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SeO_2-catalysed one-pot solvent-free synthesis of dihydropyrimidin-2(1*H*)-ones under microwave irradiation

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ABSTRACT

A series of dihydropyrimidin-2(*1H*)-ones were synthesized using the Biginelli type of reaction in presence of selenium dioxide as an efficient catalyst. The reaction was carried out under microwave irradiation to afford the dihydropyrimidin-2(1*H*)-ones in excellent yields. The reaction proceeded cleanly in less time and under solvent free condition.

KEYWORDS

Selenium dioxide;
3, 4-dihydropyrimidine-2(1*H*)-ones;
Microwave irradiation.

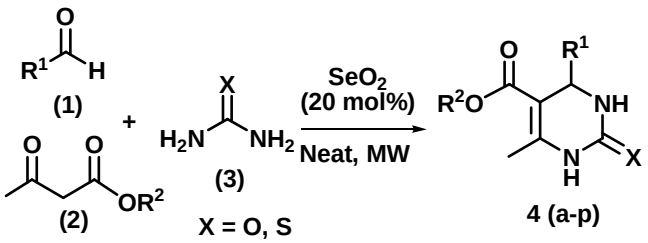
INTRODUCTION

The synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones (DHPM) has gained great importance in recent years due to their wide range of biological activities.[1] Pietro Biginelli first established the three component condensation reaction of methyl acetoacetate, urea and aldehyde which paved the way for the development of similar but more efficient synthetic methods.[2] Later several improvements have been reported by using lewis acids such as $BF_3.OEt_2$, $FeCl_3$, $LaCl_3$, $La(OTf)_3$, $Yb(OTf)_3$, InX_3, $ZrCl_4$, $BiCl_3$, $Mn(OAc)_3$ and $LiClO_4$ or a combination of lewis acids with transition metal salts, clays etc.[3] Some of the methods employed for the synthesis of DHPM however, suffer from disadvantages in the use of strongly acidic condition,[4] the accompanying side products in using protic acids[5] and prolonged reaction time. As a part of our continued interest in the development of newer synthetic methods for heterocyclic compounds and our current interest in the use of SeO_2 in organic synthesis, we wished to explore its utility as one of the reagents in one-pot three component reactions. Our literature survey reveals that SeO_2 has been employed for oxidation reaction,[6-8] reductive carbonylation,[9-12] heterocyclization[13,14] and aromatization[15a] in the presence of a sacrificial catalyst or co-oxidant. To our knowledge there is no report so far of the use of SeO_2 as a catalyst for heterocyclic synthesis. Furthermore, by virtue of the high electron density around the electronegative oxygen, selenium becomes electron deficient and behave as a Lewis acid.[15b] Therefore we decided to use selenium dioxide as a mild Lewis acid rather than an oxidant for the Biginelli reaction. Thus, when 1,3-dicarbonyl compound, urea and aldehyde were reacted under microwave irradiation condition in presence of SeO_2 as a catalyst the reaction resulted in the formation of dihydropyrimidinones. Furthermore, there is no report of SeO_2 being used independently as a catalyst for the Biginelli type of reaction.

RESULTS AND DISCUSSION

In this paper, we would like to report on the SeO_2 as

a useful catalyst for the synthesis of dihydropyrimidin-2(*1H*)-ones in one pot by a three component cyclization reaction under microwave irradiation in solvent free condition. To establish this methodology, we first heated conventionally 4-chlorobenzaldehyde, methyl acetoacetate and urea in the ratio 1:1:1 using stoichometric amount of SeO_2 under neat condition at 100 °C which resulted in the consumption of all the reactants and formation of the desired product. In another attempt, when 4-chlorobenzaldehyde, urea and methyl acetoacetate were reacted in presence of SeO_2 (10 mol %) at 100 °C in a microwave for 10 min the reaction showed the formation of the product **(4m)** with some amount of the unreacted aldehyde. When the same reaction was heated to 130 °C under microwave irradiation during the same period of time, no increase in the yield was observed. However, when the amount of SeO_2 was increased to 20 mol % the reaction proceeded to completion with no trace of the starting aldehyde left (monitored by TLC). Purification by column chromatography afforded DHPM **(4m)** in 95% yield. To confirm the participation of SeO_2 as a catalyst in the reaction, a mixture of 4-chlorobenzaldehyde, methyl acetoacetate and urea were treated under identical reaction condition but in the absence of SeO_2. Thin layer chromatographic analysis of the reaction mixture revealed the presence of the expected dihydropyrimidinone **(4m)** along with a number of side products in close proximity. Again, when benzlaldehyde (entry 2, TABLE 1), ethyl acetoacetate and thiourea were heated with catalytic selenium dioxide (20 mol %) under neat condition in the microwave at 130 °C, the reaction proceeded to completion in 7 min giving **(4b)** in 70% yield (Scheme 1).



