P₂O₅/SiO₂ as an Efficient, Green and Heterogeneous Catalytic System for the Solvent-Free Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones (and -Thiones)

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Abstract: A simple, green and efficient solventless procedure for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones) from aldehydes, β -ketoesters and urea or thiourea in the presence of catalytic amount of silica-supported P₂O₅ (P₂O₅/SiO₂) at 85 °C is described. Using this method, the title compounds were produced in high yields.

Keywords: P₂O₅/SiO₂, Solvent-free, 3,4-Dihydropyrimidin-2-(1*H*)-one, 3,4-Dihydropyrimidin-2-(1*H*)-thione, Biginelli reaction.

Introduction

Multicomponent reactions have been used as an important method for the preparation of potential biologically active substances¹. For instance, 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones) (Biginelli products) are very important heterocyclic motif in the realm of natural and synthetic organic chemistry due to possessing some biological and pharmacological activities such as antitumor², antibacterial³, and antiviral properties^{4,5}. They have also emerged as integral backbones of several calcium channel blockers⁶, vasorelaxants⁷, and antimitotic agents⁸. One of the most efficient methods for the synthesis of these compounds is one step three-component the condensation of aldehydes with β -ketoesters and urea or thiourea derivatives, which was discovered by Biginelli as early as 1893⁹. The major drawback associated with this protocol is low yields, particularly for

substituted aromatic and aliphatic aldehydes^{10,11}. Because of high importance of Biginelli reaction products, several reagents and catalysts have been used for this transformation, including ytterbium(III) resin¹², 12-molybdophosphoric acid¹³, $\text{Zn}(\text{OTf})_2$ ¹⁴, *N*-butyl-*N,N*-dimethyl- α -phenyl ethyl ammonium bromide¹⁵, $\text{Fe}(\text{HSO}_4)_3$ ¹⁶, H_3BO_3 ¹⁷, various lanthanide trifluoromethanesulfonates ($\text{Ln}(\text{OTf})_3$, $\text{Ln} = \text{Yb, Sc, La}$)¹⁸, alumina sulfuric acid¹⁹, ZrCl_4 ²⁰, $\text{Sm}(\text{NO}_3)_3$ ²¹, TMSCl ²², ionic liquid²³, and InCl_3 ²⁴. Nevertheless, many of the reported methods are associated with one or more of the following drawbacks: (i) the use of expensive reagents, (ii) unsatisfactory yield, (iii) long reaction time, (iv) the use of catalysts that are difficult to their handling, and (v) no agreement with the green chemistry protocols. Thus, development of a cheap, green and efficient catalyst for the synthesis of substituted 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones) would be desirable.

Phosphorus pentoxide/silica gel is an inexpensive, green, commercially available and heterogeneous catalytic system which has been used in several organic transformations, such as synthesis of *N*-sulfonyl imines²⁵, condensation of indoles with carbonyl compounds²⁶, esterification²⁷, oxidation of sulfides to sulfoxides²⁸, Schmidt reaction²⁹, Fries rearrangement³⁰, direct sulfonylation of aromatic rings³¹, oxime preparation³², conversion of aldehydes to acylals³³, selective deprotection of 1,1-diacetals³⁴, and acetalization of carbonyl compounds³⁵.

Solvent-free organic reactions have been applied as an useful protocol in organic synthesis^{36,37}. Solvent-free conditions often lead to shorter reaction times, increased yields, easier workup, matches with green chemistry protocols, and may enhance the regio- and stereoselectivity of reactions^{36,37}.

Considering the above facts and also in extension of our previous studies on green organic synthesis^{25,26,38-46}, herein we report an efficient, green and simple method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones) via the condensation of aldehydes with β -ketoesters and urea or thiourea in the presence of catalytic amount of $\text{P}_2\text{O}_5/\text{SiO}_2$ at 85 °C under solvent-free conditions (Scheme 1).

Scheme 1

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. Silica gel 60, 0.063-0.200 mm (70-230 mesh ASTM) was used as support. Spectra were recorded on the following apparatus: IR spectra on a Shimadzu FTIR-8300 spectrophotometer; ¹H NMR (250 MHz) and ¹³C NMR (62.5 MHz) on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm); Microanalyses on a Perkin-Elmer 240-B microanalyzer; Melting points on a Büchi B-545 apparatus in open capillary tubes.

Preparation of $\text{P}_2\text{O}_5/\text{SiO}_2$ catalytic system

A mixture of SiO_2 (3.5 g) and P_2O_5 (1.5 g) was ground vigorously to give $\text{P}_2\text{O}_5/\text{SiO}_2$ (30% w/w) catalytic system as a white powder (5 g).

