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Potassium phthalimide: An efficient and green organocatalyst for the synthesis of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]pyrimidin-2(5*H*)-ones/thiones under solvent-free conditions

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ABSTRACT

An efficient synthesis of Biginelli-type compounds using potassium phthalimide as a green, mild, and commercially available organocatalyst in a one-pot, multi-component cyclocondensation reaction of cyclopentanone, aldehydes, and urea/thiourea is reported. The present methodology is a green approach to access 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]pyrimidin-2(5*H*)-ones/thiones. It offers several merits such as simple operational procedures, no use of hazardous organic solvents, and cheap and environmentally friendly solid basic catalyst.

1. Introduction

The Biginelli compounds or 3,4-dihydropyrimidin-2(1*H*)-ones (DHMPs) and other compounds with the structural similarity constitute an eye-catching class of heterocyclic organic compounds, which exhibit significant biologic and pharmacologic activities and have become the key structural units in many drugs and drug candidates, such as monastrol, L-771688, SNAP-7941, and SQ 32926 [1–11]. So far, a wide range of biologic effects, including antiviral, antitumor, antifungal, anti-tubercular, antibacterial, antihypertensive, and anti-inflammatory activities, have been described for these compounds [12–15]. It was also reported that some of the Biginelli-type analogs such as fused pyrimidinones bearing an arylidene moiety have anticancer properties [16]. Consequently, the synthesis of this type of heterocycles is of much current importance for both organic synthesis and medicinal chemistry. These types of heterocyclic pyrimidinones are prepared by the reaction of cycloalkanones with various aldehydes and urea/thiourea [17–23]. In addition, these compounds can also be synthesized from the reaction of the α,α'-bis(arylidene)cycloalkanones with urea/thiourea [24]. Typically, processes involved in the synthesis of these compounds are catalyzed by different catalysts. Some of these catalysts include rare earth metal bis(perfluorooctanesulfonyl)imide complexes [18], $YbCl_3$ [20], Brønsted acidic ionic liquid [21], as well as strong Brønsted acid like HCl [25]. Strong Brønsted bases such as sodium ethoxide [16,19], potassium hydroxide [26], sodium butoxide [27,28], and potassium *tert*-butoxide [29] have also been used as the catalyst in Biginelli-type reactions. Recently, base-catalyzed Biginelli reactions have gained significance for the reason of the reasonable yields compared to those of the acid-catalyzed reactions [29,30]. On the other hand, solvent-free organic processes have gained in popularity in recent years from the viewpoint of green chemistry and ecological importance. The benefits of reactions in the absence of solvent are their simple workup procedures, high efficiency, mild conditions, environmental friendliness, reduction of waste, low cost, and handling [31–33].

In the 1950s when Pines and Eschinazi began studies of the solid basic catalysts, the development of these kinds of catalytic systems utilizing inexpensive, clean, environmentally benign, and commercially available catalysts has been a challenge in organic syntheses [34–36]. Potassium phthalimide (PPI) is a stable, mild, green, inexpensive, commercially available, and efficient basic recyclable catalyst. It has been utilized as a reagent in the synthesis of primary amines by the Gabriel method [37,38], and the synthesis of phthalimide derivatives [39–41]. Also, PPI showed

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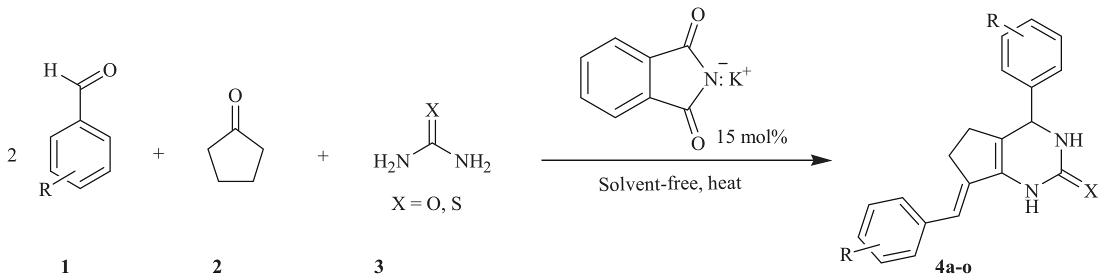

Scheme 1. Synthesis of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]pyrimidin-2(5*H*)-ones/thiones catalyzed by PPI.

high catalytic activity in the preparation of cyanohydrin trimethylsilyl ethers [42,43]. Literature survey shows that there are no reports about the synthesis of pyrimidinone derivatives using PPI as a catalyst. In the present work, we report a solvent-free and solid base PPI-catalyzed synthesis of several derivatives of Biginelli-like compounds *via* a one-pot, multi-component reaction of aryl aldehydes, cyclopentanone, and urea/thiourea (Scheme 1).

