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SOLAR ENERGY INDUCED BIGINELLI REACTION: A GREENER APPROACH FOR THE SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2-(1H)-ONE DERIVATIVES

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ABSTRACT

Current article describes solar energy induced synthesis of 3,4-dihydropyrimidin-2-(1H)-one derivatives in presence of ionic liquid. The protocol provides environmentally benign, economic and high yielding approach for the synthesis of targeted derivatives.

Keywords: Biginelli reaction, Solar energy; Green chemistry; Ionic liquid.

INTRODUCTION

Green chemistry attracts the attention of synthetic organic chemists worldwide[1]. In order to design energy efficient protocols; it is highly desirable to develop efficient methods using alternative energy sources. Sunlight is the most abundant energy source available to us freely[2]; even though we have not typically thought about the serious use of this resource as an alternative energy source for chemical transformations. Few reports are published on solar energy promoted organic transformations as compared to microwave and ultrasonic irradiations as the alternative energy sources[3]. It is important to mention that the solar energy is regarded as most clean energy and protocols induced by it proceeded with minimal or no waste. Additionally, solar energy induced protocol also help to overcome the problem of energy consumption. Ionic liquids are considered as an efficient catalyst and reaction media for the organic transformations due to their important physical properties[4]. They promote organic transformations through inherent acidity[5]. The use of ionic liquids also solves the problems of solvent emission and catalyst recovery with high efficiency[6]. This facts encourages us to think about combination of ionic liquid and solar energy for the organic transformation.

3,4-dihydropyrimidin-2-(1H)-one derivatives represent an important heterocyclic system of remarkable pharmacological properties[7]. Many 3,4-dihydropyrimidin-2-(1H)-one derivatives having broad range of biological effects including antifungal[8], antiviral[9], anticancer[10], antibacterial[11], anti-inflamatory[12] and antihypertensive[13] properties. Several alkaloids isolated from marine source also possess dihydropyrimidine nucleus and showed attractive biological properties[14]. Many synthetic protocols have been reported for the synthesis of this heterocyclic moiety by the modification of classical procedure[15]. Some of these procedures have effectively employed variety of catalysts and alternative energy sources to improve efficacy of the protocol. However, some of these methods still suffer with drawbacks such as strongly acidic reaction media, higher temperatures, use of expensive catalyst, longer reaction time and tedious work up. As a result, we thought that there is enough opportunity for further development in construction of such important heterocyclic moiety through combination of solar energy source and ionic liquid as catalyst.

Herein we report the solar energy induced, 1-carboxymethyl-3-methylimidazolium tetrafluoroborate, [cmmim][BF4] catalyzed greener approach for the synthesis of 3,4-dihydropyrimidin-2-(1H)-one derivatives.

EXPERIMENTAL

All the chemicals were used without further purification. All the reactions were performed in round bottom flask and exposed to direct sunlight on the day having full bright sun in the month of April-May. The reactions were monitored through Thin Layer Chromatography (TLC). The ionic liquid 1-carboxymethyl-3-methylimidazolium tetrafluoroborate, [cmmim][BF4] was synthesized according to the procedure reported by us[16]. IR Spectra were recorded on a Shimadzu FT-IR 8400 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400MHz spectrometer.

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

Aldehyde (10 mmol), ethyl acetoacetate (10 mmol) and urea (11 mmol) were added to the round bottom flask containing 100 mg of [cmmim][BF_4]. 5 mL ethanol was added to the reaction mixture and stirred with spatula to ensure uniform mixing of reactants. The reaction flask was then exposed to direct sunlight and the reaction was monitored through TLC. After the completion of reaction as indicated by TLC, the reaction mixture was poured onto crushed ice and stirred with glass rod for few minutes. The solid material was filtered and further washed with cold water followed by crystallization to get pure product. The filtrate obtained was heated at 80 °C in vacuum oven under reduced

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pressure of 10 mm Hg for 4 h to recover the ionic liquid. The recovered ionic liquid was tested for further six reaction cycles with same reactants and was found almost equally effective.

Spectral data of some selected compounds

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4b)

IR (KBr): 3224, 2950, 1745, 1670, 1510, 1340, 1125, 780 cm-1; ^{1}**H NMR** (400 MHz, DMSO): δ 9.34 (s,1H), 8.20 (d, 2H), 7.88 (s, 1H), 7.52 (d, 2H), 5.29 (s, 1H), 3.99 (q, J=7.2 Hz, 2H), 2.28 (s, 3H), 1.09 (t, J=7.2 Hz, 3H); ^{13}**C NMR:** δ 14.48, 18.32, 54.18, 59.82, 98.68, 124.21, 128.11, 147.17, 149.81, 152.26, 152.46, 165.50.

