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Heterogeneous catalytic efficiency of silica sulfuric acid toward the synthesis of substituted pyrimidin-2(1*H*)-one derivatives

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Pyrimidine template is a highly privileged motif for the development of molecules of biological and pharmaceutical interest due to its prebiotic nature to life. This present study deals with the synthesis of pyrimidin- 2(1H)-one derivative from chalcones by the action of silica supported sulfuric acid (SSA) or conventional refluxed in concentrated hydrochloric acid. The chemical structures were confirmed by analytical data and spectroscopic means such as UV, IR, mass spectra, ^{1}H and ^{13}CNMR. SSAwas found to be efficient method for the quantitative transformation to pyrimidine frame work. It can be re-used after simple washing with chloroform thereby rendering this procedure more economical.

Key words: Spectroscopic means, chalcones, pyrimidine, 4-phenylbut-3-en-2-one.

INTRODUCTION

Over the years,tremendous amount of literature have be accumulated on pyrimidine heterocycle, owing to its widespread application in medicinal research and occurrence in many biological entities valuable to life (Ajani et al., 2011). For instance, pyrimidine moiety is the core structure in biomolecules such asnucleic acids components (uracil**,** thymine and cytosine) and vitamin B1, and is an important constituentof numerous drug molecules in many therapeutic areas (Kakiya et al., 2002). The successful application of pyrimidine derivatives in many ways, their utility in applied chemistry and in more fundamental and theoretical studies has made the literature of the subject to be correspondingly vast. Many commercially available drugs are pyrimidine-based some of which are pyrimethamine **1**, l trimethoprim **2**, amicetin**3**, idoxuridine **4**, hexitidine **5** and phenobarbital **6** (Figure 1) (Selvam et al., 2012). Diverse methods have been reported for the synthesis of substituted pyrimidines, the commonest being the reaction of 1, 3- dielectrophiles with nitrogen donors such as urea (Barthakur et al., 2007), thiourea (Stella et al., 2013), guanidine (Soliman et al., 2014), amidine (Kim et al., 2007), benzamidine (Mathews and Asokan, 2007) and formamidine (Gupta et al., 2010). Thus, it is conceivable to develop aseries of pyrimidinones using SSA catalyst technique and also compare it with the

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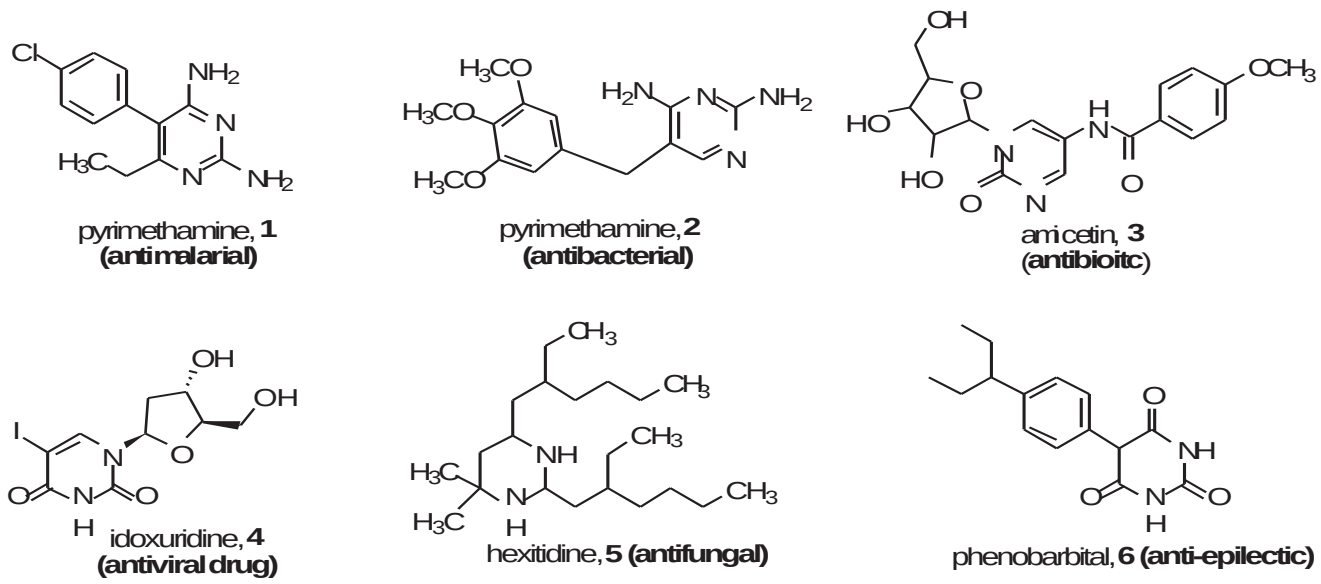


Figure 1. Selected pyrimidine-based drugs commercially available in the market.

traditional method heating approach in conc. Hcl.

