J. Chem. Sci. (2022)134:44
https://doi.org/10.1007/s12039-022-02039-z

REGULAR ARTICLE

Eosin Y photocatalyzed access to Biginelli reaction using primary alcohols *via* domino multicomponent cascade: an approach towards sustainable synthesis of 3,4-dihydropyrimidin-2(1H)-ones

GOBIND KUMAR[a], GAURAV BHARGAVA[a], YOGESH KUMAR[b,*] and RUPESH KUMAR[a,*]

[a]Department of Chemical Sciences, I. K. G. Punjab Technical University, Kapurthala, Punjab 144603, India
[b]Department of Chemistry, Durham University, Durham DH1 3LE, UK
E-mail: yogeshsynthesis@gmail.com; rupesh.manak@gmail.com

MS received 14 October 2021; revised 17 January 2022; accepted 29 January 2022

Abstract. The Eosin Y photocatalyzed Biginelli protocol has been established by a cascade one-pot three-component reaction of primary alcohols, α-ketoester, and urea to provide pharmacologically promising 3,4-dihydropyrimidin-2(1H)-ones in high yields. The key benefits of the present scheme are the capability to allow operational simplicity, readily available substrates, straightforward workup and high yields. This Eosin Y based photocatalytic approach can permit conquering traditional metal-catalyzed reactions in a sustainable manner, thus delivering economic and environmental rewards.

Keywords. Biginelli reaction; Photocatalysis; Eosin Y; 3,4-dihydropyrimidin-2(1H)-ones; Multicomponent reaction.

1. Introduction

The gradually increasing demand for greener methodology for concurrent chemical synthesis has enforced chemists to develop atomic economically and environmentally benign synthetic routes for producing well usable chemicals.[1] Visible-light-assisted transformations have especially attracted growing interest due to their green and beneficial properties, sustainability, readily availability and ease of handling.[2] In addition, compared to the conventional catalytic protocols, photo-catalysis under visible-light irradiation has been revealed as a powerful synthetic tool that produces mild and eco-friendly organic conversions.[3–6] Exhilarate by this, various dyes and metal-complexes; bearing ruthenium and iridium, are reported as photocatalysts in the last couple of years especially.[7–16]

The controlled oxidation of alcohols is one of the important transformations in organic synthetic chemistry as their products play an important intermediate role in the formation of fine chemicals, important agrochemicals, pharmaceutical entities and other high-value products.[17–19] Oxidation of primary aromatic alcohols are mostly achieved using rather strong oxidizing agents, that are toxic and hazardous to the environment *i.e.* hyperchlorite, permanganate, *etc.* and expensive noble metal catalysts including Au, Pt, Pd.[20–25] As the alternative route, oxygen plays an important role as an excellent oxidant because of prevention of toxic, hazardous and stoichiometric by-products.[26] Based on the perspective, various homogenous and heterogeneous metal catalysts have been reported. In equality, transition-metal free photocatalysts are greener and striking, because of inexpensive, easy departure from the reaction mixture and non-poisonous.[27,28] So far, several photocatalytic methods have also been reported for the oxidation of primary aromatic alcohols.[29–34]

Notably, 3,4-dihydropyrimidin-2(1H)-one (DHPMs) are the core structural motifs for many potentially active biological molecules such as calcium channel blockers, ant-inflammatory and antitumor.[35] DHPMs are identified as encouraging anticancer agents (Figure 1)

*For correspondence
Supplementary Information: The online version contains supplementary material available at https://doi.org/10.1007/s12039-022-02039-z.

Published online: 15 March 2022

especially monastrol, responsible to block the bipolar-mitotic-spindle in mammalian cells that results in triggering the arrest of G2/M mitotic phase further leading to cell apoptosis.[36,37]

Various methods have been published in the literature for the composite of 3,4-dihydropyrimidinones by using ultrasonic irradiation, microwaves, ionic liquids, Thermal methods and metal catalysts (i.e. copper (II) sulfamate, Dendrimer-PWA).[38–48] These methods and catalysts mentioned above have the common drawbacks of difficult work-up, lower product yield, noxious and steep catalysts, acidic circumstance and long-time reactions.[49]

The reported literature prompted us to explore a tandem cascade methodology for the fabrication of DHPMs utilizing primary aromatic alcohols. For a tandem cascade approach, a photooxidative system is required to be established that is selective and high yielding.

Here, we developed a greener and environmentally benign protocol for the synthesis of 3,4-DHPMs using molecular oxygen,[28,50–52] visible light irradiation as a green energy source,[53] eosin Y as photoreceptor and sensitizer, silver nitrate as an add-on photoreaction enhancer and inorganic salt $K_2S_2O_8$ as a strong oxidizing agent.[54] Eosin Y revealed unique properties like as rapid intersystem crossing to the lowest triplet state, high photo and chemical stability, ease of separation from the reaction mixture and high catalytic efficiency.[55] This strategy embraces two distinct features involving activation of the system using visible light and initial activation of the dye through light absorption followed by system activation. Our investigated style has a prominent quality like easy workup, inexpensive catalyst, simple filtration, high yield and easy scalability. Our approach combines a dye i.e. Eosin Y, a light energy acceptor, with an electron acceptor photocatalyst, silver nitrate.

2. Experimental

2.1 *General information and materials*

General standard methods were used to purify and dry the solvents. Reagents and solvents (procured from Spectrochem, Aldrich, Acros and Merck) were used as such without added purification unless otherwise required. TLC (Analytical thin layer chromatography) was performed on Merck Kieselgel-60 F-254. Silica-gel 100-200 mesh was used to perform column chromatography. M.P. (Melting points) were recorded on Mel-Temp apparatus in

