REGULAR ARTICLE

Squaric acid: an impressive organocatalyst for the synthesis of biologically relevant 2,3-dihydro-1H-perimidines in water

SUSHIL KHOPKAR and GANAPATI SHANKARLING*

Dyestuff Technology Department, Institute of Chemical Technology, N. P. Marg, Matunga,
Mumbai 400 019, Maharashtra, India
E-mail: gsshankarling@gmail.com

Abstract. Squaric acid, a green, metal-free and eco-friendly organocatalyst, has been exploited for the synthesis of biologically interesting 2,3-dihydro-1H-perimidines. The reaction was performed using water as a green reaction medium and the organocatalyst can be easily recovered and reused up to four consecutive cycles without much decrease in catalytic activity. Several advantages of the present methodology are low catalyst loading, excellent catalytic performance, easy catalyst handling, mild reaction conditions, operational simplicity, ease of product isolation, avoidance of column chromatographic separation, a higher yield of the desired product in short reaction time, high atom economy and synthesis of benzophenone based perimidine.

Keywords. Squaric acid; organocatalyst; 2,3-dihydro-1H-perimidines; green chemistry.

1. Introduction

Perimidine derivatives are one of the most important class of nitrogen-containing heterocycles which have diverse biological and pharmacological properties comprising anti-bacterial, anti-microbial, anti-cancer, anti-inflammatory activities.[1–5] The interest in perimidines originates from the presence of this heterocyclic system in various biologically and pharmacologically active compounds. Due to strong electron-donating character of 2,3-Dihydro-1H-perimidine derivatives, they have been used as intermediates in the synthesis of symmetrical squarylium dyes to shift the absorption at NIR region.[6,7] In addition, these compounds have also been used as antioxidant stabilizers,[8] photochromic compounds,[9] catalysts,[10] ligand scaffolds[11] and stoppers for supra-molecule.[12] The structures of a few perimidines with different applications are depicted in Figure 1.

The reaction of 1,8-diamino naphthalene and acetophenones have been accelerated by various protonic acids and metal catalysts such as BiCl[3,13] RuCl[3,14] Yb (OTf)[3,15] HBOB,[16] Amberlyst-[15,17] CMK-5-SO$_3$H[18] and MNPs-TBSA.[19] However, the time-consuming procedures for catalyst preparation, moisture sensitivity

of catalyst, various side products formation resulting in low yield of desired product, longer reaction time, laborious work up methods, non-recoverability of catalyst, need of chromatographic separation and high environmental factor limits the applicability of these reactions. As every method has merits and demerits, there is a need for improvement of existing methods.

Recently, organocatalysts have emerged as powerful catalysts in synthetic chemistry owing to its distinctive properties such as non-toxicity, selectivity, reusability, moisture and air insensitivity and operational simplicity.[20–27] Squaric acid (quadratic acid), a green organocatalyst, is a dibasic organic acid which has a thermal decomposition temperature of 245 °C at ambient pressure.[28] Squaric acid is soluble in water and insoluble in most of the common organic solvents. The high acidity of squaric acid in water ($Pk_a = 1.5$, 3.4) is attributed to resonance stabilization of the anion.[29] Therefore, squaric acid has been explored as an acidic catalyst in various organic transformations such as N-substituted pyrroles synthesis,[30] bis (indolyl) methanes synthesis,[31] Mannich reaction[32] and Michael addition.[33]

The third principle of green chemistry states that solvents should satisfy the different criteria such as

Antitumor agent

Antimicrobial agent

Squarylium dye

Photochromic compound
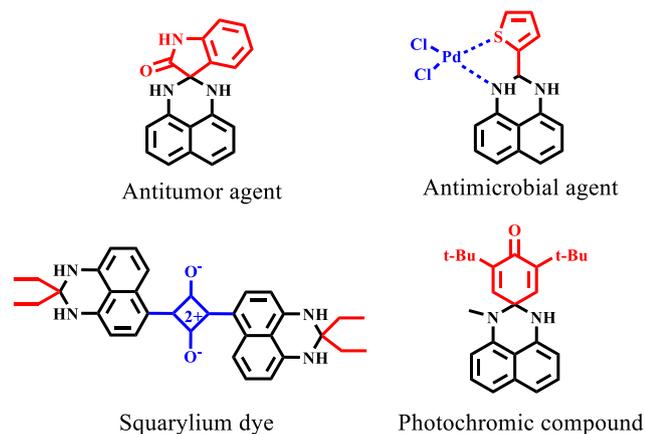
Figure 1. Representative examples containing 2,3-dihydro-1H-perimidines moiety.