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (4e)

IR (KBr): 3260, 2980, 1720, 1635, 1248, 1120, 775 cm-1; ^{1}**H NMR** (400 MHz, DMSO): δ 9.15 (s,1H), 7.68 (s, 1H), 7.12 (s, 4H), 5.10 (s, 1H), 3.98 (q, J=7.2 Hz, 2H), 2.24 (s, 3H), 2.26 (s, 3H), 1.10 (t, J=7.2 Hz, 3H); ^{13}**C NMR:** δ 14.56, 18.22, 21.10, 54.10, 59.61, 99.90, 126.61, 129.35, 136.82, 142.43, 148.60, 152.64, 165.82.

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4i)

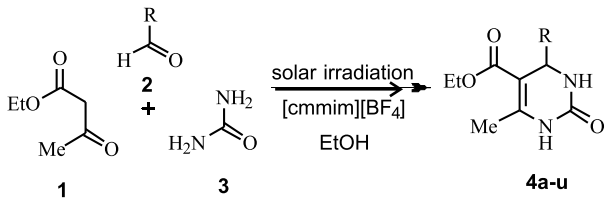
IR (KBr): 3358, 3219, 2930, 1731, 1678, 1171, 819 cm-1; ^{1}**H NMR** (400 MHz, DMSO): δ 9.34 (s,1H), 9.10 (s, 1H), 7.64 (s, 1H), 6.84 (m, 4H), 5.02 (s, 1H), 3.96 (q, J=7.0 Hz, 2H), 2.21 (s, 3H), 1.08 (t, J=7.0 Hz, 3H); ^{13}**C NMR:** δ 13.76, 17.45, 54.44, 59.23, 101.18, 115.02, 127.77, 133.89, 146.92, 153.01, 156.84, 165.45.

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4s)

IR (KBr): 3270, 1691, 1676, 1615, 1513 cm-1; ^{1}**H NMR** (400 MHz, DMSO): δ 9.34 (s,1H), 8.12 (m, 2H), 7.55 (m, 2H), 7.02 (s, 1H), 5.32 (s, 1H), 3.92 (q, J=6.9 Hz, 2H), 2.28 (s, 3H), 1.10 (t, J=6.9 Hz, 3H); ^{13}**C NMR:** δ 14.12, 17.92, 53.61, 59.48, 98.42, 121.14, 122.34, 130.20, 133.06, 147.08, 147.92, 149.47, 151.94, 165.23.

RESULTS AND DISCUSSION

Variety of 3,4-dihydropyrimidine-2(1H)-one derivatives 4a-u were synthesized by reaction between ethyl acetoacetate 1, aldehydes 2 and urea 3 in presence of [cmmim][BF_4] under solar irradiation (Scheme 1).



Scheme 1 General reaction scheme for the synthesis of 3,4-dihydropyrimidine-2(1H)-one derivatives

To optimize the reaction condition, reaction between benzaldehyde, ethyl acetoacetate and urea was selected as the model reaction. The model reaction was performed under various reaction conditions for an appropriate time as decided by TLC. The results are depicted in Table 1.

Table 1: Optimization of Reaction Condition for the Synthesis of 3,4-dihydropyrimidine-2 (1H)-one derivatives

Entry	Catalyst/co-solvent	Max. Temp. reached during reaction (°C)	Reaction Time (h)	Yield[a] (%)
1	No catalyst/5mL Ethanol	54	6.0	0
2	200 mg [cmmim][BF_4]/no co-solvent	42	6.0	58
3	200 mg [cmmim][BF_4]/5 mL Ethanol	52	4.0	86
4	200 mg [cmmim][BF_4]/5 mL Ethanol	-[b]	4.0	Trace
5	100 mg [cmmim][BF_4]/5 mL Ethanol	48	4.0	86

[a]Isolated yield after the completion of reaction as indicated by TLC
[b]Reaction was carried out under simple stirring at ambient temperature