MATERIALS AND METHODS

General condition

Melting points were determined in open capillary tubes on a Stuart melting point apparatus and were uncorrected. Infrared spectra were recorded on a Schimadzu Spectrometer. The Ultraviolet spectra were run on a Genesys Spectrometer using acetone solvent. ^{1}H and $^{13}CNMR$ were run on JEOL-JNM-GX-300spectrometer at 300 MHz and 75 MHz respectively using DMSO-d6. Mass spectra were run on Finnigan MAT 312 machine. All compounds were routinely checked by TLC on silical gel G plates using $CHCl_3$:CH_3OH (9:1, v/v) solvent system. The elemental analysis (C, H, N) of compounds were performed using a Carlo Erba- 1108 elemental analyzer.

General procedure for chalcones (7a-g)

To a solution of sodium hydroxide (2.5 g) in water (20 mL), was added ethanol (10 mL) with continuous stirring until it cools down to room temperature. To this solution was added a mixture of appropriate ketone (14.15 mmol) and benzaldehyde (14.15 mmol or 28.30 mmol*) drop-wisely with continuous stirring at room temperature for 30 min. The resulting solution formed colored precipitate which was filtered by suction, washed and recrystallized from ethanol to afford **7a-g.** Where * = double molar equiv. of benzaldehyde.

General procedure for synthesis of pyrimidinone derivatives (8a-g)

Method I

A mixture of any of chalcones **7a-g** (10 mmol) and urea (1.30 g, 21 mmol) was ground in mortar and quantitatively transferred into a 250 mL round-bottomed flask containing ethanol (30 mL). Later, concentrated hydrochloric acid (10 mL) was drop-wisely added with continuous stirring and the reaction mixture was refluxed for appropriate time and reduced by evaporation to half of it original volume. It was then cooled to room temperature and neutralized with 30% sodium hydroxide and left in the freezer chest overnight. The solid product obtained was recrystallized from ethanol to afford the corresponding pyrimidinone **8a-g** in moderate to good yields.

Method II

To a mixture of any of chalcones **7a-g** (10 mmol), urea (1.30 g, 21 mmol) and ethanol (20 mL), was added a catalytic amount of SSA (100 mg, 0.26 mmol), and the reaction mixturewas reflux for appropriate time. The SSA catalyst was extracted with chloroform (20 mL) and removed from the entire solution. The remaining solution was reduced to half its volume and cooled to room temperature. It was neutralized with 30% sodium hydroxide and left in the freezer chest over night. The solid product obtained was recrystallized from ethanol to afford the pyrimidinone **8a-g** in good to excellent yields.

4-Methyl-6-phenyl-5,6-dihydropyrimidin-2(1*H*)-one (8a)

UV-VIS{$ë_{max}$(Log)}: 325 (3.96), 274 (3.33), 244(3.78), 226 (3.44), 202 (3.13). IR [, cm^{-1},KBr]: 3241 (N-H), 2928 (CH aliphatic), 1685 (C=O), 1612 (C=C), 1575(C=N). ^{1}H NMR (300 Hz, ä ppm, DMSO-d_6): 8.0 (s, 1H, NH, D O exchangeable), 7.26-7.40 (m, 5H, Ar-H), 4.90 (t, 1H, CH,J = 7.0 Hz), 1.94 (s, 3H, CH), 1.91-1.66 (m, 2H, CH ,J = 7.0 Hz). ^{13}C NMR (75 Hz, ä ppm, DMSO- d_6):
180.1 (C=O), 160.2, 143.5, 128.7, 128.5, 128.5, 126.9, 126.9, 126.7, 47.7, 40.0, 22.1 (CH_3).