2. Experimental

To a mixture of aryl aldehyde **1** (2 mmol), cyclopentanone **2** (1 mmol), and urea or thiourea **3** (1.3 mmol) was added 15 mol% of PPI. The reaction mixture was heated at 120 °C on a heating mantle for 1.5–6 h. After the completion of the reaction (monitored by TLC analysis), the system was cooled to room temperature. Water (10 mL) was added to the reaction mixture, and the crude product was obtained by filtration followed by washing with ethyl acetate and ethanol. The solid thus obtained was further purified by recrystallization using ethanol. The catalyst was recovered by concentration of the filtrate, and was dried and reused for subsequent reactions. Selected spectral data are listed below.

Compound **4a**: IR (KBr, cm^{-1}): ν 3410, 3218, 3120, 2920, 2850, 1670, 1468, 1445, 1355, 1070, 755; ^1H NMR (400 MHz, DMSO-d_6): δ 1.96–2.03 (m, 1H), 2.49 (m, 1H), 2.73–2.84 (m, 2H), 5.16 (s, 1H), 6.63 (s, 1H), 7.19–7.37 (m, 11H), 8.79 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.5, 29.8, 58.7, 117.8, 119.6, 127.2, 127.4, 128.6, 129.0, 129.5, 129.6, 137.1, 138.8, 140.3, 144.3, 154.4.

Compound **4c**: IR (KBr, cm^{-1}): ν 3385, 3215, 3115, 2955, 2850, 1684, 1600, 1440, 1285, 1110, 895, 768; ^1H NMR (400 MHz, DMSO-d_6): δ 1.95–2.06 (m, 1H), 2.33–2.37 (m, 1H), 2.67–2.74 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 5.26 (s, 1H), 6.68 (s, 1H), 7.32 (s, 1H), 7.44 (d, 4H, J = 7.6 Hz), 7.89 (d, 2H, J = 7.6 Hz), 7.97 (d, 2H, J = 7.2 Hz), 8.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.8, 29.1, 52.6, 57.7, 116.6, 120.2, 127.1, 127.3, 128.4, 129.3, 129.8, 130.0, 136.7, 142.5, 142.9, 148.7, 155.7, 157.9.

Compound **4n**: IR (KBr, cm^{-1}): ν 3388, 3205, 2923, 2850, 1668, 1586, 1520, 1476, 1341, 1182, 1109, 856, 752; ^1H NMR (400 MHz, DMSO-d_6): δ 1.98–2.05 (m, 1H), 2.37–2.45 (m, 1H), 2.78–2.91 (m, 2H), 5.39 (s, 1H), 6.89 (s, 1H), 7.49–7.61 (m, 4H), 8.18 (d, 2H, J = 8.4 Hz), 8.29 (d, 2H, J = 7.6 Hz), 8.80 (s, 1H), 10.26 (s, 1H).

Compound **4o**: IR (KBr, cm^{-1}): ν 3405, 3224, 3124, 2920, 2852, 1675, 1488, 1450, 1406, 1350, 1270, 1090, 1015, 889, 828, 814, 754; ^1H NMR (400 MHz, DMSO-d_6): δ 1.96–2.02 (m, 1H), 2.36–2.42 (m, 1H), 2.70–2.79 (m, 2H), 5.38 (s, 1H), 6.69 (s, 1H), 7.26 (s, 1H), 7.28-7.33 (m, 4H), 7.42 (d, 2H, J = 8.7 Hz), 7.46 (d, 2H, J = 12.0 Hz), 8.82 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.6, 29.2, 57.8, 116.6, 121.1, 121.7, 121.9, 127.3, 128.4, 129.1, 129.8, 131.5, 134.9, 138.7, 156.5, 175.8

3. Results and discussion

In the present study a series of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]-pyrimidin-2(5*H*)-ones/thiones (**4a**–**o**) were prepared by condensing cyclopentanone (1 mmol) with aryl aldehydes (2 mmol) and urea/thiourea (1.3 mmol) under conventional heating conditions using 15 mol% of PPI as a solid basic catalyst without any solvent (Scheme 1).