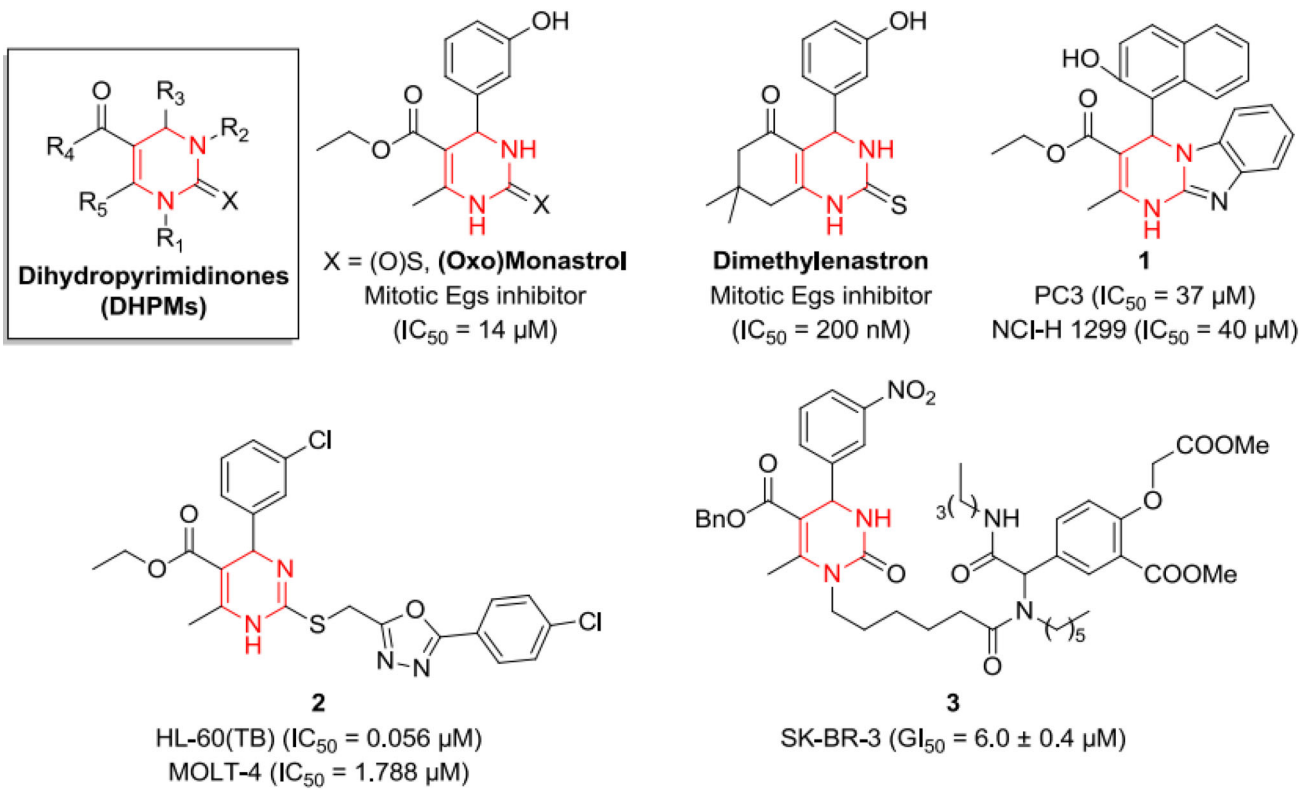


Figure 1. Some DHPM derivatives with anticancer activity.

capillary tubes and are uncorrected. Proton NMR spectra were attained at Bruker spectrometer (400 MHz) using $CDCl_3$ as solvent (7.26 ppm- referenced to residual chloroform) or *d6*-DMSO (2.50 ppm – referenced to residual and 3.34 ppm – referenced to residual water in DMSO-d6). Chemical shift values are articulated in ppm (parts per million) downfield with respect to TMS. Coupling constant values (*J* values) are presented in Hz. ^{13}C NMR spectra were obtained at 75 MHz in using Bruker spectrometers using $CDCl_3$ as solvent (77.0 ppm – referenced to residual chloroform) or *d6*-DMSO (39.5 ppm – referenced to residual DMSO). Perkin Elmer (Spectrum-II) used for IR spectra. Mass spectrophotometer (Brucker-micrOTOF-QII) used for mass spectra.

2.2 *Experimental procedures*

2.2a *General procedure of the synthesis of 3,4-dihydropyrimidin-2(1H)-ones*: Alcohol **1b** (1.0 mmol), α-ketoester **2b** (1.0 mmol) and urea **3b** (1.2 mmol) was dissolved in a mixture of acetonitrile and water (1:1) at room temperature in the presence of air bubble. Eosin Y (1.0 mmol), Silver nitrate (2.0 mol%) and potassium persulphate (1.0 mmol) was added and the reaction mixture was stirred for 48 h under visible light at room temperature. The reaction was monitored using TLC. After the completion of reaction, the reaction mixture was partitioned between water and ethyl acetate. The separated organic layer was washed with saturated brine solution, dried over anhydrous sodium sulfate, concentrated *in vacuo* to afford compounds **DHPM** with excellent yields (upto 88%). The compounds **DHPM** were further purified by using column chromatography over silica gel with the mixture of ethylacetate/hexane to get the pure **DHPMs**.

***Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate* 4a:** Yield 88%; white solid, M.p. 203–204 °C; IR (ATR) ν cm^{-1} 3243 (N-H), 1701 (C=O), 1638 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ 9.22 (1H, s, NH), 7.75 (1H, s, NH), 7.27 (5H, m, ArH), 5.15 (1H, d, J = 4.0 Hz, CH), 3.98 (2H, q, J = 15.2, 8.0 Hz, CH_2), 2.26 (3H, s, CH_3), 1.10 (3H, t, J = 8.0 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 153.1, 148.3, 145.3, 129.1, 128.2, 127.8, 98.2, 60.2, 55.5, 19.0, 14.7. MS *m/z* 261 (M+1); Anal. Calc. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; found: C, 64.59; H, 6.23; N, 10.73.

***Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate,* 4b**: Yield 80%; White solid; M.p. 208–210 °C; IR (ATR) ν cm^{-1} 3228 (N-H), 1697 (C=O), 1653 (C=C).^{1}HNMR (400 MHz, DMSO-d_6) δ 9.20 (1H, s, NH), 7.70 (1H, s, NH), 7.29 (5H, m, ArH), 5.13 (1H, d, J = 4.0 Hz, CH), 3.70 (s, OCH_3), 2.28 (3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d6) δ 164.3, 152.7, 148.9, 145.1, 128.9, 128.2, 127.5, 100.2, 55.6, 54.1, 15.7. MS *m/z*247 (M+1); Anal. Calc. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38; found: C, 63.42; H, 5.76; N, 11.33.

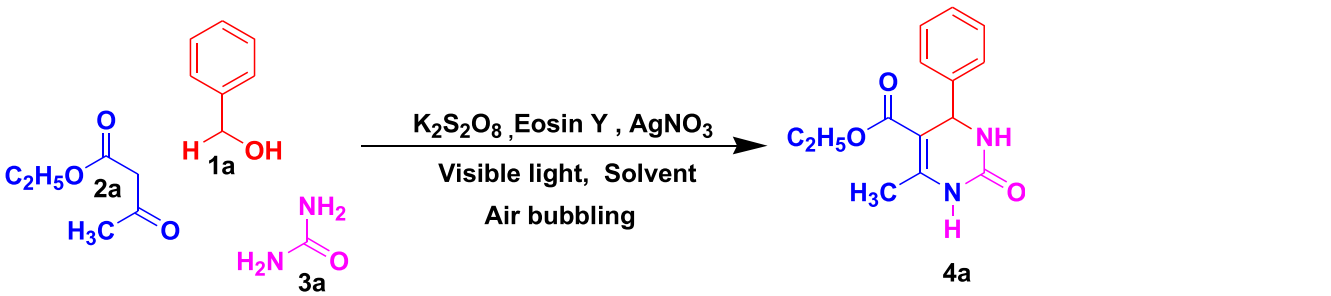
***Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate,* 4c**: Yield 75%; white solid; M.p. 213-215 °C; IR (ATR) ν cm^{-1} 3239 (N-H), 1701 (C=O), 1638 (C=C).^{1}H NMR (400 MHz $CDCl_3$) δ 7.98 (s,1H, NH), 5.81 (s, 1H, NH), 7.27-7.33 (m, 4H, ArH), 5.41 (s, 1H, CH), 4.10 (2H, q, CH_2), 2.38 (3H, s, CH_3), 1.21 (3H, t, CH_3); ^{13}C NMR (75MHz, $CDCl_3$) δ 165.4, 153.0, 146.3, 142.1, 133.7, 128.9, 128.0,101.1, 60.2, 55.17, 18.7; MS *m/z* 296 (M+2); Anal. Calc. for $C_{14}H_{15}ClN_2O_3$: C, 57.05; H, 5.13; N, 9.50; found: C, 57.04; H, 5.18; N, 9.42.

***Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate,* 4d**: Yield 73%; white solid; M.p. 180-181 °C; IR (ATR) ν cm^{-1} 3225 (N-H), 1706 (C=O), 1635 (C=C).^{1}H NMR (400 MHz DMSO-d_6) δ 9.30 (s,1H, NH), 7.72 (s, 1H, NH), 7.39 (m, 4H, ArH), 5.12 (s, 1H, CH), 3.59 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); ^{13}C NMR (75MHz, DMSO-d_6) δ 165.3, 152.8, 149.5, 132.8, 132.3, 129.5, 128.4, 128.0, 127.7, 98.9, 51.5, 51.4, 18.7; MS *m/z* 282 (M+2); Anal. Calc. for $C_{13}H_{13}ClN_2O_3$: C, 55.62; H, 4.67; N, 9.98; found: C, 55.64; H, 4.71; N, 9.94.

***Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate,* 4e:** Yield 85%; light brown solid; M.p. 205-206 °C; IR (ATR) ν cm^{-1} 3227 (N-H), 1705 (C=O), 1643 (C=C).^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H, NH), 8.30 (s, 1H, NH), 7.30 (m, 2H, ArH), 6.79 (m, 2H, ArH), 5.25 (s, 1H, CH), 3.95 (2H, q, J = 16.0, 8.0 Hz, CH_2), 3.84 (s, 3H, Ar-OCH_3), 2.30 (3H, s, CH_3), 1.09 (3H, t, J = 8.0 Hz, CH_3). ^{13}C NMR (75MHz, DMSO-d_6) δ 165.6, 160.5, 153.8, 134.5, 127.9, 113.8, 106.6, 55.8, 52.5, 52.9, 19.3; MS *m/z*291 (M+1); Anal. Calc. for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65; found: C, C, 62.08; H, 6.28; N, 9.60.

***Methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate,* 4f:** Yield 82%; light brown solid; M.p. 187-188 °C; IR (ATR) ν cm^{-1} 3226 (N-H), 1708 (C=O), 1653 (C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H, NH), 8.57 (s, 1H, NH), 7.36 (m, 2H, ArH), 6.83 (m, 2H, ArH), 5.28 (s, 1H, CH), 3.83 (s, 3H, Ar-OCH_3), 3.45 (s, 3H, OCH_3), 2.30 (s, 3H, CH_3). ^{13}C NMR (75MHz, DMSO-d_6) δ 166.0, 160.8, 154.2, 134.8, 127.4, 113.2, 106.5, 56.5, 51.8, 51.2, 19.9; MS *m/z* 277 (M+1); Anal. Calc.

Table 1. Optimization of reaction conditions.



Entry	Eosin Y (mole %)	$K_2S_2O_8$ (eq.)	$AgNO_3$ (mole %)	Solvent	Time (h)	Yield (%)[b]
1	-	1	-	CH_3CN/H_2O	48	0[c]
2	-	1	1	CH_3CN/H_2O	48	0
3	-	1	1	CH_3CN/H_2O	48	0[d]
4	-	1	1	CH_3CN/H_2O	48	Trace
5	1	1	1	CH_3CN/H_2O	48	45
6	2	1	1	CH_3CN/H_2O	48	46
7	1	-	1	CH_3CN/H_2O	48	30
8	1	2	1	CH_3CN/H_2O	48	35
9	1	1	1.5	CH_3CN/H_2O	48	75
10	1	1	2	CH_3CN/H_2O	40	88
11	1	1	3	CH_3CN/H_2O	40	85
12	1	1	2	DMSO	40	Trace
13	1	1	2	EtOH	40	Trace
14	1	1	2	H_2O	40	0
15	1	1	2	Chloroform	40	0
16	1	1	2	CH_3CN	40	25
17	1 (RhodamineB)	1	2	CH_3CN/H_2O	48	Trace
18	1 (Methylene Blue)	1	2	CH_3CN/H_2O	48	Trace

[a]All reaction were carried out with benzyl alcohol (1 eq.), ethyl acetoacetate (1 eq.) and urea (1.2 eq.) in presence of solvents. [b]yield of isolated product.[c]Reaction performed in dark. [d]silver acetate and TiO_2 used instead of $AgNO_3$. [e]All the reactions were performed in air bubbling. [f]The white LED lamp is used as the source of visible light.

for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14; found: C, 60.90; H, 5.81; N, 10.10.

Ethyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4g:** Yield 78%; light brown solid; M.p. 209-210 °C; IR (ATR) ν cm^{-1} 3241 (N-H), 1700 (C=O), 1641 (C=C).^{1}H NMR (400 MHz, DMSO-d_6,) δ 10.36 (s, 1H, NH), 8.47 (s, 1H, NH), 7.20 (m, 2H, ArH), 6.72 (m, 2H, ArH), 5.31 (s, 1H, CH), 3.91 (2H, q, J = 16.0, 8.0 Hz, CH_2), 2.32 (3H, s, CH_3), 2.21 (s, 3H, Ar-CH_3), 1.11 (3H, t, J = 8.0 Hz, CH_3); ^{13}C NMR (75MHz, DMSO-d_6) δ 165.2, 152.7, 151.1, 139.9, 134.7, 129.9, 128.5, 107.7, 53.9, 51.7, 21.0, 19.1; MS *m/z*275 (M+1); Anal. Calc. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21; found: C, 65.70; H, 6.66; N, 10.19.

Methyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate **4h:** Yield 80%; light brown solid; M.p. 214-215 °C; IR (ATR) ν cm^{-1} 3245 (N-H), 1703 (C=O), 1632 (C=C).^{1}H NMR (400 MHz, DMSO-d_6,) δ 10.50 (s, 1H, NH), 8.35 (s, 1H, NH), 7.01 (m, 4H, ArH), 5.20 (s, 1H, CH), 3.54 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 2.24 (s, 3H, Ar-CH_3); ^{13}C NMR (75MHz, DMSO-d_6) δ 165.3, 152.2, 151.0, 139.6, 134.0, 129.2, 128.4, 107.0, 53.3, 51.5, 21.7, 19.5; MS *m/z* 261 (M+1); Anal. Calc. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; found: C, 64.53; H, 6.23; N, 10.68.