non-toxicity, biodegradability, inflammability and renewability. Development of water as a green solvent instead of organic solvents in organic synthesis led to remarkable progress in recent years as water is more abundant, low cost, sustainable and environmentally friendly solvent. Reactions which uses water as a solvent has gained much attention, as these reactions follow one of the principles of green chemistry, reduce the environmental factor (E-factor) and simplifies the isolation and purification processes.[34–36] Moreover, water enhances the reactivity and selectivity of organic reactions due to solvent polarity, hydrogen bonding, and hydrophobic packing.[37,38]

In continuation of our research to explore eco-efficient transformations, in the present study, we wish to report for the greener synthesis of 2,3-dihydro-1H-perimidines from 1,8-diamino naphthalene and acetophenones using squaric acid organocatalyst and water as a green solvent. This is the first report on the synthesis of 2,3-dihydro-1H-perimidines in water.

2. Experimental

2.1 *Materials and instrumentation*

Squaric acid, ketones and 1,8-naphthalene diammine were purchased from Sigma Aldrich. [1]H (500 MHz) and ^{13}C (101 MHz) NMR spectra of synthesized compounds were recorded on Agilent spectrophotometer in CDCl$_3$ or DMSO-d6 as a solvent. FT-IR spectra were recorded on Bruker alpha spectrometer using KBr pellets.

2.2 *General procedure for the synthesis of 2, 3-dihydro-1H-perimidine derivatives (3a-o)*

The mixture of 1, 8-diamino naphthalene **1** (1 mmol), ketones **2a-o** (1 mmol) and squaric acid (10 mol %) was heated in

water (5 mL) at 80 °C for the appropriate time shown in Table 2. The reaction mixture was then cooled to room temperature and pure products were afforded by filtration of the reaction mixture with multiple washing of water. Most of the synthesized compounds (**3a-o**) being well reported were primarily identified by melting points.[13–17] The synthesized compounds were further confirmed by ^{1}H and ^{13}C NMR.

3. Results and Discussion

In order to determine the catalytic activity of squaric acid in the 2,3-dihydro-1H-perimidines synthesis, we initiated our study by taking 1,8-naphthalene diamine (**1**, 1 mmol) and acetophenone (**2g**, 1 mmol) as the model substrates for the synthesis of 2-methyl-2-phenyl-2,3-dihydro-1H-perimidine **3g**.

Initially, we inspected the reaction under solvent-free conditions at 80 °C using model substrates and squaric acid as a catalyst but less yield of product **3g** (24%) was observed even after long reaction time (Table 1, entry 1). Then, the same reaction was repeated in different polar and non-polar solvents for the synthesis of **3g** (Table 1, entries 2-8). After the screening of solvents, water came out as the best solvent which not only gave a higher yield of **3g** (95%) but also higher reaction rate (45 min.) (Table 1, entry 2). This is possible because of the good solubility and high acidity of squaric acid in water. In Ethanol, the reaction gave 70% yield of **3g** in 2 h (Table 1, entry 3). Next, to achieve the maximum yield of **3g**, we standardized the catalyst loading. First, the blank experiment was performed in the absence of catalyst in water (5 mL), but the reaction resulted in a poor yield of product **3g** (12%) even after a long reaction time of 12 h (Table 1, entry 9). When the same reaction was performed in the presence of 10 mol% squaric acid, the desired product **3g** formed in excellent yield (95%) within 45 min (Table 1, entry 13). Further increasing the catalyst loading did not result in any substantial improvement of the yield, but decreasing the catalyst loading (< 10 mol %) reduced the product yield (Table 1, entries 9-12, 14). Further, the study of reaction temperature was explored and 80 °C was the optimum temperature for **3g** formation (Table 1, entry 18). Consequently, the effect of reaction time was also studied and 45 min was the adequate time for **3g** synthesis (Table 1, entry 24). From these screening studies, the optimal reaction conditions for the synthesis of **3g** were **1** (1.0 mmol), **2g** (1.0 mmol), squaric acid (10 mol%), 5.0 mL water, 80 °C, 45 min.