At first, in order to optimize the amount of PPI, the cyclocondensation reaction of benzaldehyde (1 mmol), cyclopentanone (1 mmol), and thiourea (1.3 mmol) was carried out under neat conditions at 120 °C in the presence of different quantities of PPI as the catalyst (Table 1).

As shown in Table 1, in the absence of the catalyst, the formation of product **4l** was not observed (Table 1, entry 1). By adding catalyst (2.5 mol%) to the reaction mixture, the product was formed with relatively low yield (Table 1, entry 2). The yield of product **4l** was improved as the amount of PPI increased from 2.5 to 5, 7.5, 10, and 15 mol% (Table 1, entries 2–6). A further increase in mol% of PPI (20 mol%) did not have any significant effect on the yield of the product or reaction time. It was observed that 15 mol% loading of the catalyst provided the best yield. Therefore, 15 mol% was chosen as the optimal quantity of PPI. Then, the same reaction was tested under different temperatures including room temperature, 50, 80, 100, and 120 °C. The maximum yield in shorter reaction time was achieved under neat conditions at 120 °C. Furthermore, the influence of solvent was also optimized; the model reaction was conducted in various solvents under similar reaction conditions. When the reaction was performed in EtOH, CH_2Cl_2, and CH_3CN, the product **4l** was obtained in yields of 60%, 58%, and 50%, respectively.

With the above-mentioned optimized conditions in hand, we then proceeded to probe the substrate diversity of this multicomponent reaction by using readily available starting materials. It was found that the reaction proceeded efficiently and afforded the targeted products (**4a**–**o**) in good to high yields. The results are offered in Table 2.

Based on the results presented in Table 2, it can be seen that the reaction of aryl aldehydes bearing both electron-donating and electron-withdrawing substituents with cyclopentanone and urea or thiourea worked well, and the corresponding 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]-pyrimidin-2(5*H*)-ones/thiones were obtained in reasonable yields. The

Table 1
Optimization of the amounts of catalyst PPI.[a]

Entry	Catalyst amount (mol%)	Time (h)	Yield (%)[b]
1	–	4	–
2	2.5	4	35
3	5.0	4	60
4	7.5	4	65
5	10.0	4	72
6	15.0	2	84
7	20.0	2	85

[a] Reaction conditions: benzaldehyde (2 mmol), cyclopentanone (1 mmol), thiourea (1.3 mmol), 120 °C.
[b] Isolated yields.

Table 2
Synthesis of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]-pyrimidin-2(5*H*)-ones/thiones (**4a**–**o**) catalyzed by PPI.[a]

Entry	R/Product	X	Time (h)	Yield (%)[b]	Mp (°C)	
					Observed	Reported [Ref.]
1	H/**4a**	O	1.5	88	242–246	236–239 [18]
2	4-CH_3/**4b**	O	2	90	239–241	238–241 [17]
3	4-OCH_3/**4c**	O	6	90	253–254	250–252 [17]
4	3-OCH_3/**4d**	O	3	89	225–227	226–227 [20]
5	2-OCH_3/**4e**	O	4	86	249–251	250–251 [20]
6	4-CN/**4f**	O	3	92	224–226	225–228 [21]
7	2-Cl/**4g**	O	2	94	233–235	232–234 [17]
8	4-Cl/**4h**	O	3	90	257–259	252–255 [17]
9	4-Br/**4i**	O	2.5	90	253–256	252–255 [17]
10	3-NO_2/**4j**	O	4	88	233–236	235–239 [17]
11	4-NO_2/**4k**	O	3	90	275–277	280–283 [20]
12	H/**4l**	S	2	84	225–227	219–223 [17]
13	2-OCH_3/**4m**	S	2.5	80	224–227	223–226 [20]
14	4-NO_2/**4n**	S	4	93	204–207	203–207 [17]
15	4-Cl/**4o**	S	4	93	228–230	226–228 [17]

[a] Reaction conditions: aryl aldehyde (2 mmol), cyclopentanone (1 mmol), urea/thiourea (1.3 mmol), PPI (15 mol%), 120 °C.
[b] Isolated yields.