4-(4-Ethylphenyl)-6-phenyl-5,6-dihydropyrimidin-2(1*H*)-one (8b)

UV-VIS{$ë_{max}$(Log)}: 310 (3.68), 265(3.86), 230 (3.97), 215(3.77). IR [, cm-1, KBr]: 3133 (N-H), 1685 (C=O), 1570 (C=N). ^{1}HNMR (300 Hz, ä ppm, DMSO-d_6): 8.0 (s, 1H, NH, D_2O exchangeable), 7.27-

7.40 (m, 7H, 2×Ar-H), 7.78 (d, 2H, Ar-H, J = 7.5 Hz), 4.90 (t, 1H, CH, J = 7.0 Hz), 1.91-1.66 (m, 2H, CH2, J = 7.0 Hz). 2.60 (q, 2H, CH2, J = 8.0 Hz), 1.25 (t, 3H, CH3, J = 8.0 Hz). ^{13}CNMR (75 Hz, ä ppm, DMSO-d_6): 164.6 (C=O), 160.1, 146.7, 143.5, 137.8, 128.5, 128.5, 127.8, 127.8, 127.0, 127.0, 126.9, 126.9, 126.7, 47.3 (CH), 42.7 (CH_2), 28.2 (CH_2), 14.5 (CH_3).

4-Phenyl-3,4,4a,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-one (8c)

UV-VIS{$ë_{max}$(Log)}: 328 (4.12), 274 (3.39), 247 (3.41), 208 (4.02). IR [, cm^{-1}, KBr]: 3295 (NH), 2928 (CH aliphatic), 1690 (C=O), 1600 (C=C), 1565 (C=N). 1H NMR (300 Hz, ä ppm, DMSO-d_6): 8.01 (s, 1H, NH, D O exchangeable), 7.25-7.41 (m, 5H, Ar- H), 4.92 (d, 1H, CH), 2.67-2.84 (m, 5H, Cp-H), 1.22-1.41 (m, 4H, 2×CH, J = 7.1 Hz). ^{13}C NMR (75 Hz, ä ppm, DMSO-d_6): 208.4 (C=O), 150.0, 146.1, 142.9, 135.0, 135.0, 128.1, 128.1, 115.0, 115.0, 39.1(CH_2), 23.8(CH_2),20.4(CH_2).MS m/z 214 [M+, 12.5%], 137 [M+ – Ph, 75%], 109 [M+ – Ph – CO, 100%].

7-Benzylidene-4-phenyl-3,4,4a,5,6,7-hexahydro-2*H*-cyclopenta[*d*]pyrimidin-2-one (8d)

UV- VIS{$ë_{max}$ (Log)}: 330 (3.98), 208 (4.14). IR [cm^{-1}, KBr]: 3387 (NH), 1685 (C=O), 1612 (C=C), 1575 (C=N). 1H NMR (300 Hz, ä ppm, DMSO-d_6): 8.0 (s, 1H, NH, D_2O exchangeable), 7.27-7.60 (m, 10H, 2×Ar-H), 6.34 (s, 1H, CH), 4.91 (d, 1H, CH,J = 7.0 Hz), 2.69 (t, 1H, CH,J = 7.0 Hz), 1.22-2.02 (m, 4H, 2×CH ,J = 7.1 Hz). ^{13}C NMR (75Hz, ä ppm, DMSO-d6): 163.0 (C=O), 160.1, 141.5, 137.1, 135.2, 130.8, 128.6, 128.6, 128.5 (four times), 128.1, 128.1, 127.9, 125.9, 49.9, 45.3, 33.6 (CH_2), 31.3 (CH_2).

7-(3-Methoxybenzylidene)-4-(3-methoxyphenyl)-3,4,4a,5,6,7-hexahydro-2*H*-cyclopent- a[*d*]pyrimidin- 2-one (8e)

UV-VIS{ $ë_{max}$ (Log)}: 366 (3.98), 345 (3.77), 210 (4.14). IR [cm^{-1}, KBr]: 3387 (NH), 1685 (C=O), 1612 (C=C), 1575 (C=N). ^{1}H NMR (300 Hz, ä ppm, DMSO-d_6): 8.0(s, 1H, NH, D O exchangeable), 6.82-7.59 (m, 8H, 2×Ar-H), 6.35 (s, 1H, CH), 4.90 (d, 1H, CH,*J* = 7.0 Hz), 3.84 (s, 6H, 2×CH_3, *J* = 7.0 Hz), 1.81-2.32 (m, 5H, Cp-H,*J* = 7.1 Hz).