General procedure for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones)

To a mixture of compounds consisting of aldehyde (1 m mol), β - ketoester (1 m mol) and urea or thiourea (1.5 m mol) in a 10 mL round-bottomed flask connected to a reflux

condenser was added P₂O₅/SiO₂ (1 g), and the resulting mixture was stirred in an oil-bath (85 °C) for the times reported in Table 3. Afterward, the reaction mixture was cooled to room temperature and was suspended in warm ethylacetate (50 mL), filtered and the filtrate was washed with saturated solution of Na₂CO₃ (2×50 mL) and water (2×50 mL) and dried with MgSO₄. The solvent was evaporated and the crude product was purified by recrystallization from ethyl alcohol.

Selected spectral data of the products

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 3, entry 1)

IR (KBr): 3233, 3101, 2940, 1718, 1697, 1595, 1218 cm⁻¹; ¹H NMR (CDCl₃): δ 1.22 (t, 3H, *J* = 7.0 Hz), 2.36 (s, 3H), 4.07 (q, 2H, *J* = 7.0 Hz), 5.29 (s, 1H), 5.91 (s, 1H), 7.09–7.21 (m, 5H), 8.28 (s, 1H); ¹³C NMR (CDCl₃): δ 14.1, 18.2, 54.5, 61.1, 102.0, 126.4, 127.3, 128.2, 143.0, 146.5, 163.2; Anal. calcd. for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.78; H, 6.04; N, 0.97.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 3, entry 7)

IR (KBr): 3238, 3105, 2963, 1710, 1696, 1594, 1219 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 1.17 (t, 3H, *J* = 7.1 Hz), 2.27 (s, 3H), 3.68 (s, 3H), 4.04 (q, 2H, *J* = 7.1 Hz), 5.16 (s, 1H), 6.82 (d, 2H, *J* = 8.6 Hz), 7.09 (d, 2H, *J* = 8.6 Hz), 7.76 (s, 1H), 9.06 (s, 1H); ¹³C NMR (DMSO-*d*₆): δ 14.2, 17.7, 53.6, 56.0, 60.4, 101.2, 114.3, 127.6, 136.9, 148.4, 152.6, 158.5, 164.9; Anal. calcd. for C₁₅H₁₈N₂O₄: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.21; H, 6.07; N, 9.79.

Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 3, entry 13)

IR (KBr): 3204, 3172, 2979, 1713, 1663, 1596, 1527, 1272 cm⁻¹; ¹H NMR (DMSO-*d*₆): δ 1.16 (t, 3H, *J* = 7.1 Hz), 2.31 (s, 3H), 4.10 (q, 2H, *J* = 7.1 Hz), 5.32 (s, 1H), 7.58–7.63 (m, 2H), 8.01 (s, 1H), 8.11 (m, 1H), 9.64 (s, 1H), 10.39 (s, 1H); ¹³C NMR (DMSO-*d*₆): δ 14.3, 17.3, 54.7, 61.5, 102.0, 121.2, 122.9, 131.2, 133.9, 145.1, 146.9, 148.2, 162.7, 174.1; Anal. calcd. for C₁₄H₁₅N₃O₄S: C, 52.33; H, 4.70; N, 13.08. Found: C, 52.54; H, 4.52; N, 12.85

Result and Discussion

To optimize reaction conditions, the reaction of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.5 mmol) was selected as a model reaction to provide the desired dihydropyrimidin-2-(1*H*)-one (Scheme 1). At first, the reaction was examined using various amounts of P₂O₅/SiO₂ (30% w/w) at different temperatures. The results are displayed in Table 1. As Table 1 indicates, higher yield and shorter reaction time were obtained when the reaction was carried out in the presence of 1 g catalyst at 85 °C. Thus, we applied these optimal conditions for all other reactions. The model reaction was also tested in the presence of only P₂O₅ or only SiO₂ at 85 °C under solvent-free conditions; however, these reagents were not efficient separately. P₂O₅ afforded the Biginelli product in 61% yield after 4 h and SiO₂ gave the product in 65% after 7 h (Table 1, entries 11 and 12). Thus, it is necessary to support P₂O₅ on SiO₂.

In order to compare the efficiency as well as capacity of the solvent-free procedure with respect to solution conditions, the condensation of benzaldehyde with ethyl acetoacetate and

urea was examined in the presence of silica-supported P_2O_5 in several solvents (Table 2). As it can be seen from Table 2, the solvent-free method is more efficient.

Table 1. Optimization of reaction conditions relative to amount of P_2O_5/SiO_2 and temperature.

Entry	Conditions	Time, h	Yield ^a , %
1	$[P_2O_5/SiO_2]$ (1 g)/60 °C	5	45
2	$[P_2O_5/SiO_2]$ (1 g)/70 °C	4.5	69
3	$[P_2O_5/SiO_2]$ (1 g)/80 °C	2.5	91
4	$[P_2O_5/SiO_2]$ (1 g)/85 °C	2	95
5	$[P_2O_5/SiO_2]$ (1 g)/90 °C	2	95
6	$[P_2O_5/SiO_2]$ (1 g)/100 °C	2	93
7	$[P_2O_5/SiO_2]$ (0.3 g)/85 °C	4	47
8	$[P_2O_5/SiO_2]$ (0.6 g)/85 °C	4	58
9	$[P_2O_5/SiO_2]$ (0.8 g)/85 °C	3	71
10	$[P_2O_5/SiO_2]$ (1.2 g)/85 °C	2	93
11	P_2O_5 (0.4 g)/85 °C	4	61
12	SiO_2 (1 g)/85 °C	7	65

^aIsolated pure product.

