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Microwave Promoted Solvent-Free Biginelli Reaction for the One Pot Synthesis of Dihydropyrimidin-2-(1*H*)-ones Catalyzed by Sulfamic Acid

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An efficient synthesis of 3,4-dihydropyrimidinones (DHPMS) using sulfamic acid as catalyst from an aldehyde, β-keto ester, urea and thiourea under the conventional heating and solvent-free microwave irradiations is described. The solvent-free microwave assisted green procedure offer advantages such as shorter reaction times, simple work-up, excellent yield over the conventional heating.

Key Words: Biginelli reaction, Sulfamic acid, Ethyl acetoacetate, 3,4-Dihydropyrimidin-2(1*H*)-ones, Microwave-irradiation.

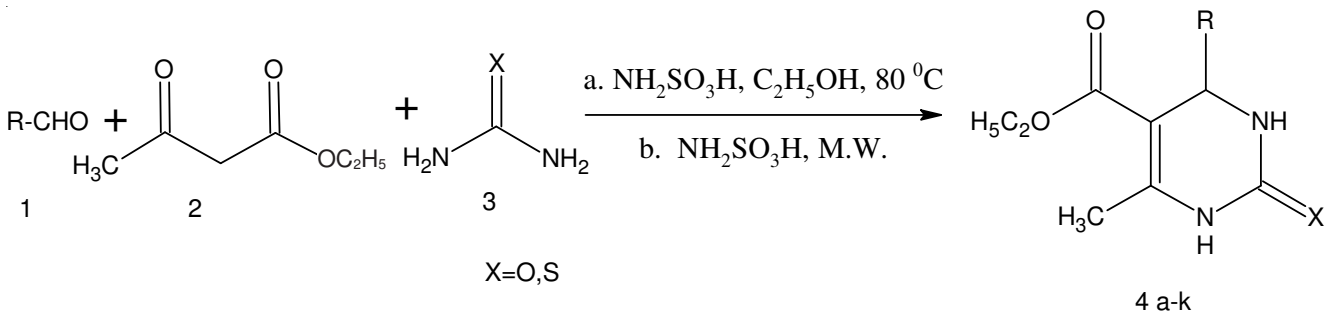
INTRODUCTION

Recently multi-component reactions (MCR's) are governing importance due to its wide variety of applications in organic and medicinal chemistry[1]. Multi-component reactions involves the reaction between three or more reactants in single reaction vessel to form new products, which essentially contain part of all starting materials. Multi-component reactions are diversity oriented efficient and speedy reactions, due to which they have received tremendous attention in the drug discovery process[2]. One of the multi-component reactions of current interest is the Biginelli dihydropyrimidine synthesis[3]. Organic synthesis involving green processes and under solvent-free conditions have been investigated world wide due to stringent environment and economic regulations[4]. However, processes involving conventional acids are inherently associated with problems such as high toxicity, corrosive and polluting reagents, catalyst waste and difficulty in separation and recovery of products[5a]. Today 3,4-dihydro-pyrimidin-2(1*H*)-ones (DHPM) and its derivatives have received considerable amount of attention due to its several biological activities such as antiviral, antibacterial, antitumor and antiinflammatory properties[3b]. Many of these compounds act as α-1a-antagonist calcium channel[4], antihypertensive agent[4]. Therefore the synthesis of this heterocyclic moiety has gained an immense importance in organic synthesis.

Synthetic strategies for the synthesis of dihydropyrimidinone first reported by Biginelli, involves the one pot condensation of an aldehyde, β-ketoester and urea under strong acidic condition often suffer from low yields of the product particularly in the substituted aromatic aldehydes. Hence several attempts have been made to synthesize the 3,4-dihydropyrimidin-2(1*H*)-ones (**Scheme-I**). In the attempt to prepare 3,4-dihydropyrimidin-2(1*H*)-ones different types of acidic catalyst such as H_2SO_4[5b], BF_3·EtOH/CuCl[6], $LaCl_3$·$7H_2O$ with catalytic concentrated HCl[7], $CeCl_3$·$7H_2O$[8], $InCl_3$[9], heteropolyacids[10], $BiCl_3$[11], $Cu(OTf)_2$[12], TMSCl[13], $LiClO_4$[14], LiBr[15], $InBr_3$[16], $FeCl_3$·$6H_2O$/HCl[17], TMSI[18] and $CdCl_2$[19] have been used. Many of the above catalyst used are not ecofriendly and cause the problem during disposal. Further the methods used for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones requires long reaction times, strong acidic condition, vigorous reaction conditions (high temperature) and they are difficult to handle on a large scale. Recently, it was shown that sulfamic acid (SA) and silica sulfuric acid (SSA) have potential to be used as substitutes for conventional acidic catalytic materials. Sulfamic acid and silica sulfuric acid have been extensively used as catalysts for many organic reactions by now[20] and they also have been used in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones[21].