4-Phenyl-4,4a,5,6,7,8-hexahydroquinazolin-2(3*H*)-one (8f)

UV-VIS{ëmax(Log)}: 375 (3.69), 344 (3.87), 210 (4.02). IR [cm-1, KBr]: 3387 (NH), 1685 (C=O), 1600 (C=C), 1573 (C=N). ^{1}H NMR (300 Hz, ä ppm, DMSO-d_6): 8.0 (s, 1H, NH, D_2O exchangeable), 7.27-7.41 (m, 5H, Ar-H), 4.91 (d, 1H, CH, J = 7.0 Hz), 2.19 (q, 1H, CH, J= 7.0 Hz), 1.19-1.41 (m, 8H, 4×CH, J = 7.1 Hz). 13C NMR (75 Hz, ä ppm, DMSO-d_6): 164.7 (C=O), 160.1, 137.1, 128.5, 128.5, 128.1, 128.1, 125.9, 49.8, 41.9, 33.8, 27.0, 24.8, 24.2.

RESULTS AND DISCUSSION

In continuation of our recent works concerned with the synthesisof a variety of heterocyclic systems for biological evaluation10, we reporthere on the facile synthesis of substituted pyrimidine motifs under the influence of silica sulfuric acid (SSA) as heterogeneous catalyst. The synthetic route of the precursor, á,-unsaturated carbonyls, otherwise known as chalcones, was as illustrated in Scheme 1 wherein á,-unsaturated carbonyls (7a-g) were synthesized via condensation of benzaldehyde with ketones in basic medium.Compounds 7a-g were formed in good yields via a continuous stirring and agitation at room temperature. They were subsequently reacted with urea under two different conditions which include the common technique in the presence of concentrated HCl (Method I) and the proposed technique using solid support catalyst, Silica Sulfuric Acid (SSA) (Method II), to afford pyrimidin-2(1H)-one derivatives (8a-g). As a case study, the condensation of an equimolar mixture of benzaldehyde andacetoneafforded4- phenylbut-3-en-2-one, 7a. The reactive intermediate chalcone 7a was subsequently treated with urea in ethanol in the presence of either concentrated hydrochloric acid (Method I) or Silica Sulfuric Acid, SSA (Method II) under reflux at 140°C to afford 4-methyl-6-phenyl-5,6-dihydropyrimidin-2(1H)-one,8a. This procedure was repeated for the chemical transformation of other chalcones to their corres ponding pyrimidinone derivatives8b-g (Scheme 2). In Method I, upon completion (TLC), the reaction was worked up to afford 8a in low yield 44% after refluxing for 8 h. However, in Method II, where conc. HCl was replaced with solid support catalyst SSA, the reaction time did not only reduced drastically to 3 h but also led to the formation of the product 8a at a higher yield, 77% (Figure 2). The SSA catalyst was recovered with chloroform (20 mL).

The resulting filtrate was reduced to half its volume and cooled. It was neutralized with ammonium hydroxide and filtered by suction to afford **8a**. In a nutshell, it was observed that SSA did not only emerge as an efficient catalyst in this study but also afforded the pyrimidinone products **8a-g** in higher yields (75-95%) within smaller reaction time (3-4 h) compared with concentrated hydrochloric acid which gave smaller yields (45-71%) at higher reaction time of 8-9 h (Figure 2). The physico-chemical parameters and analytical data were as shown in Table 1 and were consistent with the proposed structures of **8a-g.**

Conclusion

The pyrimidine derivatives were successful achieved by synthetic modification of the various chalcone precursors via Silica sulfuric acid (SSA) heterogeneous catalytic approach. SSAwas found to be a mild, efficient and reusable solid catalyst for the reaction of á,-unsaturated carbonyl with urea to furnish the corresponding pyrimidinone derivatives in good to excellent yield.The interesting behaviour of SSA lies in the fact that it can be re-used after simple washing with chloroform thereby rendering this procedure more economical compared with concentrated HCl method.