Scheme 1

The present procedure was then employed for the condensation of aldehydes (entries 1, 3, and 5, TABLE 1) and β-keto ester with urea to give the corresponding DHPMs in good yields. Furthermore, the cyclocondensation of cinnamaldehyde and furfuraldehyde (entries 14 and 15, TABLE 1) afforded the corresponding DHPMs in 75% and 70% yields respectively. Similarly, when crotonaldehyde was treated with methyl acetoacetate and urea in presence of SeO_2 under microwave for 8 min, the reaction led to the formation of the desired DHPM **(4p)** in 63% yield. A number of aromatic, substituted aromatic and heterocyclic aldehydes were used with 1,3-dicarbonyl compounds and urea or thiourea to demonstrate the generality of the condensation. All the substrates (entries 1-16, TABLE 1) efficiently underwent cyclization to furnish corresponding dihydropyrimidin-2(1H)-ones in presence of SeO_2 catalyst under microwave irradiation without affecting the substituents. The DHPMs were fully characterized by ^1H NMR, ^{13}C NMR, IR analyses and by comparison of the melting points with those of the authentic compounds (TABLE 1).

TABLE 1 : SeO_2 catalyzed synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones under microwave irradiation.

Entry	R_1	R_2	X	Time/ min	Product[a]	Yield[b]/ (%)[c]
1	C_6H_5	Me	O	7	4a	90[4]
2	C_6H_5	Et	S	7	4b	70
3	4-(MeO) C_6H_4	Et	O	8	4c	77[4]
4	4-(MeO) C_6H_4	Et	S	8	4d	64[17c]
5	4-(NO_2) C_6H_4	Me	O	8	4e	85
6	4-(NO_2) C_6H_4	Et	O	8	4f	67[4]
7	3-(MeO) C_6H_4	Et	O	8	4g	78[17d]
8	4-(OMe)C_6H_4	Me	O	6	4h	87[17d]
9	4-Br C_6H_4	Et	O	6	4i	85
10	2,5-$(MeO)_2C_6H_3$	Et	O	9	4j	90
11	3,4,5-$(MeO)_3C_6H_2$	Et	O	9	4k	85
12	4-(Me)C_6H_4	Et	O	8	4l	85
13	4-ClC_6H_4	Me	O	6	4m	95[4]
14	Cinnamyl	Et	O	7	4n	75
15	Furyl	Et	O	7	4o	70[18]
16	Crotonyl	Me	O	8	4p	63

[a]**Products have been characterized by comparison of ^1H, ^{13}C NMR, IR, elemental analysis and melting points with the authentic compounds.** [b]**Isolated yields.** [c]**Reference.**

It is noteworthy to mention that, literature is almost silent of crotonaldehyde being used in the one pot three component condensations to give DHPM **(4p)** in the earlier reported protocols. Significantly, no oxidation takes place at the allylic methylene group of compound **(4p)**.[16]