Table 3
Comparison of the results of the reaction of benzaldehyde, cyclopentanone, and urea using PPI with those obtained by reported catalysts.

Catalyst/conditions	Catalyst amount (mol%)	Time (h)	Yield (%)	Ref.
$YbCl_3$/90 °C, neat	3	3	79	[20]
Ytterbium bis(perfluorooctanesulfonyl)imide/$C_{10}F_{18}$/90 °C	1	2	91	[18]
$AlCl_3$/PEG, 45 °C	30	2.5	94	[44]
TMSCl/DMF-CH_3CN, r.t.	10	2–3	93	[17]
Ionic liquid/100 °C, neat	15	0.083	86	[21]
PPI/120 °C, neat[a]	15	1.5	88	–

[a] Current work.

reusability of the catalyst for the synthesis of **4l** was also examined. After the completion of the reaction, the solid product was treated with water and filtered off. The catalyst was recovered after the removal of water from the aqueous filtrate and reused for subsequent cycles. It showed nearly the same activity as a fresh catalyst along but with a slight decrease of yield. In four consecutive recycles in which the model reaction was carried out, the desired product was obtained in 82%, 78%, 75%, and 70% isolated yields, respectively. To compare the effectiveness of PPI with other catalysts in the synthesis of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]-pyrimidin-2(5*H*)-ones/thiones, results of the reaction of benzaldehyde, cyclopentanone, and urea have been tabulated in Table 3. As shown in Table 3, PPI is comparable to the previously reported methods in terms of reaction time and yields.

4. Conclusion

In summary, we have established a simple, efficient, mild, and environmentally benign method for the synthesis of 4-aryl-7-(arylmethylene)-3,4,6,7-tetrahydro-1*H*-cyclopenta[*d*]-pyrimidin-2-(5*H*)-ones/thiones. This green protocol offers advantages such as good to high yields of the products, green, simple operational procedures, and reusability of the catalyst.

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References

[1] T.U. Mayer, T.M. Kapoor, S.J. Haggarty, et al., Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen, Science 286 (1999) 971–974.
[2] Z. Maliga, T.M. Kapoor, T.J. Mitchison, Evidence that monastrol is an allosteric inhibitor of the mitotic kinesin Eg5, Chem. Biol. 9 (2002) 989–996.
[3] J.C. Barrow, P.G. Nantermet, H.G. Selnick, et al., In vitro and in vivo evaluation of dihydropyrimidinone C-5 amides as potent and selective alpha$_{1A}$ receptor antagonists for the treatment of benign prostatic hyperplasia, J. Med. Chem. 43 (2000) 2703–2718.
[4] C. Goldstein, J.C. Schroeder, J.P. Fortin, et al., Two naturally occurring mutations in the type 1 melanin-concentrating hormone receptor abolish agonist-induced signaling, J. Pharm. Exp. Ther. 335 (2010) 799–806.
[5] K.S. Atwal, B.N. Swanson, S.E. Unger, et al., Dihydropyrimidine calcium channel blockers. 3,3-carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarbox-ylic acid esters as orally effective antihypertensive agents, J. Med. Chem. 34 (1991) 806–811.
[6] M. Matache, C. Dobrota, N.D. Bogdan, et al., Synthesis of fused dihydro-pyrimido[4, 3-d]coumarins using Biginelli multicomponent reaction as key step, Tetrahedron 65 (2009) 5949–5957.
[7] Y.X. Da, Z. Zhang, Z.J. Quan, Intermolecular cyclocondensation reaction of 3,4-dihydropyrimidine-2-thione under the Mitsunobu reaction conditions, Chin. Chem. Lett. 22 (2011) 679–682.
[8] T.N. Akhaja, J.P. Raval, Design, synthesis, in vitro evaluation of tetrahydropyrimidine-isatin hybrids as potential antibacterial, antifungal and anti-tubercular agents, Chin. Chem. Lett. 23 (2012) 446–449.
[9] A. Ghorbani-Choghamarani, P. Zamani, Three component reactions: An efficient and green synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones and thiones using silica gel-supported l-pyrrolidine-2-carboxylic acid-4-hydrogen sulfate, Chin. Chem. Lett. 24 (2013) 804–808.
[10] S. Rostamnia, K. Lamei, Diketene-based neat four-component synthesis of the dihydropyrimidinones and dihydropyridine backbones using silica sulfuric acid (SSA), Chin. Chem. Lett. 23 (2012) 930–932.
[11] M.M. Heravi, N. Karimi, H. Hamidi, et al., Cu/SiO_2: a recyclable catalyst for the synthesis of octahydroquinazolinone, Chin. Chem. Lett. 24 (2013) 143–144.
[12] C.O. Kappe, 100 years of the Biginelli dihydropyrimidine synthesis, Tetrahedron 49 (1993) 6937–6963.
[13] C.O. Kappe, Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog, Acc. Chem. Res. 33 (2000) 879–888.
[14] C.O. Kappe, Biologically active dihydropyrimidones of the Biginelli-type-a literature survey, Eur. J. Med. Chem. 35 (2000) 1043–1052.
[15] K.S. Atwal, G.C. Rovnyak, S.D. Kimball, et al., Dihydropyrimidine calcium channel blockers. 2, 3-substituted-4-aryl-1,4-dihydro-6-methyl-5-pyrimidinecarboxylic acid esters as potent mimics of dihydropyridines, J. Med. Chem. 33 (1990) 2629–2635.
[16] H.I. El-Subbagh, S.M. Abu-Zaid, M.A. Mahran, F.A. Badria, A.M. Al-Obaid, Synthesis and biological evaluation of certain α, β-unsaturated ketones and their corresponding fused pyridines as antiviral and cytotoxic agents, J. Med. Chem. 43 (2000) 2915–2921.