In this pursuit and during the course of our studies aimed comparative study of synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones under the conventional heating and microwave assisted solvent-free procedures.

Herein, a simple, efficient and effective protocol is reported for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and thiones by one pot three component cyclocondensation reaction of 1,3-dicarbonyl compound (ethyl acetoacetate), aromatic aldehyde and urea using sulfamic acid catalyst under the solvent and microwave assisted solventless condition (**Scheme-I**). One pot microwave assisted synthesis under



Scheme-I

solventfree condition not only reduced the reaction time drastically but also consistently produced excellent yields of dihydropyrimidines-2-(1*H*)-ones and thiones with simple work up of the product.

EXPERIMENTAL

All commercial reagents are used as received without purification and all solvents were reagent grade. Reactions were carried out in domestic microwave oven (Samsung model). The reaction was monitored by TLC using 0.25 mm E-Merck silica gel 60 F_{254} precoated glass plates, which were visualized with UV light. Melting points were taken in open capillaries. The IR spectra were recorded on a Perkin-Elmer 257 spectrometer using KBr discs. ^{1}H NMR spectra in DMSO-d_6 were recorded on VXR-300 MHz using TMS as internal standard.

Spectroscopic characterization data

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a): m.p. 206-208 ºC; IR (KBr, ν_{max}, cm^{-1}): 3340, 3240, 1704, 1643, 740; ^{1}H NMR (DMSO-d_6): δ 9.20 (1H, s, NH), 7.75 (1H, s, NH), 7.22-7.34 (5H, m, Ar-H), 4.13-5.14 (1H, d, CH), 3.94-4.01 (2H, q, CH_2), 2.46 (3H, s, CH_3), 0.99-1.47 (t, 3H, CH_3); MS: m/z = 260.28 (m$^+$).

Ethyl-4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b): m.p. 201-202 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240, 3109, 2954, 1704, 1650, 1458, 1226, 1087; ^{1}H NMR (DMSO-d_6): δ 8.83 (1H, s, NH), 7.67 (1H, s, NH), 6.76 (2H, d, Ar-H), 7.14 (2H, d, Ar-CH), 5.18 (1H, d, CH), 3.70 (3H, s, OCH_3), 3.99 (2H, q, CH_2), 2.09 (3H, s, CH_3), 1.03 (3H, t, CH_3); MS: m/z = 290 (m$^+$).

Ethyl-4-(2-furyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c): m.p. 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240, 3116, 2977, 1704, 1634, 1465, 1226, 1095; ^{1}H NMR (DMSO-d_6): 8.87 (1H, s, NH), 7.75 (1H, s, NH), 7.19 (1H, d, CH), 6.10 (1H, t, CH), 5.89 (d, 1H, CH), 5.12 (1H, d, CH), 3.83 (2H, q, CH_2), 2.09 (3H, S, CH_3), 1.03 (3H, t, CH_3). Mass: m/z = 250 (m$^+$).

Ethyl-6-methyl-2-oxo-4-(-2-phenyl vinyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d): m.p. 225-227 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240, 3116, 2977, 1704, 1650, 1026, 1095; ^{1}H NMR (DMSO-d_6): δ 8.79 (1H, s, NH), 7.71-7.73 (1H, s, NH), 7.03-7.19 (5H, m, phenyl), 6.21-6.29 (1H, d, CH), 5.95-6.06 (1H, dd, CH), 4.69 (d, 1H, CH), 3.93-4.02 (2H, q, CH_2), 2.09 (3H, s, Ar-CH_3), 1.077 (3H, t, CH_3); mass: m/z = 287(m$^+$).

