_3), 2.33 (s, 3H, CH_3), 1.02 (t, 3H, J = 7.2 Hz, OCH_2CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 164.65, 150.89, 150.10, 146.70, 143.57, 138.60, 131.11, 123.82, 123.64, 96.86, 59.25, 52.06, 17.72, 13.82. MS (ES+): m/z (%) = 381.52 (M^+ + 1 + CH_3CN, 64), 340.39 (M^+ + 1, 87).

5-tert-Butoxycarbonyl-4-(2-chloro-5-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4h). White solid. R_f = 0.24 (50% ethyl acetate/hexane). IR (ATR, neat): 3368, 3227, 3097, 2968, 1710, 1648, 1574, 1520 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.38 (br s, 1H, NH), 8.22 (dd, 1H, J = 6.1, 2.7 Hz, H_{ar}), 8.09 (d, 1H, J = 2.7 Hz, H_{ar}), 7.96 (br s, 1H, NH), 7.84 (d, 1H, J = 8.9 Hz, H_{ar}), 5.71 (d, 1H, J = 2.3 Hz, CH), 2.36 (s, 3H, CH_3), 1.25 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR (100 MHz, DMSO-d_6): 164.08, 151.43 149.93, 147.07, 143.73, 139.36, 131.74, 124.33, 123.92, 98.23, 79.99, 28.22, 18.13, 14.32. MS (ES+): m/z (%) = 390.54 (M^+ + Na, 100), 368.54 (M^+ + 1, 10).

5-Allyloxycarbonyl-4-(2-chloro-5-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4i). White solid. R_f = 0.21 (50% ethyl acetate/hexane). IR (ATR, neat): 3226, 3099, 2958, 1706, 1651, 1575, 1527 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 9.66 (br s, 1H, NH), 8.19 (dd, 1H, J = 5.9, 2.7 Hz, H_{ar}), 8.12 (d, 1H, J = 2.7 Hz, H_{ar}), 7.98 (br s, 1H, NH), 7.79 (1H, d, J = 8.7 Hz, H_{ar}), 5.80–5.76 (m, 2H, CH_2═C*H* and C*H*NH), 5.12–5.08 (m, 2H, CH_2═CH), 4.48–4.47 (m, 2H, OCH_2), 2.24 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 164.79, 151.38, 151.14, 147.19, 143.84, 139.17, 133.18, 131.16, 124.36, 124.08, 117.59, 97.05, 64.35, 52.52, 18.34. MS (ES+): m/z (%) = 393.57 (M^+ + 1 + CH_3CN, 100), 352.34 (M^+ + 1, 77).

4-(2-Chloro-5-nitrophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4j). Pale yellow solid. R_f = 0.72 (50% ethyl acetate/hexane). IR (ATR, neat): 3320, 3188, 3107, 2985, 1713, 1682, 1651, 1558, 1522 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.54 (br s, 1H, NH), 9.74 (br s, 1H, NH), 8.17 (dd, 1H, J= 6.0, 2.7 Hz, H_{ar}), 8.06 (d, 1H, J = 2.7 Hz, H_{ar}), 7.76 (d, 1H, J = 8.8 Hz, H_{ar}), 5.74 (d, 1H, J = 2.8 Hz, CH), 3.93 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 2.35 (s, 3H, CH_3), 1.01 (t, 3H, J = 7.1 Hz, OCH_2CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 174.48, 164.96, 147.14, 146.77, 142.81, 139.31, 131.76, 124.70, 99.21, 60.12, 52.69, 17.56, 14.27. MS (ES+): m/z (%) = 358.42 (M^+ + 2, 37), 356.43 (M^+ + 1, 100).

5-tert-Butoxycarbonyl-4-(2-chloro-5-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4k). Pale yellow solid. R_f = 0.76 (50% ethyl acetate/hexane). IR (ATR, neat): 3330, 3170, 3105, 2950, 1711, 1653, 1585, 1520 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.44 (br s, 1H, NH), 9.64 (br s, 1H, NH), 8.20 (dd, 1H, J = 6.0, 2.7 Hz, H_{ar}), 8.03 (d, 1H, J = 2.7 Hz, H_{ar}), 7.80 (d, 1H, J = 8.8 Hz, H_{ar}), 5.67 (d, 1H, J = 2.46 Hz, CH), 2.23 (s, 3H, CH_3), 1.21 (s, 9H, $(CH_3)_3C$). ^{13}C-NMR (100 MHz, DMSO-d_6): 173.94, 163.87, 146.48 145.66, 141.87, 139.06, 131.43, 124.15, 99.62, 80.13, 52.58, 30.66, 27.67, 17.00. MS (ES +): m/z (%) = 386.61 (M^+ + 3, 37), 384.57 (M^+ + 1, 100).