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, **4i**: Yield 82%; white solid; M.p. 230-232 °C; IR (ATR) ν cm^{-1} 3229 (N-H), 1706 (C=O), 1639 (C=C).^{1}H NMR (400 MHz DMSO-d_6) δ 9.53 (s,1H, NH), 7.84 (s, 1H, NH), 7.13 (m, 2H, ArH), 6.79 (m, 2H, ArH), 5.10 (s, 1H, CH), 3.87 (2H, q, J = 16.0, 8.0 Hz, CH_2), 2.28 (3H, s, CH_3), 1.07 (3H, t, J = 8.0 Hz, CH_3); ^{13}C NMR (75MHz, DMSO-d_6) δ 165.1, 152.7, 149.8, 132.4, 132.8, 129.7,

128.1, 128.0, 127.7, 98.7, 51.7, 51.4, 18.9; MS *m/z*277 (M+1); Anal. Calc. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14; found: C, 60.88; H, 5.94; N, 10.08.

Methyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, **4j**: Yield 80%; white solid; M.p. 240-242 °C; IR (ATR) ν cm^{-1} 3231 (N-H), 1704 (C=O), 1636 (C=C).^{1}H NMR (400 MHz DMSO-d_6) δ 9.43 (s,1H, NH), 7.77 (s, 1H, NH), 7.00 (m, 4H, ArH), 5.08 (s, 1H, CH), 3.60 (s, 3H, OCH_3), 2.27 (s, 3H, CH_3); ^{13}C NMR (75MHz, DMSO-d_6) δ 166.5, 152.9, 149.8, 132.5, 132.4, 129.7, 128.9, 128.4, 127.8, 98.7, 51.7, 51.6, 18.6; MS *m/z*263 (M+1); Anal. Calc. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; found: C, 59.55; H, 5.47; N, 10.60.

Ethyl 6-methyl-2-oxo-4-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate, **4k**: Yield 5%; White solid; M.p. 154-156 °C IR (ATR) ν cm^{-1} 3246 (N-H), 1708 (C=O), 1632 (C=C).^{1}HNMR (400 MHz, $CDCl_3$) δ7.65 (1H, s, NH), 5.60 (1H, s, NH), 4.25 (1H, t, CH), 4.11 (2H, q, CH_2), 2.22 (3H, s, CH_3), 1.64 (4H, m, CH_2-CH_2), 1.21 (t, 3H, -CH_3), 0.85 (t, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ165.9, 154.2, 146.5, 101.7, 59.9, 51.4, 39.1, 18.6, 17.6, 14.3.MS *m/z*227 (M+1); Anal. Calc. for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38; found: C, 58.43; H, 8.14; N, 12.31.

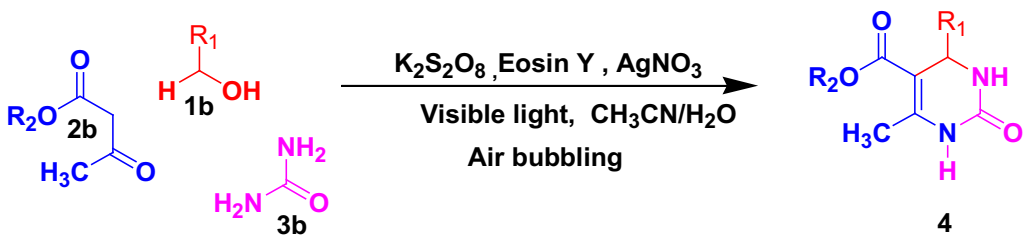
Ethyl 4-ethynyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, **4l**: Yield 22%; White solid; IR (ATR) ν cm^{-1} 3247 (N-H), 1705 (C=O), 1635 (C=C).^{1}HNMR (400 MHz, DMSO-d_6) δ 9.30 (1H, s, NH), 7.69 (1H, s, NH), 5.03 (1H, s, CH), 3.90 (2H, q, *J* = 16.0, 8.0 Hz, CH_2), 3.16 (1H, s, CH), 2.27 (3H, s, CH_3), 1.25 (t, *3*H, -CH_3); ^{13}C NMR (75 MHz, DMSO-d6) δ 167.1, 150.4, 147.9, 106.5, 81.1, 72.9, 65.7, 45.2, 17.4, 15.1. MS *m/z*209 (M+1); Anal. Calc. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45; found: C, 57.66; H, 5.85; N, 13.39.

Ethyl 4-(3-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, **4m**: Yield 72%; yellow solid; M.p. 228-230 °C; IR (ATR) ν cm^{-1} 3333 (N-H), 1707 (C=O), 1621(C=C).^{1}H NMR (400 MHz DMSO-d_6) δ9.38 (s,1H, NH), 8.16 (s, 1H, NH), 7.6-8.10 (m, 4H, ArH), 5.31 (s, 1H, CH), 4.0 (2H, q, CH_2), 2.28 (3H, s, CH_3), 1.11 (3H, t, CH_3); ^{13}C NMR (75MHz, DMSO -d_6) δ165.5, 152.2, 149.9, 148.2, 147.4133.4, 130.7, 122.8, 121.4,98.8, 59.8, 54.0, 18.3, 14.4.

3. Results and Discussion

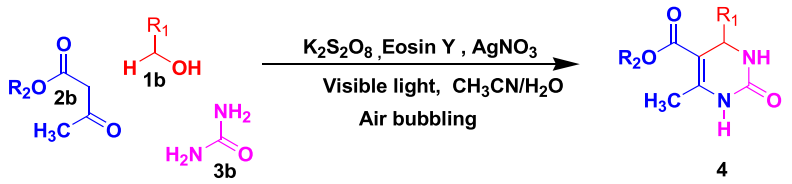
The exploration was started by performing the reaction of benzyl alcohol (**1a**), ethyl acetoacetate (**2a**), urea (**3a**) and $K_2S_2O_8$ (1 eq.) in acetonitrile/water (1:1) mixture under an open atmosphere and in a dark place at room temperature. The entire substrate was unreacted (Table 1, entry 1) and did not proceed at all even after 48 h. The above testing reaction was also performed at an elevated temperature of 50 °C but could not enhance the result of the reaction. The above test reaction was further studied in the presence of silver nitrate which does not afford any product (Table 1, entry 2). Silver nitrate was replaced with silver acetate and TiO_2 but the formation of the product may not be realized (Table 1, entry 3). Following, we examined a similar investigation in visible light (source: white LED bulb), which enabled the formation of traces of the final product on spending 48 h with **1a** (Table 1, entry 4). Besides, a similar model reaction was conducted using Eosin Y as photocatalyst (1 mol%), which provided the synthesis of desired 3,4-DHPM **4a** was obtained in 48 h with 45% yield under photoreaction (Table 1, entry 5). The characterization of **4a** was furnished by ^{1}H NMR, ^{13}C NMR, Mass-Spectrum and IR spectral studies, and found to be matched identically with the previously reported compounds.