[17] Y.L. Zhu, S.L. Huang, Y.J. Pan, Highly chemoselective multi-component Biginelli-type condensations of cycloalkanones, urea or thiourea and aldehydes, Eur. J. Org. Chem. 2005 (2005) 2354–2367.

[18] M. Hong, C. Cai, Three-component one-pot synthesis of pyrimidinone derivatives in fluorous media: ytterbium bis(perfluorooctanesulfonyl)imide complex catalyzed Biginelli-type reaction, J. Heterocycl. Chem. 46 (2009) 1430–1432.

[19] N.T.A. Dawoud, An efficient and environmentally friendly procedure for synthesis of quinazolinone derivatives by use of a Biginelli-type reaction, Chem. Sci. Trans. 2 (2013) 129–134.

[20] H.H. Zhang, Z.Q. Zhou, Z.G. Yao, F. Xu, Q. Shen, Efficient synthesis of pyrimidinone derivatives by ytterbium chloride catalyzed Biginelli-type reaction under solvent-free conditions, Tetrahedron Lett. 50 (2009) 1622–1624.

[21] A.R. Hajipour, Y. Ghayeb, N. Sheikhan, A.E. Ruoho, Brønsted acidic ionic liquid as an efficient and reusable catalyst for one-pot, three-component synthesis of pyrimidinone derivatives via Biginelli-type reaction under solvent-free conditions, Synth. Commun. 41 (2011) 2226–2233.

[22] M. Rahman, A. Majee, A. Hajra, Microwave-assisted Brønsted acidic ionic liquid-promoted one-pot synthesis of heterobicyclic dihydropyrimidinones by a three-component coupling of cyclopentanone, aldehydes, and urea, J. Heterocycl. Chem. 47 (2010) 1230–1233.

[23] M. Lei, L. Ma, L.H. Hu, An efficient and environmentally friendly procedure for synthesis of pyrimidinone derivatives by use of a Biginelli-type reaction, Monatsh. Chem. 141 (2010) 1005–1008.

[24] M.I. Ali, A. El-Fotooh, G. Hammam, Reactions with (arylmethylene)cycloalkanones, 1,2,6-bis(arylmethylene)cyclohexanenes, J. Chem. Eng. Data 23 (1978) 351–352.

[25] G.E.H. Elgemeie, A.M.E. Attia, S.S. Alkabai, Nucleic acid components and their analogues: new synthesis of bicyclic thiopyrimidine nucleosides, Nucleos. Nucleot. Nucl. 19 (2000) 723–734.

[26] M.I. Ali, A. El-Fotooh, G. Hammam, N.M. Youssef, Reactions with (arylmethylene)cycloalkanones, 3,synthesis of 11-(arylmethylene)octahydrocycloocta[*d*]thiazolo[3,2-a]pyrimidin-3-one derivatives of expected biological activity, J. Chem. Eng. Data 26 (1981) 214–215.