Further, we have explored the substrate scope and generality of this methodology by condensation of several aliphatic, alicyclic and aromatic ketones with

Table 1. Optimization of reaction parameters for the synthesis of 2-methyl-2-phenyl-2, 3-dihydro-1H-perimidine **3g**[a].
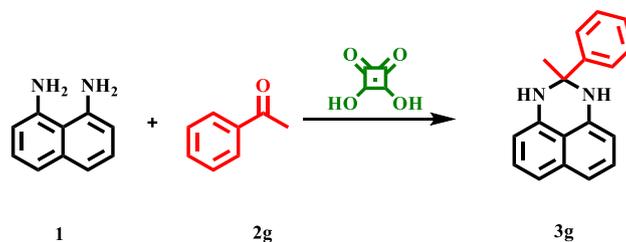
Entry	Solvent	Catalyst loading (mol %)	Temperature (°C)	Time (h)[b]	Yield[c] (%)
Effect of solvent					
1	No solvent	10	80	12	24
2	**Water**	**10**	**80**	**0.45**	**95**
3	Ethanol	10	Reflux	2	70
4	Acetonitrile	10	Reflux	12	16
5	Tetrahydrofuran	10	Reflux	12	28
6	DMF	10	Reflux	12	22
7	Toluene	10	Reflux	12	NR[d]
8	Dichloromethane	10	Reflux	12	NR[d]
Effect of catalyst loading					
9	Water	–	80	12	12[d]
10	Water	2.5	80	4	24
11	Water	5	80	2	50
12	Water	7.5	80	1.15	68
13	**Water**	**10**	**80**	**0.45**	**95**
14	Water	15	80	0.45	95
Effect of temperature					
15	Water	10	RT	12	NR[d]
16	Water	10	50	4	40
17	Water	10	70	2	74
18	**Water**	**10**	**80**	**0.45**	**95**
19	Water	10	100	0.45	95
Effect of time					
20	Water	10	80	10	25
21	Water	10	80	20	48
22	Water	10	80	30	60
23	Water	10	80	40	84
24	**Water**	**10**	**80**	**45**	**95**
25	Water	10	80	50	95

The bold values indicate the best results obtained

[a]Reaction conditions: 1,8-diamino naphthalene **1** (1 mmol), acetophenone **2g** (1 mmol).

[b]The progress of the reaction was monitored by TLC.

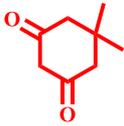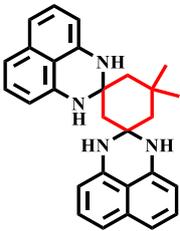[c]Isolated yield.

[d]No reaction.

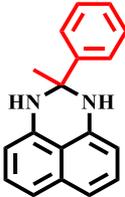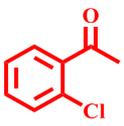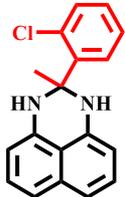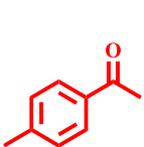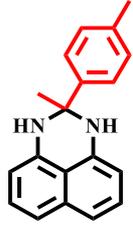1,8-diamino naphthalene (Table 2). With aliphatic and alicyclic ketones, the reactions provided better product yields in less reaction times than with aromatic ketones. The low reactivity of aromatic ketones over aliphatic and alicyclic ketones could be attributed to the steric crowding of the phenyl ring. Thus, the reaction with diethyl ketone (**2b**) completed in 20 min (Table 2, entry 2) while with acetophenone the reaction (**2g**) required 45 min (Table 2, entry 7) for completion. Furthermore, the aromatic ketones containing an electron-deficient group kinetically favored the reaction compared to the electron-rich group. For example, the reaction with 4-nitro acetophenone (**2m**) was found to be completed within 30 min to afford 96% yield of **3m** (Table 2, entry 13), while reaction with 4-methoxy acetophenone (**2k**) required 105 min to furnish 86% of **3k** (Table 2, entry 11). Benzophenone generally gives the poor yield of the