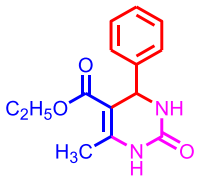
The above outcome was extremely encouraging, for further optimization of the reaction to get an elevated yield of required product **4a**. Subsequently, the template reaction was executed by varying amounts of photocatalyst Eosin Y, which does not improve the yield of the wanted product **4a** (Table 1, entry 6). We used an organic dye Eosin Y as a photo-catalyst to initiate the reaction, which leads to the dehydrogenation of alcohol into desired carbonyl compound.[53]



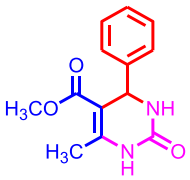
Scheme 1. Synthesis of various derivatives of 3,4-dihydropyrimidin-2(1H)-ones.

Table 2. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPM) (Scheme 1)[a].

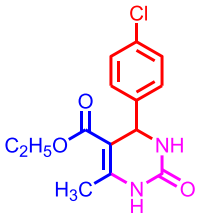




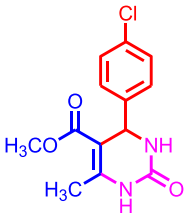
(**4a**, 88%[b])[47, 61-64]



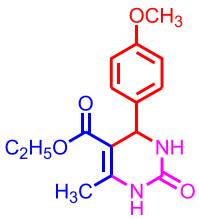
(**4b**, 80%)[47, 65]



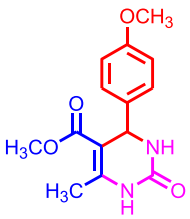
(**4c**, 75%)[61-64]



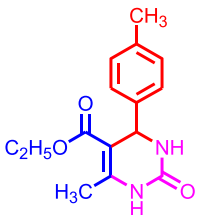
(**4d**, 73%)[47, 61]



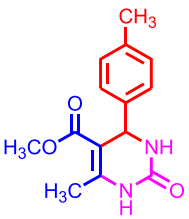
(**4e**, 85%)[62-64]



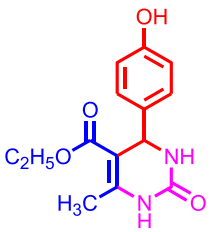
(**4f**, 82%)[47, 61, 65]



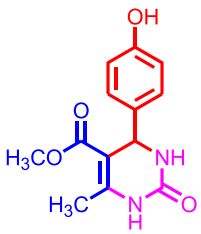
(**4g**, 78%)[61, 62, 64]



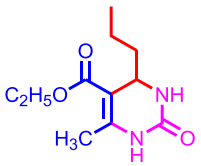
(**4h**, 80%)[64]



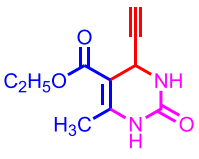
(**4i**, 82%)[63, 64, 66]



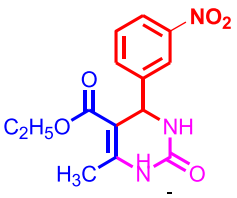
(**4j**, 80%)[63, 65]



(**4k**, 5%)[66]

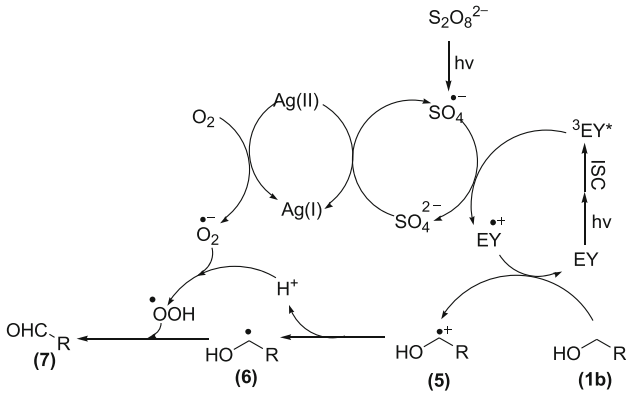


(**4l**, 22%)



(**4m**,72%)[61 63]

[a]For reaction condition see supporting information. [b]yield of isolated product.



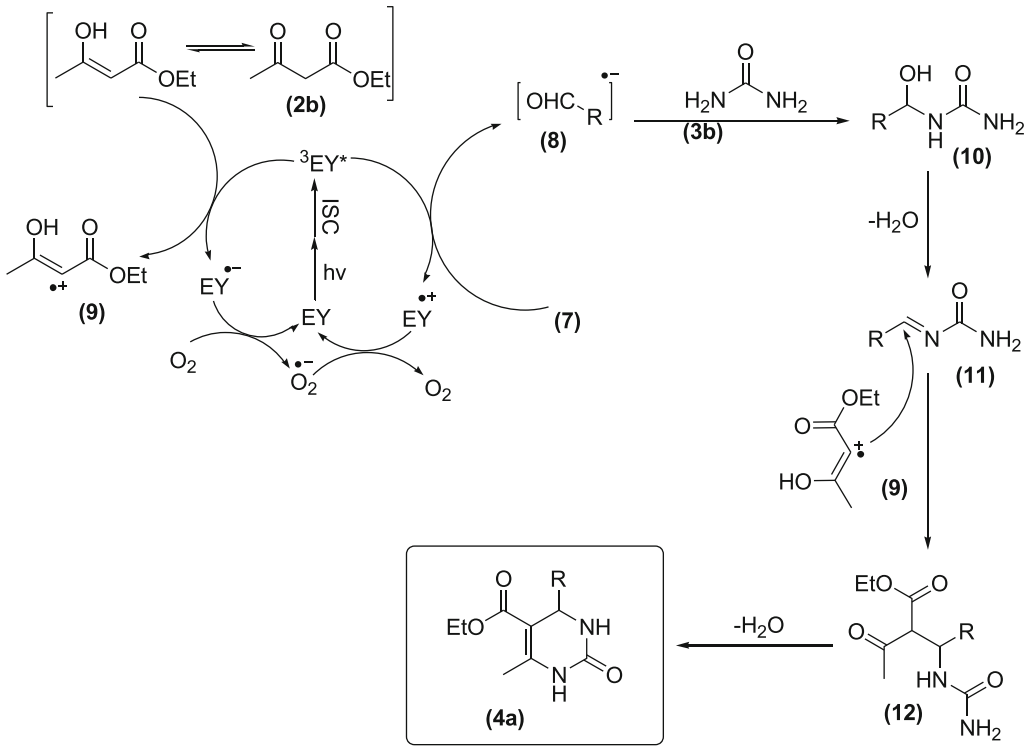
Scheme 2. Proposed mechanism step-I in-situ oxidation of primary alcohol.

Eosin Y worked as photocatalyst in the reaction. Then, we performed the reaction with varying amounts of $K_2S_2O_8$ which revealed a decline in the yield of the desired product **4a** (Table 1, entries 7 & 8). Potassium persulphate ($K_2S_2O_8$) used in this protocol is not a photocatalyst, but photolysis of $S_2O_8^{2-}$ to generate sulphate radical anion ($SO_4^{\bullet-}$), which acts as a strong oxidizing agent in an aqueous system.[54] The activity of $K_2S_2O_8$ also depends on the amount of $K_2S_2O_8$ used in the reaction. The reaction with a high amount of $K_2S_2O_8$ reduced the desired yield by over-oxidation of alcohol into a carboxylic acid.