[27] M.A. Al-Omar, K.M. Youssef, M.A. El-Sherbeny, S.A.A. Awadalla, H.I. El-Subbagh, Synthesis and in vitro antioxidant activity of some new fused pyridine analogs, Arch. Pharm. Chem. Life Sci. 338 (2005) 175–180.

[28] S.M. Rajesh, R.S. Kumar, L.A. Libertsen, et al., A green expedient synthesis of pyridopyrimidine-2-thiones and their antitubercular activity, Bioorg. Med. Chem. Lett. 21 (2011) 3012–3016.

[29] Z.L. Shen, X.P. Xu, S.J. Ji, Brønsted base-catalyzed one-pot three-component Biginelli-type reaction: an efficient synthesis of 4,5,6-triaryl-3,4-dihydropyrimidin-2(1H)-one and mechanistic study, J. Org. Chem. 75 (2010) 1162–1167.

[30] F. Tamaddon, Z. Razmi, A.A. Jafari, Synthesis of 3,4-dihydropyrimidin-2(1H)-ones and 1,4-dihydropyridines using ammonium carbonate in water, Tetrahedron Lett. 51 (2010) 1187–1189.

[31] J.O. Metzger, Solvent-free organic syntheses, Angew. Chem. Int. Ed. 37 (1998) 2975–2978.

[32] M.S. Singh, S. Chowdhury, Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis, RSC Adv. 2 (2012) 4547–4592.

[33] K. Tanaka, F. Toda, Solvent-free organic synthesis, Chem. Rev. 100 (2000) 1025–1074.

[34] M.J. Climent, A. Corma, S. Iborra, Homogeneous and heterogeneous catalysts for multicomponent reactions, RSC Adv. 2 (2012) 16–58.

[35] L. Chen, J. Zhao, S.F. Yin, C.T. Au, A mini-review on solid superbase catalysts developed in the past two decades, RSC Adv. 3 (2013) 3799–3814.

[36] M.J. Climent, A. Corma, S.B.A. Hamid, S. Iborra, M. Mifsud, Chemicals from biomass derived products: synthesis of polyoxyethyleneglycol esters from fatty acid methyl esters with solid basic catalysts, Green Chem. 8 (2006) 524–532.

[37] P.L. Salzberg, J.V. Supniewski, in: H. Gilman, A.H. Blatt (Eds.), Organic Synthesis Collection, 1, John Wiley, New York, 1995, p. 119.

[38] M.B. Smith, J. March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th ed., John Wiley, New York, 2001.

[39] S.H. Chan, K.H. Lam, C.H. Chui, et al., The preparation and in vitro antiproliferative activity of phthalimide based ketones on MDAMB-231 and SKHep-1 human carcinoma cell lines, Eur. J. Med. Chem. 44 (2009) 2736–2740.

[40] P. Singh, S. Kaur, S. Kumar, et al., Synthesis and in vitro cytotoxic evaluation of *N*-alkylbromo and N-alkylphthalimido-isatins, Bioorg. Med. Chem. Lett. 21 (2011) 3017–3020.

[41] C.I. Manley-King, J.J. Bergh, J.P. Petzer, Inhibition of monoamine oxidase by C5-substituted phthalimide analogues, Bioorg. Med. Chem. 19 (2011) 4829–4840.

[42] M.G. Dekamin, Z. Karimi, Activation of trimethylsilyl cyanide by potassium phthalimide for facile synthesis of TMS-protected cyanohydrins, J. Organomet. Chem. 694 (2009) 1789–1794.

[43] M.G. Dekamin, S. Sagheb-Asl, M.R. Naimi-Jamal, An expeditious synthesis of cyanohydrin trimethylsilyl ethers using tetraethylammonium 2-(carbamoyl)benzoate as a bifunctional organocatalyst, Tetrahedron Lett. 50 (2009) 4063–4066.

[44] A. Amoozadeh, S. Rahmani, F. Nemati, Poly(ethylene)glycol/$AlCl_3$ as a new and efficient system for multicomponent Biginelli-type synthesis of pyrimidinone derivatives, Heterocycl. Commun. 19 (2013) 69–73.