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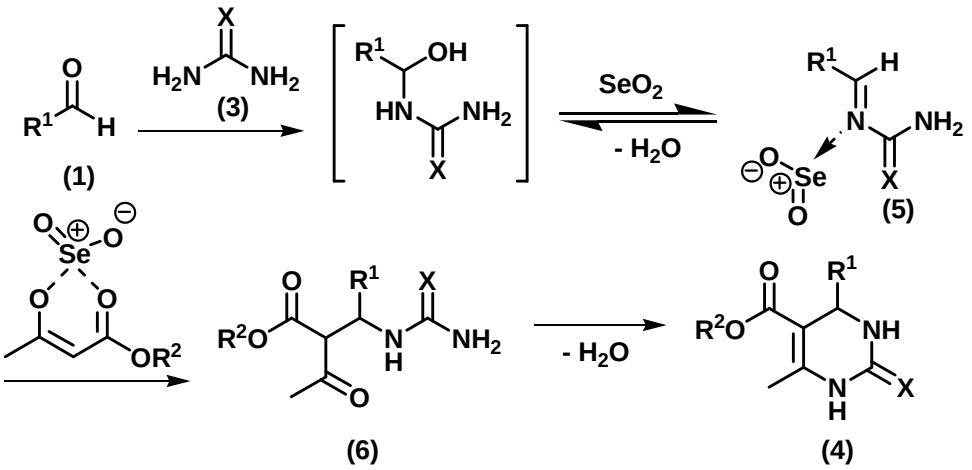

Scheme 2 : Plausible mechanism.

The plausible mechanism may be depicted as in Scheme 2. The intermediate **(5)** is formed by the reaction of the aldehyde and urea or thiourea and then stabilized by selenium dioxide through a coordinate bond due to the electron deficient selenium center. Subsequent addition of ethyl acetoacetate enolate to the acylimine **(5)**, followed by cyclization of compound **(6)** and dehydration, affords the corresponding dihydropyrimidinones **(4)**.

EXPERIMENTAL SECTION

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. IR spectra were recorded on a Perkin-Elmer FT-IR instrument. The ^{1}H- and ^{13}C-NMR spectrum were recorded on a Bruker Avance II 400 NMR machine. Unless otherwise specified, $CDCl_3$ was used as solvent. Mass spectra were recorded with a Water ZQ-4000 equipped with ESI and APCI mass detector and CHN was done on Perkin-Elmer PE 2400 Series II. CEM Discover microwave reactor was used for microwave reaction.

General procedure 4(a-p)

A pre-stirred mixture of aldehyde (2.134 mmol), methyl acetoacetate or ethyl acetocetate (2.134 mmol) and urea or thiourea (2.561 mmol) in a clean and oven dried vessel was irradiated in a CEM Discover microwave reactor at 130 °C (260 W), for 5-10 min in the presence of SeO_2 (20 mol %). The completion of the reaction was monitored by thin layer chromatography. The crude was passed through a short column or silica gel and eluted with ethyl acetate-hexane (3:7) to afford 3, 4-dihydropyrimidin-2(1*H*)-ones.

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b, TABLE 1)

Off white solid, mp 195-197°C (lit.[17d] mp 199-200°C). IR (KBr): 3177, 2989, 2935, 1708, 1653, 1595, 1571, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 1H), 7.45-7.24 (m, 6H), 5.39 (d, J = 2.8 Hz, 1H), 4.12-4.04 (m, 2H), 2.36 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 174.2, 165.1, 145.0, 143.5, 128.5, 127.6, 126.3, 100.6, 59.5, 54.0, 17.1, 14.0. Anal. calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14. Found: C, 60.76; H, 5.93; N, 10.03. MS (ES+) calcd for $C_{14}H_{16}N_2O_2S$ 276.09, found *m/z* 277.0 $(M+H)^+$; 299.0 $(M+Na)^+$.

CONCLUSION

In summary, we have developed an alternative protocol for the synthesis of dihydropyrimidin-2(*1H*)-ones using SeO_2 as a catalyst thus introducing a new variation in the Biginelli reaction. This one-pot protocol has a simple work-up and gives excellent yields of the substituted dihydropyrimidin-2(*1H*)-ones. The present work is expected to provide a new insight in the use of SeO_2 as a catalyst in tandem with other reagents in organic synthesis.

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SUPPLEMENTARY INFORMATION AVAILABLE

Experimental procedures, compound characterization data for each reaction, and representative spectra.

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