To improve the effectiveness of this reaction, we examined the altering amount of $AgNO_3$ commencing 1.0 to 3.0 mol % (Table 1, entries 9-11). It was detected that 2.0 mol % was found as the best possible protocol, which facilitated the yield of the avidity product **4a** to 88% in 40 h (Table 1, entry 10). Further increase in the quantity of silver nitrate could not get better yield (Table 1, entry 11). Silver nitrate helps in increasing the oxidation in reaction.[56] The role of silver is to activate the molecular oxygen by adsorbing on their surface. It also enhanced the efficiency of eosin Y under the aqueous phase.[57–59]

Afterwards, we carefully evaluated the model reaction with different solvent systems such as DMSO, ethanol, H_2O, chloroform, CH_3CN and found that the CH_3CN/H_2O mixture was the most suitable solvent for this reaction as it increases the yield to 88% (Table 1, entries 12-16). Acetonitrile is a good solvent for photo-oxidation.[60] It does not only possess strong polarity but also have a good dissolvent capacity of oxygen. To find out the impact of other photocatalysts, we examined the model reaction with different organic photocatalysts (Table 1, entries 17 & 18), which did not enhance the yield of the product.

Hence, the evaluated eosin Y (1.0 mol %), $K_2S_2O_8$ (1.0 equiv.), $AgNO_3$ (2.0 mol %) were the best choices



Scheme 3. Proposed mechanism step-II formation of 3,4-DHPMs.

with visible light irradiation at room temperature under an oxygen atmosphere.

With the optimized reaction conditions in hand, the substrate coverage of this photocatalytic oxidation system was explored (Scheme 1). Based on our initial efforts to obtain the high efficiency of photocatalytic conversion into the desired product, different primary aromatic and aliphatic alcohols were evaluated (Table 2). All the substituted benzyl alcohols with electron-donating and electron-withdrawing groups were easily utilized in this cascade approach in getting substituted 3,4-DHPMs in high yields (Table 2, compound **4a-4j**, **4m**). Electron-releasing substituents at *para,* position on the phenyl group were found to be efficient in accelerating the reaction, while electron-withdrawing groups substituents at *meta* and *para* position on phenyl group needed longer reaction times for their optimized conversions. Compared with the primary aromatic alcohols, primary aliphatic alcohols are found to be very less reactive.

We evaluated various derivatives by using different types of primary alcohol (Benzyl alcohol, 4-chlorobenzyl alcohol, propargyl alcohol, methanol and butanol etc.) and α-ketoester (ethyl acetoacetate and methyl acetoacetate) in the reaction (Scheme 1). We used benzyl alcohol with ethyl acetoacetate and urea under similar reaction conditions, which gave 88% yield (**4a**) and reaction accomplished in 48 h (entry 1, Table 2).

Further benzyl alcohol treated with methyl acetoacetate and reaction conditions remained same which obtained 80% yield of the product (**4b**) in 48 h (entry 2, Table 2). We also found that both methyl acetoacetate and ethyl acetoacetate under similar optimized conditions gave good to excellent yields between 73-88% with aromatic alcohols (Table 2, entries **4c-4j**, **4m**). Further, we also treated aliphatic alcohols under similar reaction condition with ethyl acetoacetate that yielded in poor (Table 2, entries **4k-4l**) even after an extended duration of time up to 72 h.

A plausible mechanism has been proposed for the in-situ oxidation of alcohol and the formation of 3,4-DHPMs which is summarized in Scheme 2. The sulphate radical anion ($SO_4^{\cdot\,-}$) acts as an oxidizing agent under photo-irradiative conditions.[54,67] It accepts one electron from ^{3}EY* forming sulphate anion (SO_4^{2-}) and converts it into radical cation ($EY^{+\cdot}$) Subsequently, $EY^{+\bullet}$ accepts an electron from benzyl alcohol (**1b**) to regenerate EY and produce benzyl alcohol radical cation (**5**, Scheme 2). Further, benzyl alcohol radical (**6**) is formed due to the removal of a proton from **5**.[53] The Ag(I) activates the molecular oxygen (O_2) and transforms it into radical anion ($O_2^{-\cdot}$)[58] that further accepts proton form superoxide radical ($^{\cdot}$OOH). The $^{\cdot}$OOH transforms **6** into carbonyl compound (**7**) (Scheme 2).[17]

The eosin Y gets involve in both the reductive and oxidative quenching cycles.[68,69] The eosin Y activates both **7** and β-keto ester (**2b**) by donating and accepting one electron respectively. The activated aldehyde (**8**) further interacts with urea to form imine (**11**) and releases a molecule of H_2O. The activated β-keto ester (**9**) attacks on imine (**11**) to form 3,4-DHPM by releasing water molecule (Scheme 3).[47,70]

4. Conclusions

We have disclosed a robust, efficient, and domino multicomponent cascade novel protocol to design 3,4-dihydropyrimidin-2(1H)-one derivative utilizing Biginelli reaction of primary alcohols using visible-light as green energy source. The key features of the present protocol include the capability to allow an operational simplicity, readily available substrates, straightforward workup, and high yields of the products. The synthetic efficacy and practicality of this Eosin Y based photocatalytic approach can allow in capacitating conventional metal-catalyzed reactions and could be rousing towards functionalization of a broad variety of C-C, and C-N bonds in a sustainable manner.

Supplementary Information (SI)

Supplementary information related to this article is available at www.ias.ac.in/chemsci.

References

1. Zhou Q Q, Zou Y Q, Lu L Q and Xiao W J 2019 Visible-light-induced organic photochemical reactions through energy-transfer pathways *Angew. Chem. Int. Edit.* **58** 1586
2. Schultz D M and Yoon T P 2014 Solar synthesis: prospects in visible light photocatalysis *Science* **343** 6174
3. Prier C K, Rankic D A and MacMillan D W 2013 Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis *Chem. Rev.* **113** 5322
4. Xi Y, Yi H and Lei A 2013 Synthetic applications of photoredox catalysis with visible light *Org. Bio. Chem.* **11** 2387
5. Welin E R, Le C, Arias-Rotondo D M, McCusker J K and MacMillan D W 2017 Photosensitized, energy transfer-mediated organometallic catalysis through electronically excited nickel (II) *Science* **355** 380