Table 2. Comparative reaction of benzaldehyde (1 m mol), ethyl acetoacetate (1 m mol) and urea (1.5 m mol) in the presence of P_2O_5/SiO_2 (30% w/w) (1 g) in solution conditions (10 mL of solvent) *versus* the solvent-free method.

Entry	Solvent	Temperature, °C	Time, h	Yield ^a , %
1 ^b	-	85	2	95
2	EtOH	Reflux	4	21
3	H ₂ O	85	5	Trace
4	EtOAc	Reflux	5	63
3	DMF	85	5	Trace
4	CH ₃ CN	Reflux	5	64
5	CH ₂ Cl ₂	Reflux	5	48
6	CHCl ₃	Reflux	5	54
7	THF	Reflux	6	46

^aIsolated pure product. ^bThe Solvent-free conditions.

After optimization of the reaction conditions, the Biginelli reaction was examined with structurally diverse aldehydes, β -ketoesters and urea or thiourea. The results are summarized in Table 3. As it is clear from Table 3, all reaction proceeded efficiently and the desired 3,4-dihydropyrimidin-2-(1*H*)-ones (and -thiones) were produced in high to excellent yields. The influence of electron-releasing and electron-withdrawing substituents on the aromatic ring of aldehydes upon results of the reaction was investigated. The results showed that both electron-donating and electron-withdrawing substituents had no significant effect on the reaction yields; however, these groups increased the reaction times (Table 3). Thiourea was also used as one of the ingredients with similar success to provide the corresponding 3,4-dihydropyrimidin-2-(1*H*)-thiones, which are also of interest for their biological activities⁶ (Table 3, entries 3, 4, 6, 9, 13 and 15). In all cases, 3,4-dihydropyrimidin-2(1*H*)-ones (and -thiones) were the sole products and no by-products were observed.

Table 3. Preparation of Biginelli compounds in the presence of P₂O₅/SiO₂ at 85 °C under solvent-free conditions.

Entry	Ar	R	X	Time, h	Yield ^a , %	M.p. °C (Lit.) ^b
1	C ₆ H ₅	Et	O	2	95	203-205(201-203) ¹⁶
2	C ₆ H ₅	Me	O	2	93	230-231(231-233) ¹⁶
3	C ₆ H ₅	Et	S	2.5	83	208-210(209-211) ¹⁷
4	C ₆ H ₅	Me	S	2.5	84	230-232(229-231) ¹⁷
5	4-MeC ₆ H ₄	Et	O	2.5	92	218-220(216-217) ¹⁹
6	4-MeC ₆ H ₄	Et	S	3	85	189-191(192-193) ¹⁹
7	4-OMeC ₆ H ₄	Et	O	4	91	199-201(202-203) ¹⁶
8	4-ClC ₆ H ₄	Et	O	3	92	212-214(210-213) ¹⁶
9	4-ClC ₆ H ₄	Et	S	4	84	193-195(191-193) ¹⁶
10	4-NO ₂ C ₆ H ₄	Et	O	4.5	94	212-214(210-211) ¹⁹
11	4-NO ₂ C ₆ H ₄	Me	O	4.5	92	230-232(233-235) ¹⁶
12	3-NO ₂ C ₆ H ₄	Et	O	4	89	225-227(226-227) ⁴⁷
13	3-NO ₂ C ₆ H ₄	Et	S	4.5	81	207-209(206-207) ¹⁷
14	3-OHC ₆ H ₄	Et	O	5	89	187-189(184-186) ¹⁹
15	3-OHC ₆ H ₄	Et	S	6	78	181-183(183-184) ¹⁹
16	2-OMeC ₆ H ₄	Et	O	4	89	262-264(261-262) ¹⁷
17	2,3,4-(OMe) ₃ C ₆ H ₂	Et	O	5	88	195-197(198-200) ¹⁹
18	2,4,6-(OMe) ₃ -C ₆ H ₂	Et	O	5	84	254-256(255-256) ¹⁹

^aIsolated pure product. ^bAll compounds are known and their structures were identified by comparison of their melting points and spectral data with those in the authentic samples.

Conclusions

In summary, we have developed a new solvent-free strategy for the preparation of 3,4-dihydropyrimidin-2-(1H)-ones (and -thiones) as biologically interesting compounds via the condensation of aldehyde with β -ketoesters and urea or thiourea. The advantages of this method are high yields, relatively short reaction times, low cost, simple experimental and as isolation procedures, and finally, it is in agreement with the green chemistry protocols.

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