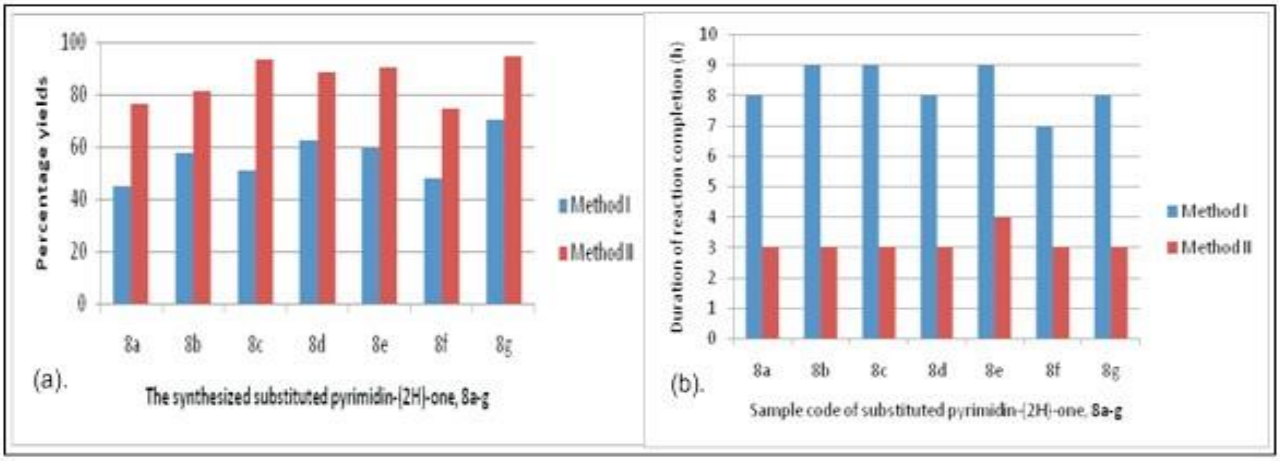
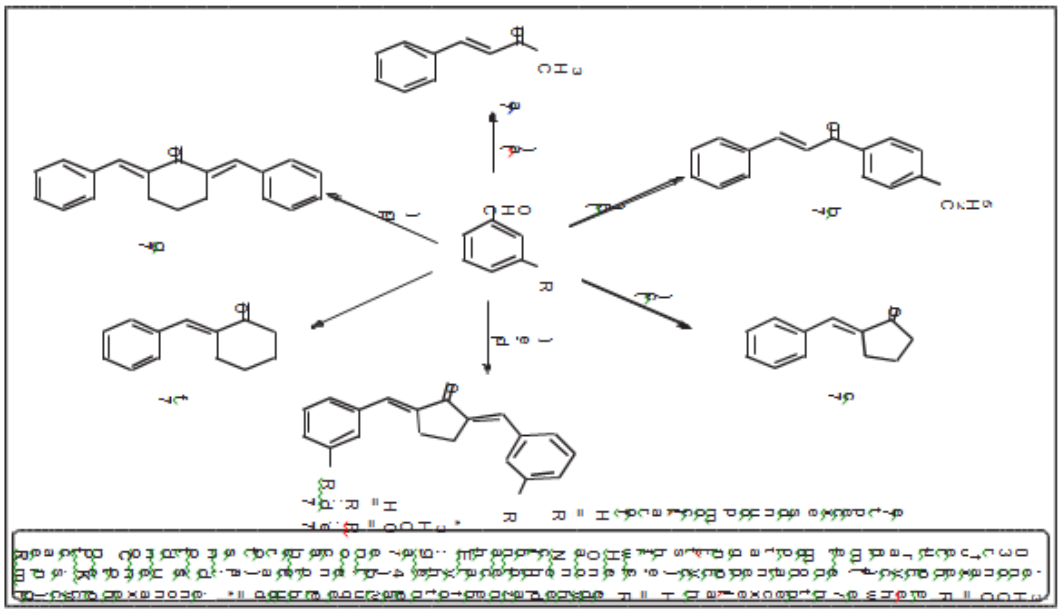


Figure 2. The comparative study of efficiency of tradition method using conc. HCl (Method I) to that of new approach using SSA (Method II) (a) considering % yields factor. (b). considering reaction time (h) factor.