Initially, the reaction was performed in absence of ionic liquid under solar irradiation; ethanol was used as a solvent to maintain homogeneity of the reaction mixture. Product formation was not observed even after long exposure to solar irradiation (Entry 1). At the same time, other reaction was performed by taking 200 mg IL in absence of ethanol to result only 58% of yield (Entry 2). The lower yield might be obtained due to non-homogeneity of the reaction mixture. It was thought that the co-solvent ethanol is necessary to maintain homogeneous nature of the reaction. All further reactions were performed in presence of ethanol. The model reaction in presence of 200 mg IL and Ethanol as co-solvent showed significant conversion of starting materials in to the final product (Entry 3). To check the effect of solar irradiation, the same reaction was performed by stirring at ambient temperature. After a long period of stirring only trace amount of product was observed (Entry 4). The model reaction was also performed by taking 100 mg IL with 5 mL of co-solvent which proceeded without any change in the yield of the final product (Entry 5). Hence it was chosen to be the most optimum reaction condition for the synthesis of 3,4-dihydropyrimidine-2(1H)-one derivatives under solar irradiation.

Table 2 Synthesis of 3,4-dihydropyrimidine-2(1H)-one derivatives under solar irradiation

Compound	R	X	Reaction timea (h)	Yield (%)[b]
4a	Ph–	O	4.0	86
4b	4- O_2N–C_6H_4–	O	6.5	81
4c	4-F–C_6H_4–	O	5.5	76
4d	3-Cl–C_6H_4–	O	4.5	88
4e	4-H_3C–C_6H_4–	O	4.5	84
4f	4-MeO–C_6H_4–	O	5.0	85
4g	2-Furyl-	O	4.0	82
4h	2-Cl–C_6H_4–	O	4.0	83
4i	4-HO–C_6H_4–	O	4.5	78
4j	3,4,5-$(MeO)_3$-C_6H_2-	O	5.5	86
4k	4-HO,3-MeO– C_6H_3-	O	5.0	82
4l	2-Thienyl	O	4.5	78
4m	2-HO–C_6H_4–	O	4.5	84
4n	2-Br–C_6H_4–	O	5.5	81
4o	3-Br–C_6H_4–	O	5.0	89
4p	2,5-$(MeO)_2$-C_6H_3-	O	5.5	91
4q	3,4-$(MeO)_2$-C_6H_3-	O	6.0	93
4r	2-Pyridyl	O	5.0	85
4s	3- O_2N–C_6H_4–	O	5.5	79
4t	2- O_2N–C_6H_4–	O	6.0	81
4u	4-Cl–C_6H_4–	O	4.0	84

[b]yield after crystallization

After the optimization, all the reactions by varying aldehydes were carried out and continuously monitored through TLC. The reaction time and % yield obtained from variety of aldehydes are shown in Table 2. It was observed that all the aldehydes reacted very smoothly and afforded 3,4-dihydropyrimidine-2(1H)-one derivatives in excellent isolated yields.

The recyclability of the ionic liquid was checked by model reaction between benzaldehyde, ethyl acetoacetate and urea. After the completion of reaction the IL was recovered from the filtrate by vacuum distillation. The recovered ionic liquid was used in the next cycle of the same model reaction. No significant change in the activity of IL was observed for at least six consecutive cycles. The reusability of ionic liquid is shown in Figure 1.

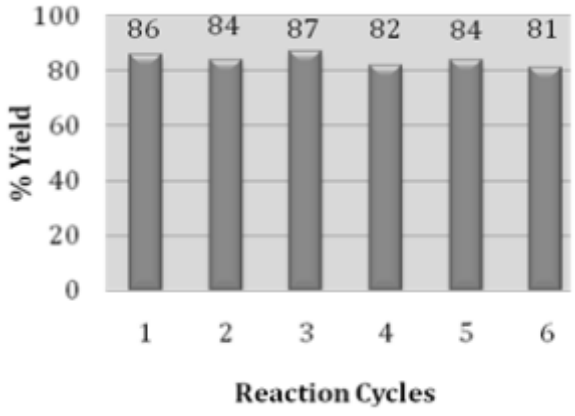


Figure 1 Recyclability of ionic liquid.

CONCLUSION

We have successfully developed a versatile method promoted by the synergetic effect of IL and solar energy to synthesize 3,4-dihydropyrimidine-2(1H)-one derivatives in excellent yields. The milder reaction conditions, excellent yields, easy work up and combined use of ionic liquid and solar energy have made this procedure an improved alternative to the conventional processes.

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