Table 2. Synthesis of different 2, 3-dihydro-1H-perimidines derivatives[a] (**3a-o**).
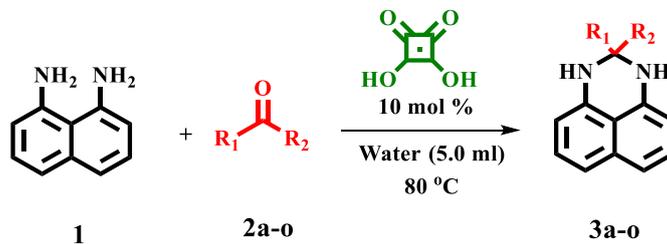
Entry	Ketone	Product[b]	Reaction time[c] (min.)	Yield[d] (%)	Melting point (°C) Reported	Observed
1	**2a**	**3a**	20	91	115–116[13]	116
2	**2b**	**3b**	20	90	96–97[17]	97
3	**2c**	**3c**	20	91	105–107[17]	106
4	**2d**	**3d**	20	94	84–85[17]	84
5	**2e**	**3e**	30	91	110–111[13]	110

Table 2.   continued

6	2f	3f	30	92	226–227[17]	226
7	2g	3g	45	95	136–138[17]	138
8	2h	3h	60	93	129–130[17]	130
9	2i	3i	70	91	157–158[13]	157
10	2j	3j	90	89	118–119[17]	118
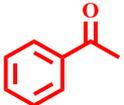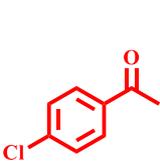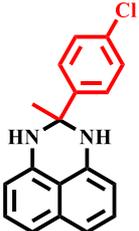
corresponding perimidine using existing protocols.[13–15,17] Interestingly, our protocol gave a 55% yield of **3o** by reaction with benzophenone. The low yield of **3o** can be attributed to steric crowding of two phenyl rings (Table 2, entry 15).

In order to make the protocol economically and environmentally more feasible, we also inspected the reusability of squaric acid. For this purpose, the model reaction of 1,8-diamino naphthalene **1** and acetophenone **2g** in presence of squaric acid in water was

Table 2.   continued
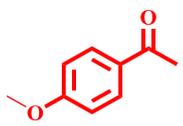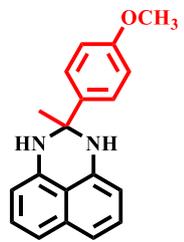
11	**2k**	**3k**	105	86	179–180[17]	180
12	**2l**	**3l**	120	81	–	196
13	**2m**	**3m**	30	96	193–194[17]	194
14	**2n**	**3n**	40	95	242–244[17]	244
15	**2o**	**3o**	360	55	209–210[13]	210
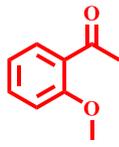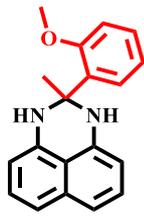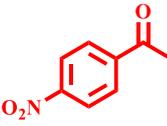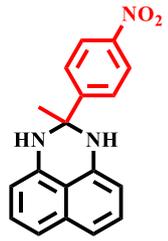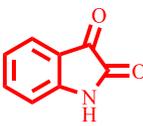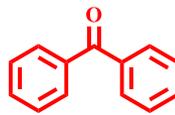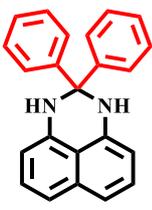
[a]Reaction conditions: 1,8-diamino naphthalene **1** (1 mmol), ketone **2a-o** (1 mmol), squaric acid (10 mol%), water (5.0 mL)

[b]Products are characterized by ^{1}H NMR, ^{13}C NMR and melting points.

[c]Reaction progress was monitored by TLC.