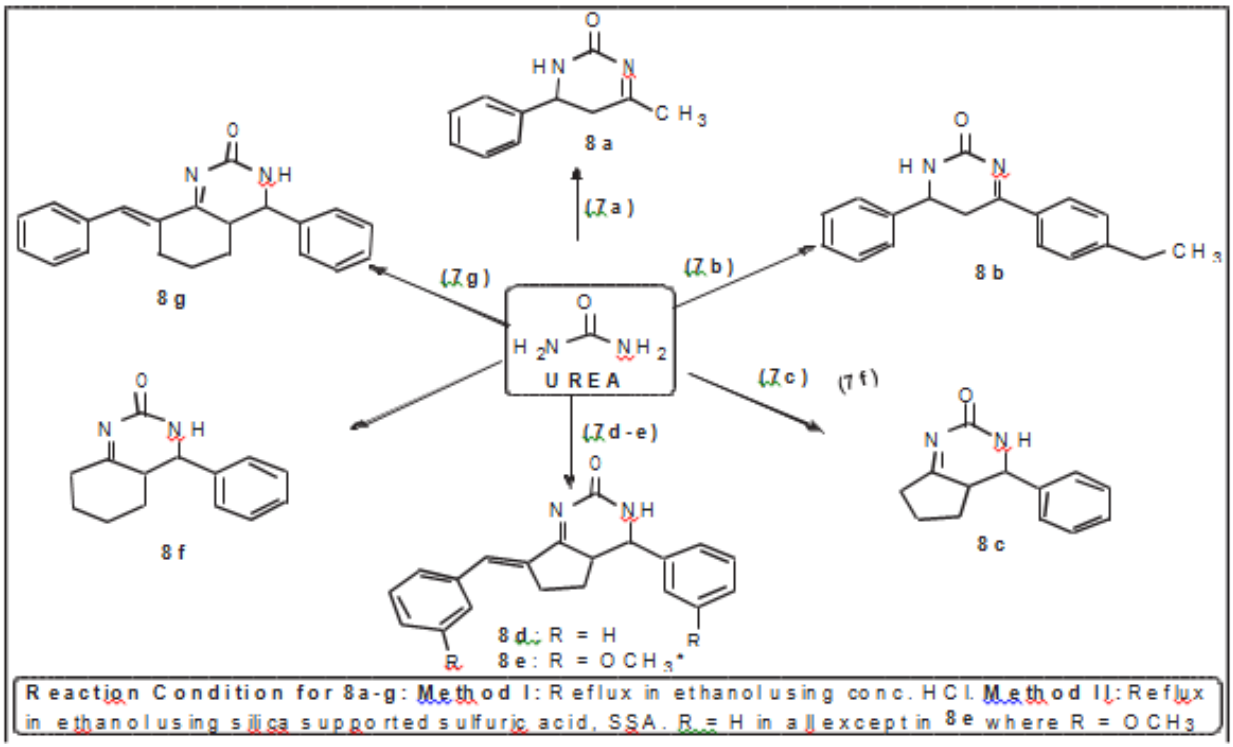
Table 1. Physico-chemical properties of synthesized pyrimidin-2(1H)-ones (8a-g).

Molecular Formula	Mol. Wt.	M.P. (°C)	R_f[a]	Colour	Elemental analysis %Calcd. (%Found)		
					CH		N
$C_{11}H_{12}N_2O$	188	124-127	0.77	Yellow	70.21(70.73)	6.38(6.09)	14.89(15.01)
$C_{18}H_{18}N_2O$	278	211-213	0.56	white	77.70(77.31)	6.47(6.72)	10.07(9.85)
$C_{13}H_{14}N_2O$	214	184-186	0.85	Green	72.90(72.71)	5.04(5.52)	13.08(13.53)
$C_{20}H_{18}N_2O$	302	227-229	0.49	green	79.47(79.95)	5.98(5.82)	9.27(9.45)
$C_{22}H_{22}N_2O_3$	362	240-242	0.69	green	72.93(73.04)	6.08(5.97)	7.73(7.55)
$C_{14}H_{16}N_2O$	228	198-200	0.76	Orange	73.68(73.81)	7.02(7.16)	12.28(12.33)
$C_{21}H_{20}N_2O$	316	>320	0.63	black	79.75(79.11)	6.33(6.72)	8.86(8.43)

[a]$CHCl_3$:CH_3 OH (9:1, v/v), Mol, Wt. = Molecular Weight, M.P. = Melting Point.



Scheme 1. The pathway for the synthesis of á,â-unsaturated carbonyl, chalcones, 7a-g.



Scheme 2: The pathway for the synthesis of substituted pyrimidin-2(1H)-ones, 8a-g.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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