

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

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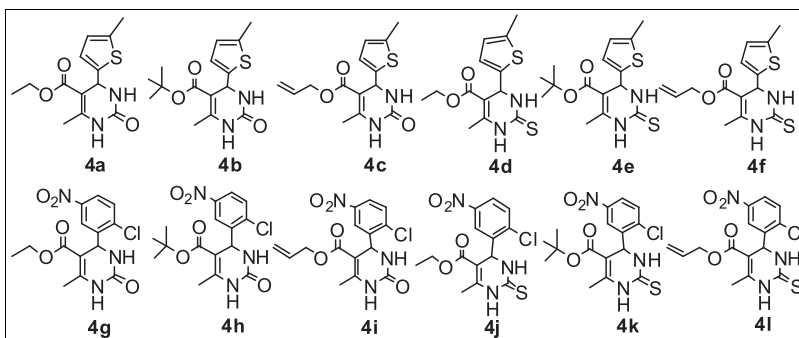
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Biologically important 12 new important 3,4-dihydropyrimidin-2-(1*H*)-ones (-thiones) were synthesized with in one-pot three-component Biginelli reaction from the corresponding aromatic aldehydes (5-methyl-2-thiophenecarboxaldehyde and 2-chloro-5-nitrobenzaldehyde), 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%).

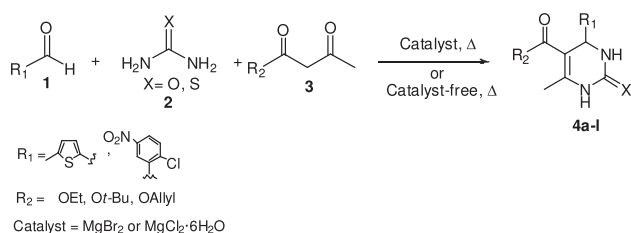
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INTRODUCTION

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 MgBr₂ and MgCl₂·6H₂O 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.

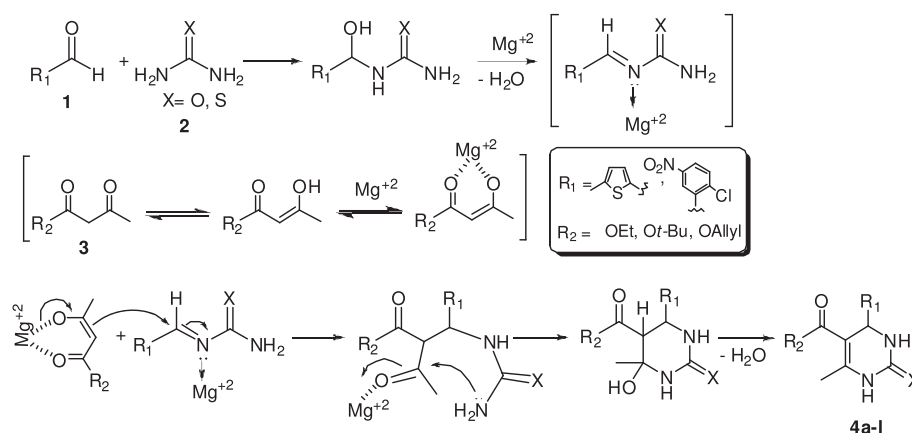
Entries	R ₁	R ₂	X	Product	Time (min)	Yield (%)	Mp (found) (°C)/(lit.) (°C)
1		OEt	O	4a	45 ^a , 90 ^b , 200 ^c	88 ^a , 85 ^b , 55 ^c	232–234/–
2		Or-Bu	O	4b	90 ^a , 100 ^b , 210 ^c	78 ^a , 75 ^b , 44 ^c	226–227/–
3		OAllyl	O	4c	45 ^a , 100 ^b , 210 ^c	85 ^a , 82 ^b , 50 ^c	206–208/–
4		OEt	S	4d	95 ^a , 90 ^b , 210 ^c	91 ^a , 89 ^b , 52 ^c	209–210/–
5		Or-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		Or-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		Or-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:

^aMethod I: MgBr₂ (0.2 mmol), solvent-free, 100°C.

^bMethod II: MgCl₂·6H₂O (0.4 mmol), solvent-free, 80°C.

^cMethod III: catalyst-free, EtOH (2 mL), 100°C.

Scheme 2. The plausible mechanism for MgBr₂ and MgCl₂·6H₂O 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 MgBr₂ as a catalyst, we found that its isolated yield was higher than when MgCl₂·6H₂O was used as a catalyst. Magnesium chloride hexahydrate was very much moisture sensitive. Therefore, we determined that MgBr₂ 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 R₂ (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 ¹H- and ¹³C-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/UV₂₅₄) 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: MgBr₂). The mixture of aldehyde (2 mmol), β -keto ester (2 mmol), urea/thiourea (3 mmol), and MgBr₂ (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: MgCl₂·6H₂O). The mixture of aldehyde (2 mmol), β -keto ester (2 mmol), urea/thiourea (3 mmol), and MgCl₂·6H₂O (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. ¹H-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, OCH₂CH₃), 2.36 (s, 3H, CH₃), 2.21 (s, 3H, CH₃), 1.18 (t, 3H, *J* = 7.1 Hz, OCH₂CH₃). ¹³C-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} . 1H -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} . 1H -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, $CH_2=CH$), 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} . 1H -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 ($C_{13}H_{16}N_2O_2S_2 \cdot 0.15H_2O$): 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} . 1H -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} . 1H -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, $CH_2=CH$), 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

($C_{14}H_{16}N_2O_2S_2 \cdot 0.38H_2O$): 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} . 1H -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} . 1H -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} . 1H -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, $CH_2=CH$ and $CHNH$), 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} . 1H -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} . 1H -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} . $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): 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, $\text{CH}_2=\text{CH}$ and CHNH), 5.08–5.00 (m, 2H, $\text{CH}_2=\text{CH}$), 4.43–4.48 (m, 2H, OCH_2), 2.33 (s, 3H, CH_3). $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$): 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 ($\text{M}^+ + 1$, 100).

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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. Patent 4738965, 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.; McCarthy, 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.; Boume, 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. *Mendelev Comm* 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, 46, 4275.
- [42] Ostras, K. S.; Gorobets, N. K.; Desenko, S. M.; Musatov, V. I. *Mol Divers* 2006, 10, 483.
- [43] Fazaali, R.; Tangestaninejad, S.; Aliyan, H.; Moghadam, M. *Appl Catal A: Gen* 2006, 309, 44.
- [44] Azizian, J.; Mohammadi, A. A.; Karimi, A. R.; Mohammadzadeh, 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-Domínguez, 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 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.