5-Allyloxycarbonyl-4-(2-chloro-5-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4l). Pale yellow solid. R_f = 0.72

(50% ethyl acetate/hexane). IR (ATR, neat): 3377, 3308, 3267, 3176, 3004, 1712, 1645, 1609, 1523 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): 10.58 (br s, 1H, NH), 9.75 (br s, 1H, NH), 8.17 (dd, 1H, J = 6.1, 2.7 Hz, H_{ar}), 8.05 (d, 1H, J = 2.7 Hz, H_{ar}), 7.77 (d, 1H, J = 8.8 Hz, H_{ar}), 5.70–5.79 (m, 2H, CH_2═C*H* and C*H*NH), 5.08–5.00 (m, 2H, CH_2═CH), 4.43–4.48 (m, 2H, OCH_2), 2.33 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO-d_6): 184.33, 174.51, 164.62, 147.22, 147.13, 142.60, 139.35, 132.97, 131.83, 124.73, 117.90, 98.91, 64.68, 52.67, 17.68. MS (ES+): m/z (%) = 368.38 (M^+ + 1, 100).

Acknowledgments. The author thanks to Çanakkale Onsekiz Mart University (BAP 2008/28) for financial support. The author also thanks to NMR Analysis Laboratory of Hacettepe University for recording NMR spectra and Central Laboratory of Pharmacy, Ankara University, for the measurement of the mass spectra and elemental microanalyses.

REFERENCES AND NOTES

[1] Baldwin, J. J.; Pitzenberger, S. M.; McClure, D. E. U.S. Patent 4675321,1988.

[2] Kastron, V.V.; Vitrolin, R. O.; Khanina, E. L.; Dubur, G. Y.; Kimenis, A. A.; Kondratenko, N. V.; Popov, V. I.; Yagupolsky, L. M.; Kolomeitsev, A. A. U.S. Patent4738965,1988.

[3] Atwal, K. S.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. F. J Med Chem 1990, 33, 1510.

[4] Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. J Med Chem 1990, 33, 2629.

[5] Ertan, M.; Balkan, A.; Saraç, S.; Uma, S.; Renaud. J. F.; Rollad, Y. Arch Pharm 1991, 324, 135.

[6] Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. J Med Chem 1991, 34, 806.

[7] Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. J Med Chem 1992, 35, 3254.

[8] Kappe, C. O. Tetrahedron 1993, 49, 6937.

[9] Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; Dimarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; Mcarthy, J. P.; Zhang, R.; Moreland, S. J. J Med Chem 1995, 38, 119.

[10] Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normandin, D. E.; Parham, C. S.; Sleph, P. G.; Moreland, S. J Cardiovasc Pharmacol 1995, 26, 289.

[11] Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. Tetrahedron 1997, 53, 2803.

[12] Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. Science 1999, 286, 971.

[13] Barrow, J. C.; Nantermet, P. G.; Nagarathnam, D.; Forray, C. J Med Chem 2000, 43, 2703.

[14] Kappe, C. O. Acc Chem Res 2000, 33, 879.

[15] Kappe, C. O. Eur. J Med Chem 2000, 35, 1043.

[16] Kappe, C. O.; Shishkin, O. V.; Uray, G.; Verdino, P. Tetrahedron 2000, 56, 1859.

[17] Brands, M.; Endermann, R.; Gahlmann, R.; Krüger, J.; Raddatz, S. Bioorg Med Chem Lett 2003, 13, 241.

[18] Horton, D. A.; Bourne, G. T.; Smythe, M. L. Chem Rev 2003, 103, 893.

[19] Kappe, C. O. QSAR Comb Sci 2003, 22, 630.

[20] Yarim, M.; Saraç, S.; Kilic, F. S.; Erol, K.II Farmaco 2003, 58, 17.

[21] Bahekar, S. S.; Shinde, D. B. Bioorg. Med Chem Lett 2004, 14, 1733.

[22] Kappe, C. O. The Biginelli reaction. Multicomponent reactions. Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH, Weinheim, 2005; p95.

[23] Zorkun, I. S.; Saraç, S.; Çelebi, S.; Erol, K. Bioorg Med Chem 2006, 14, 8582.

[24] Sujatha, K.; Shanmugam, P.; Perumal, P. T.; Muralidharan, D.; Rajendran, M. Bioorg Med Chem Lett 2006, 16, 4893.

[25] Ashok, M.; Holla, B. S.; Kumari, N. S. Eur J Med Chem 2007, 42, 380.

[26] Saraç, S.; Çiftçi, M.; Zorkun, I. S.; Tunç, O.; Erol, K. Arzneim-Forsch/Drug Res 2007, 57, 137.

[27] Singh, K.; Arora, D.; Falkowski, D.; Liu, Q.; Moreland, R. Eur J Org Chem 2009, 19, 3258.