Ethyl-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e): m.p. 226-228 ºC; IR (KBr, ν_{max}, cm^{-1}): 3502, 3186, 3016, 1704, 1634, 1581, 1481, 1230, 1095; ^{1}H NMR (DMSO-d_6): δ 10.24 (1H, s, NH), 9.55 (1H, s, NH), 9.54 (1H, bs, Ar-OH), 6.99 (2H, d, Ar-H), 6.702(2H, d, Ar-H), 5.04 (1H, s, CH), 3.99 (t, 2H, CH_2), 2.26 (3H, s, CH_3), 1.09 (3H, q, CH_3). Mass: m/z = 276 (m$^+$).

Ethyl-4-(2-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f): m.p. 199-200 ºC; IR (KBr, ν_{max}, cm^{-1}): 3502, 3255, 3186, 3016, 1634, 1581, 1203, 1095: ^{1}H NMR (DMSO-d_6): δ 10.25 (1H, s, NH), 9.55 (1H, s, NH), 9.43 (1H, s, Ar-OH), 6.99-7.02 (2H, d, Ar-H), 6.69-6.72 (2H, d, Ar-H), 5.05-5.06 (1H, d, CH), 3.96-4.03 (2H, q, CH_2), 2.27 (3H, s ,CH_3), 1.07-1.12 (3H, t, CH_3); mass: m/z = 276 (m$^+$).

Ethyl-4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g): m.p. 215-217 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240, 3116, 2977, 1704, 1634, 1465, 1226, 1095, ^{1}H NMR (DMSO-d_6): δ 10.35 (1H, s, NH), 9.60 (1H, s, NH), 7.40 (2H, d, Ar-H), 7.30 (2H, d, Ar-H), 5.62 (1H, s, CH), 3.91 (2H, q, CH_2), 2.31 (3H, s, CH_3), 1.0 (3H, q, CH_3). Mass: m/z = 294 (m$^+$).

Ethyl-4-(3-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h): m.p. 227-228 ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 3178, 1674, 1573, 1565; ^{1}H NMR (DMSO-d_6): δ 10.25 (1H, s, NH), 9.43 (1H, s, NH), 7.276-7.379 (4H, m, Ar-H), 5.05-5.06 (1H, d, CH), 3.96-4.03 (2H, q, CH_2), 2.27 (3H, s, CH_3), 1.07-1.12 (3H, t, CH_3); mass: m/z = 305 (m$^+$).

Ethyl-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i): m.p. 204-206 ºC; IR (KBr, ν_{max}, cm^{-1}): 3325, 3178, 1674, 1573, 1565; ^{1}H NMR (DMSO-d_6): δ 10.34 (1H, s, NH), 9.66 (1HNH), 7.20-7.37 (m, 5H, m, Ar-H), 5.16 (1H, d, CH), 3.9-4.04 (2H, q, CH_2), 2.29 (3H, s, Ar-CH_3), 1.03-1.12 (t, 3H, q, CH_3); mass: m/z = 276 (m$^+$).

Ethyl-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j): m.p. 191-193 ºC; IR (KBr, ν_{max}, cm^{-1}): 3502, 3255, 3186, 3016, 1634, 1581, 1203, 1095, 856; ^{1}H NMR (DMSO-d_6): δ 9.58 (1H, s, NH), 9.55 (1H, s, NH), 9.10 (1H, bs, Ar-OH), 6.95 (2H, d, Ar-H), 6.68 (2H, d, Ar-H), 5.16 (1H, d, CH), 3.97 (2H, q, CH_2), 2.29 (3H, s, CH_3), 1.05-1.12 (3H, t, CH_3); mass: m/z = 292 (m$^+$).

Ethyl-6-methyl-2-thioxo-4-(-2-phenyl vinyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k): m.p. 224-225 ºC; IR (KBr, ν_{max}, cm^{-1}): 3240, 3116, 2977, 1704, 1650, 1026, 1095; ^{1}H NMR (DMSO-d_6): δ 9.39 (1H, s, NH), 8.79 (1H, s, NH), 7.05-7.21 (5H, m, Ar-H), 6.21-6.25 (1H, d, CH), 5.91-6.06 (1H, dd, CH), 4.65-4.70 (1H, d, CH), 3.95-4.04 (q, 2H, q, CH_2), 2.09 (s, 3H, s, Ar-CH_3), 1.10 (t, 3H, t, CH_3); mass: m/z = 303 (m$^+$).