6. Kainz Q M, Matier C D, Bartoszewicz A, Zultanski S L, Peters J C and Fu G C 2016 Asymmetric copper-catalyzed CN cross-couplings induced by visible light *Science* **351** 681
7. Lang X, Ma W, Chen C, Ji H and Zhao J 2014 Selective aerobic oxidation mediated by TiO_2 photocatalysis *Acc. Chem. Res.* **47** 355
8. Tsukamoto D, Shiraishi Y, Sugano Y, Ichikawa S, Tanaka S and Hirai T 2012 Gold nanoparticles located at the interface of anatase/rutile TiO_2 particles as active plasmonic photocatalysts for aerobic oxidation *J. Am. Chem. Soc.* **134** 6309
9. Hering T, Slanina T, Hancock A, Wille U and König B 2015 Visible light photooxidation of nitrate: the dawn of a nocturnal radical *Chem. Comm.* **51** 6568
10. Yoon T, Ischay M and Du J 2010 Visible light photocatalysis as a greener approach to photochemical synthesis *Nat. Chem.* **2** 527
11. Zuo Z, Ahneman D T, Chu L, Terrett J A, Doyle A G and MacMillan D W 2014 Merging photoredox with nickel catalysis: coupling of α-carboxyl sp3-carbons with aryl halides *Science* **345** 437
12. Narayanam J M, Tucker J W and Stephenson C R 2009 Electron-transfer photoredox catalysis: development of a tin-free reductive dehalogenation reaction *J. Am. Chem. Soc.* **131** 8756
13. Cuthbertson J D and MacMillan D W 2015 The direct arylation of allylic sp 3 C–H bonds via organic and photoredox catalysis *Nature* **519** 74
14. Hari D P, Schroll P and König B 2012 Metal-free, visible-light-mediated direct C–H arylation of heteroarenes with aryl diazonium salts *J. Am. Chem. Soc.* **134** 2958
15. Ghosh I, Ghosh T, Bardagi J I and König B 2014 Reduction of aryl halides by consecutive visible light-induced electron transfer processes *Science* **346** 725
16. Meng Q Y, Zhong J J, Liu Q, Gao X X, Zhang H H, Lei T, et al. 2013 A cascade cross-coupling hydrogen evolution reaction by visible light catalysis *J. Am. Chem. Soc.* **135** 19052
17. Ji X, Chen Y, Paul B and Vadivel S 2019 Photocatalytic oxidation of aromatic alcohols over silver supported on cobalt oxide nanostructured catalyst *J. All. Comp.* **783** 583
18. Enache D I, Edwards J K, Landon P, Solsona-Espriu B, Carley A F, Herzing A A, et al. 2006 Solvent-free oxidation of primary alcohols to aldehydes using Au-Pd/TiO_2 catalysts *Science* **311** 362
19. Pillai U R and Sahle-Demessie E 2003 Oxidation of alcohols over Fe3+/montmorillonite-K10 using hydrogen peroxide *App. Cat. A Gen.* **245** 103
20. Ding J, Xu W, Wan H, Yuan D, Chen C, Wang L, et al. 2018 Nitrogen vacancy engineered graphitic C3N4-based polymers for photocatalytic oxidation of aromatic alcohols to aldehydes *App. Cat. B Env.* **221** 626
21. Lee J and Lee J C 2018 An efficient oxidation of alcohols by aqueous H_2O_2 with 1, 3-dibromo-5, 5-dimethylhydantoin *Lett. Org. Chem.* **15** 895
22. ten Brink G J, Arends I W and Sheldon R A 2000 Green, catalytic oxidation of alcohols in water *Science* **287** 1636
23. Mori K, Hara T, Mizugaki T, Ebitani K and Kaneda K 2004 Hydroxyapatite-supported palladium nanoclusters: a highly active heterogeneous catalyst for selective oxidation of alcohols by use of molecular oxygen *J. Am. Chem. Soc.* **126** 10657
24. Marko I E, Giles P R, Tsukazaki M, Brown S M and Urch C J 1996 Copper-catalyzed oxidation of alcohols to aldehydes and ketones: an efficient, aerobic alternative *Science* **274** 2044
25. Fu R, Yang Y, Ma X, Sun Y, Li J, Gao H, et al. 2017 An efficient, eco-friendly and sustainable one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones directly from alcohols catalyzed by heteropolyanion-based ionic liquds *Molecules* **22** 1531
26. Dai Y, Ren P, Li Y, Lv D, Shen Y, Li Y, et al. 2019 Solid base $Bi_{24}O_{31}Br_{10}(OH)\delta$ with active lattice oxygen for the efficient photo-oxidation of primary alcohols to aldehydes *Angew. Chem. Int. Edit.* **58** 6265
27. Schilling W, Riemer D, Zhang Y, Hatami N and Das S 2018 Metal-free catalyst for visible-light-induced oxidation of unactivated alcohols using air/oxygen as an oxidant *ACS Cat.* **8** 5425
28. Zhang Y, Schilling W, Riemer D and Das S 2020 Metal-free photocatalysts for the oxidation of non-activated alcohols and the oxygenation of tertiary amines performed in air or oxygen *Nature Prot.* **15** 822
29. Zhang X, Rakesh K, Ravindar L and Qin H L 2018 Visible-light initiated aerobic oxidations: a critical review *Green Chem.* **20** 4790
30. Yu X, Wang L and Cohen S M 2017 Photocatalytic metal–organic frameworks for organic transformations *CrystEngComm* **19** 4126
31. Chen B, Wang L and Gao S 2015 Recent advances in aerobic oxidation of alcohols and amines to imines *ACS Cat.* **5** 5851
32. Fan W, Yang Q, Xu F and Li P 2014 A visible-light-promoted aerobic metal-free C-3 thiocyanation of indoles *J. Org. Chem.* **79** 10588
33. Mitra S, Ghosh M, Mishra S and Hajra A 2015 Metal-free thiocyanation of imidazoheterocycles through visible light photoredox catalysis *J. Org. Chem.* **80** 8275
34. Yadav A K and Yadav L D S 2015 Visible-light-mediated difunctionalization of styrenes: an unprecedented approach to 5-aryl-2-imino-1, 3-oxathiolanes *Green Chem.* **17** 3515
35. Cui Y, Li C and Bao M 2019 Deep eutectic solvents (DESs) as powerful and recyclable catalysts and solvents for the synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones/thiones *Green Pro. Syn.* **8** 568
36. Mayer T U, Kapoor T M, Haggarty S J, King R W, Schreiber S L and Mitchison T J 1999 Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen *Science* **286** 971
37. Russowsky D, Canto R M F, Sanches S A, D'Oca M G, De F Â, Pilli R A, et al. 2006 Synthesis and differential antiproliferative activity of Biginelli compounds against cancer cell lines: monastrol, oxo-monastrol and oxygenated analogues *Bio. Chem.* **34** 173
38. Chen X H, Xu X Y, Liu H, Cun L F and Gong L Z 2006 Highly enantioselective organocatalytic Biginelli reaction *J. Am. Chem. Soc.* **128** 14802