[28] Kolosov, M. A.; Orlov, V. D.; Beloborodov, D. A; Dotsenko, V. V. Mol Divers 2009, 13, 5.

[29] Snider, B. B.; Shi, Z. J Org Chem 1993, 58, 3828.

[30] Heys, L.; Moore, C. G.; Murphy, P. J Chem Soc Rev 2000, 29, 57.

[31] Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K.; Westley, J. W.; Potts, B. C. M. J Org Chem 1995, 60, 1182.

[32] Rama Rao, A. V.; Gurjar, M. K.; Vasudevan, J. J Chem Soc Chem Commun 1995,1369.

[33] Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. Tetrahedron Lett 1996, 37, 6977.

[34] Kapoor, T. M.; Mayer, T. M.; Coughlin, M. L.; Mitchison, T. J. J Cell Biol 2000, 150, 975.

[35] Haggarty, S. J.; Mayer, T. M.; Miyamoto, D. T.; Fathi, R.; King, R. W.; Mitchison, T. J.; Schreiber, S. L. Chem Biol 2000, 7, 275.

[36] Lu, J.; Bai, Y. Synthesis 2002,466.

[37] Wang, Z. T.; Xu, L. W.; Xia, C. G.; Wang, H. Q. Tetrahedron Lett 2004, 45, 7951.

[38] Bahekar, S. S.; Kotharkar, S. A.; Shinde, D. B. Mendeleev Commun 2004, 14, 210.

[39] Bose, D. S.; Sudharshan, M.; Chavhan, S. W. ARKIVOC 2005,(iii),228.

[40] Heravi, M. M.; Derikvand, F.; Bamoharram, F. F. J Mol Catal A: Chem 2005, 242, 173.

[41] Cepanec, I.; Litvić, M.; Bartolinčić, A.; Lovrić, M. Tetrahedron Lett 2005, 61, 4275.

[42] Ostras, K. S.; Gorobets, N. K.; Desenko, S. M.; Musatov, V. I. Mol Divers 2006, 10, 483.

[43] Fazaeli, R.; Tangestaninejad, S.; Aliyan, H.; Moghadam, M. Appl Catal A: Gen 2006, 309, 44.

[44] Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadizadeh, M. R. Appl Catal A: Gen 2006, 300, 85.

[45] Ahmed, N.; van Lier, J. E. Tetrahedron Lett 2007, 48, 5407.

[46] Shaabani, A.; Maleki, A. Chem Pap 2007, 61, 333.

[47] Adibi, H.; Samimi, H. A.; Beygzadeh, M. Catal Commun 2007, 8, 2119.

[48] Rodríguez-Domínquez, J. C.; Bernardi, D.; Kirsch, G. Tetrahedron Lett 2007, 48, 5777.

[49] Chen, X.; Peng, Y. Catal Lett 2008, 122, 310.

[50] Khaleghi, S.; Heravi, M. M.; Khosroshahi, M.; Behbahani, F, K.; Daroogheha, Z. Green Chem Lett Rev 2008, 1, 133.

[51] Jain, S. L.; Prasad, V. V. D. N.; Sain, B. Catal Commun 2008, 9, 499.

[52] Boumoud, T.; Boumoud, B.; Rhouati, S.; Belfaitah, A.; Debache, A.; Mosset, P. Acta Chim Slov 2008, 55, 617.

[53] Quan, Z. J.; Da, Y. X.; Zhang, Z.; Wang, X. C. Catal Commun 2009, 10, 1146.

[54] Kashima, C.; Takahashi, K.; Fukusaka, K. J. J Heterocycl Chem 1995, 32, 1775.

[55] Kim, D. Y.; Lee, Y. M.; Choi, Y. J. Tetrahedron 1999, 55, 12983.

[56] Jui, W. H.; Chair, D. C.; Man, K. L. Tetrahedron Lett 1999, 40, 8647.

[57] Matsumoto, A.; Nakamura, S. J. Appl. Polym. Sci 1999, 74, 290.

[58] Kashima, C.; Fukusaka, K.; Takahashi, K.; Yokoyama, Y. J Org Chem 1999, 64, 1108.

[59] Pansare, S. V.; Malusare, M. G.; Rai, A. N. Synth Commun 2000, 30, 2587.

[60] Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. Org Lett 2002, 4, 1127.

[61] Salehi, H.; Guo, Q. X. Synth Commun 2004, 34, 171.

[62] Salehi, H.; Guo, Q. X. Chin J Chem 2005, 23, 91.

[63] Salehi, H.; Li, Q. R.; Guo, Q. X. Chin. J Chem Phys 2006, 19, 84.

[64] Zhang, G. L.; Cai, X. H. Synth Commun 2004, 35, 829.

[65] Ranu, B. C.; Hajra, A.; Dey, S. S. Org Proc Res Dev 2002, 6, 817.