TABLE-1
SULFAMIC ACID CATALYZED ONE POT SYNTHESIS OF DIHYDROPYRIMIDINE-2-(1*H*)-ONES AND THIONES*

Entry	R	X	Product	Conventional heating		Microwave irradiations		m.p. Experimental (Lit.) ºC
				Time (h)	Yield (%)**	Time (min)	Yield (%)**	
1	C_6H_5	O	**4a**	6	72	2	93	206-208 (204)[22a]
2	4-$OCH_3C_6H_4$	O	**4b**	6	75	2.5	87	201-202 (199-201)[22b]
3	2-Furyl	O	**4c**	7	65	2	88	210-212 (209-210)[22c]
4	C_6H_5CH=CH	O	**4d**	6	80	3	86	225-227 (232)[4f]
5	4-OHC_6H_4	O	**4e**	6	67	3	92	226-228 (227-229)[19c]
6	2-OHC_6H_4	O	**4f**	6	66	3	91	199-200 (201-203)[22d]
7	2-ClC_6H_4	O	**4g**	6	72	3	90	215-217 (215-218)[22c]
8	3-$N0_2C_6H_4$	O	**4h**	6	68	3.5	90	227-228 (227-228)[19c]
9	C_6H_5	S	**4i**	6	70	3	90	204-205 (205-207)[22f]
10	4-OHC_6H_4	S	**4j**	6	65	3	92	191-193 (193-194)[22e]
11	C_6H_5CH=CH	S	**4k**	7	64	3	84	224-225 (223-225)[22c]

*Yields refer to pure products and all products were characterized by comparison of their physical and spectral data with that of authentic samples.
**All the compounds are known, structure of the products were confirmed from their spectral IR, ^{1}H NMR and MS) data.

Typical experimental procedure

By solvent free microwave irradiation: Aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and sulfamic acid (20 mol %) were placed in 100 mL beaker covered with watch glass and irradiated at 300 watt for a certain period of time as required to complete the reaction (TLC). Each pulse was of 20 s with intermittent cooling to avoid overheating. After the completion of the reaction ice cold water was added in a reaction mixture to yield a solid, which was washed thoroughly with water to remove unreacted urea or thiourea, filtered and recrystalized from ethanol to afford pure product.

Conventional heating method: A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and sulfamic acid (20 mol %) were taken in ethyl alcohol as a solvent in 100 mL round bottom flask fitted with reflux condenser. The mixture was heated at 80 ºC in an oil bath for different interval time. After the completion of the reaction, reaction mixture was poured in an ice-cold water to yield a solid, which was washed thoroughly with water to remove unreacted urea or thiourea, filtered and recrystallized from ethanol to afford pure product.

RESULTS AND DISCUSSION

Comparative study of one pot synthesis of dihydropyrimidines by the reaction of aldehydes, ethyl acetoacetate, urea or thiourea and sulfamic acid catalyst in presence of ethyl alcohol as a solvent at 80 ºC and solvent free microwave assisted condition revealed that microwave assisted reaction reduced the reaction time drastically from hours to few minutes (Table-1). Physical and spectral data of known compounds are in agreement with those reported in the literature. A broad range of structurally diverse aromatic and heterocyclic aldehydes have been used in this condensation. α,β unsaturated aldehyde react selectively with aldehyde functional group whereas acid sensitive heterocyclic aldehydes exclusively gave dihydropyrimidones in high yield. It is found that electron donating or withdrawing groups on aromatic aldehydes gave almost good to excellent yield.

Conclusion

Microwave assisted synthesis of dihydropyrimidones using sulfamic acid catalyst offers several advantages over the conventional heating methods such as shorter reaction times, excellent yields and simple experimental workup procedures. Also this solvent free approach is nonpolluting and does not employ any toxic materials quantifying it as a green approach to Biginelli reaction. The mildness of the method together with ease of operation should largely extend the scope of microwave assisted synthesis which is safe, environmental friendly and inexpensive for the three component Biginelli reaction.

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