39. Rahman M, Majee A and Hajra A 2010 Microwave-assisted Brønsted acidic ionic liquid-promoted one-pot synthesis of heterobicyclic dihydropyrimidinones by a three-component coupling of cyclopentanone, aldehydes, and urea *J. Het. Chem.* **47** 1230
40. Shen Z L, Xu X P and Ji S J 2010 Brønsted base-catalyzed one-pot three-component Biginelli-type reaction: an efficient synthesis of 4, 5, 6-triaryl-3, 4-dihydropyrimidin-2 (1 H)-one and mechanistic study *J. Org. Chem.* **75** 1162
41. Moosavifar M 2012 An appropriate one-pot synthesis of dihydropyrimidinones catalyzed by heteropoly acid supported on zeolite: an efficient and reusable catalyst for the Biginelli reaction *Comp. Ren. Chim.* **15** 444
42. Ramos L M, Ponce L T A Y, dos Santos M R, de Oliveira H C, Gomes A F, Gozzo F C, et al. 2012 Mechanistic studies on lewis acid catalyzed biginelli reactions in ionic liquids: evidence for the reactive intermediates and the role of the reagents *J. Org. Chem.* **77** 10184
43. Fu R, Yang Y, Lai W, Ma Y, Chen Z, Zhou J, et al. 2015 Efficient and green microwave-assisted multicomponent Biginelli reaction for the synthesis of dihydropyrimidinones catalyzed by heteropolyanion-based ionic liquids under solvent-free conditions *Synth. Comm.* **45** 467
44. Mansoor S S, Shafi S S and Ahmed S Z 2016 An efficient one-pot multicomponent synthesis of 3, 4-dihydropyrimidine-2-(1H)-ones/thiones/imines via a Lewis base catalyzed Biginelli-type reaction under solvent-free conditions *Arab. J. Chem.* **9** S846
45. Mohammadi B and Behbahani F K 2018 Recent developments in the synthesis and applications of dihydropyrimidin-2 (1H)-ones and thiones *Mol. Div.* **22** 405
46. Safaei G J, Tavazo M and Mahdavinia G H 2018 Ultrasound promoted one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones/thiones using dendrimer-attached phosphotungstic acid nanoparticles immobilized on nanosilica *Ultra Sono.* **40** 230
47. Harsh S, Kumar S, Sharma R, Kumar Y and Kumar R 2020 Chlorophyll triggered one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones via photo induced electron transfer reaction *Arab. J. Chem.* **13** 4720
48. Wang J, Li Y, Peng Y and Song G 2014 Silver nitrate-catalyzed selective air oxidation of benzylic and allylic alcohols to corresponding aldehydes or ketones *J. Chin. Chem. Soc.* **61** 517
49. Ghosh S, Saikh F, Das J and Pramanik A K 2013 Hantzsch 1, 4-dihydropyridine synthesis in aqueous ethanol by visible light *Tetrahedron Lett.* **54** 58
50. Choudhary V R, Dhar A, Jana P, Jha R and Uphade B S 2005 A Green process for chlorine-free benzaldehyde from the solvent-free oxidation of benzyl alcohol with molecular oxygen over a supported nano-size gold catalyst *Green Chem.* **7** 768
51. Nikitas N F, Tzaras D I, Triandafillidi I and Kokotos C G 2020 Photochemical oxidation of benzylic primary and secondary alcohols utilizing air as the oxidant *Green Chem.* **22** 471
52. Prebil R, Stavber G and Stavber S 2014 Aerobic oxidation of alcohols by using a completely metal-free catalytic system *Eur. J. Org. Chem.* **2014** 395
53. Yang X J, Zheng Y W, Zheng L Q, Wu L Z, Tung C H and Chen B 2019 Visible light-catalytic dehydrogenation of benzylic alcohols to carbonyl compounds by using an eosin Y and nickel–thiolate complex dual catalyst system *Green Chem.* **21** 1401
54. Ghosh P P, Mukherjee P and Das A R 2013 Triton-X-100 catalyzed synthesis of 1, 4-dihydropyridines and their aromatization to pyridines and a new one pot synthesis of pyridines using visible light in aqueous media *RSC Adv.* **3** 8220
55. Srivastava V, Singh P K and Singh P P 2019 Eosin Y catalysed visible-light mediated aerobic oxidation of tertiary amines *Tetrahedron Lett.* **60** 151041
56. Jeena V and Robinson R S 2012 Convenient photooxidation of alcohols using dye sensitised zinc oxide in combination with silver nitrate and TEMPO *Chem. Comm.* **48** 299
57. Alwan D B 2016 Effect of solvent type and annealing temperature on efficiency for Eosin-y dye sensitized solar cells *Ir. J. Sci.* **57(4A)** 2429
58. Nagaraju P, Balaraju M, Reddy K M, Prasad P S and Lingaiah N 2008 Selective oxidation of allylic alcohols catalyzed by silver exchanged molybdovanado phosphoric acid catalyst in the presence of molecular oxygen *Cat. Comm.* **9** 1389
59. Beier M J, Hansen T W and Grunwaldt J D 2009 Selective liquid-phase oxidation of alcohols catalyzed by a silver-based catalyst promoted by the presence of ceria *J. Cat.* **266** 320
60. Reimers J R and Hall L E 1999 The solvation of acetonitrile *J. Am. Chem. Soc.* **121** 3730
61. Fu N Y, Yuan Y F, Cao Z, Wang S W, Wang J T and Peppe C 2002 Indium (III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction *Tetrahedron* **58** 4801
62. Heravi M M, Derikvand F and Bamoharram F F 2005 A catalytic method for synthesis of Biginelli-type 3, 4-dihydropyrimidin-2 (1H)-one using 12-tungstophosphoric acid *J. Mol. Cat. A Chem.* **242** 173
63. Mohamadpour F and Lashkari M 2018 Three-component reaction of β-keto esters, aromatic aldehydes and urea/thiourea promoted by caffeine, a green and natural, biodegradable catalyst for eco-safe Biginelli synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones/thiones derivatives under solvent-free conditions *J. Serb. Chem. Soc.* **83** 673
64. Yao B J, Wu W X, Ding L G and Dong Y B 2021 Sulfonic acid and ionic liquid functionalized covalent organic framework for efficient catalysis of the Biginelli reaction *J. Org. Chem.* **86** 3024
65. Karimi J Z and Moaddeli M S 2012 Synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones and their corresponding 2 (1H) thiones using trichloroacetic acid as a catalyst under solvent-free conditions *ISRN Org. Chem.* **2012** 474626
66. Tu S, Fang F, Zhu S, Li T, Zhang X and Zhuang Q 2004 A new Biginelli reaction procedure using potassium hydrogen sulfate as the promoter for an efficient

synthesis of 3, 4-dihydropyrimidin-2 (1H)-one *J. Het. Chem.* **41** 253
67. Hori H, Yamamoto A, Hayakawa E, Taniyasu S, Yamashita N, Kutsuna S, et al. 2005 Efficient decomposition of environmentally persistent perfluorocarboxylic acids by use of persulfate as a photochemical oxidant *Environ. Sci. Technol.* **39** 2383
68. Figg C A, Hickman J D, Scheutz G M, Shanmugam S, Carmean R N, Tucker B S, et al. 2018 Color-coding visible light polymerizations to elucidate the activation of trithiocarbonates using Eosin Y *Macromolecules* **51** 1370
69. Meyer A U, Straková K, Slanina T and König B 2016 Eosin Y (EY) photoredox-catalyzed sulfonylation of alkenes: scope and mechanism *Chem. A Eur. J.* **22** 8694
70. Devthade V, Kamble G, Ghugal S G, Chikhalia K H and Umare S S 2018 Visible light-driven Biginelli reaction over mesoporous g-C3N4 Lewis-base catalyst *Chem. Select* **3** 4009