[d]Isolated yield.
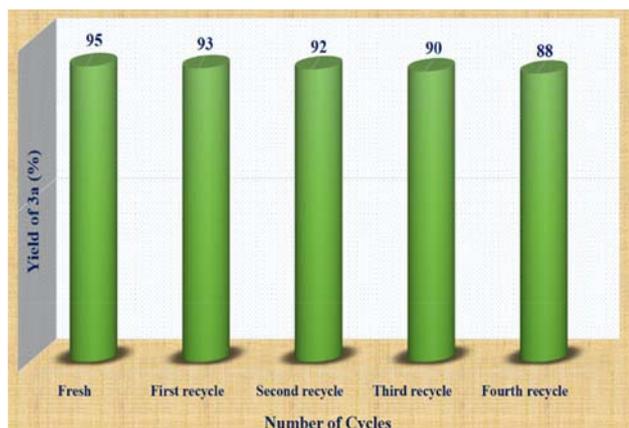
Figure 2. Recyclability of squaric acid in the synthesis of **3g**.
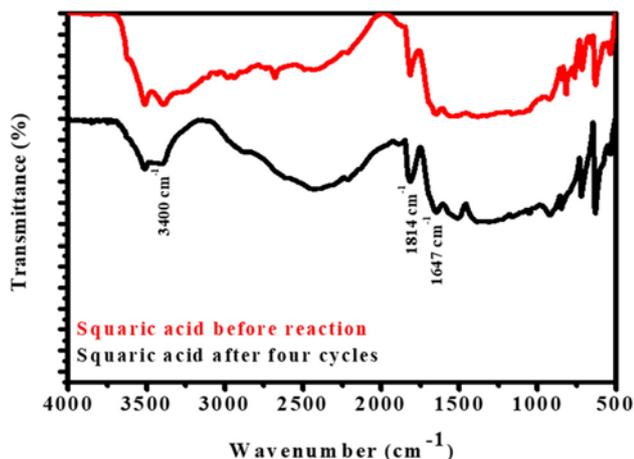
Figure 3. Overlaid FT-IR spectra of fresh and four times recycled squaric acid.

carried out. Squaric acid is insoluble in most of the organic solvents and soluble in water. Thus, after completion of the reaction, the reaction mass was filtered and thoroughly washed with water. Then the filtrate was collected and reused up to four successive cycles without noticeable loss in the catalytic activity of squaric acid (Figure 2). The recovered squaric acid after the fourth cycle was then characterized by FT-IR (Figure 3). There is no change observed in FT-IR spectra of recycled squaric acid after four runs indicates that the structure of squaric acid remains intact even after four recoveries.

To check the applicability of this methodology for industrial applications, we carried out gram scale experiments for the synthesis of **3g**. For this purpose, the condensation reactions of 1,8-diamino naphthalene **1** and acetophenone **2g** in presence squaric acid with different scales were carried out (Table 3, entries 1–8). The reactions proceeded smoothly with large scales

Table 3. Large-scale synthesis of 2-methyl-2-phenyl-2, 3-dihydro-1H-perimidine **3g**.

| Entry	Scale (mmol)	H$_2$O (ml)	Yield (%)[a]
1	1	5	95
2	20	100	93
3	40	120	90
4[b]	40	120	88
5[c]	40	120	86
6[d]	40	120	83
7[e]	40	120	81
8	60	300	87

[a]Isolated yield.
[b]First run.
[c]Second run.
[d]Third run.
[e]Fourth run.

and the desired products were afforded in good yields. These results revealed that the present protocol can be applied for the industrial synthesis of perimidines.

Based on the experimental results and previous reports,[18,19] the plausible mechanistic pathway for squaric acid-catalyzed synthesis of **3g** is outlined in Figure 4. First, the highly acidic squaric acid facilitates the condensation between acetophenone and 1,8-diamino naphthalene to form Schiff's base intermediate **III** *via* intermediates **I** and **II**. Then, the intermediate **III** undergoes protonation and an intramolecular cyclization followed by proton abstraction by dianion of squaric acid to produce the final product **3g** with regeneration of squaric acid for subsequent cycles.

Finally, we compared the results of the present method with that of other reported methodologies for the synthesis of **3g** as shown in Table 4. For non-metal catalyst (entry 1 and 4), the methodologies gave a low yield of **3g** and required more reaction time for reaction completion (c.f. present methodology). For entry 2, the methodology utilized the metal catalyst BiCl$_3$, which is moisture sensitive and forms oxychlorides in presence of water. For entries 3, 5, 6, the methodologies used the metal catalysts and gave less yield of product in prolonged reaction time. For entry 7, although the catalyst used for the reaction is recyclable and metal-free, it required comparatively more reaction time than the present method for reaction completion. Moreover, some of the catalysts mentioned in Table 4 are non-recyclable and some methodologies do not give the benzophenone-based perimidines. In conclusion, the present protocol is superior over the reported methods with respect to the metal-free catalyst, catalyst loading, catalytic activity, reaction time, catalyst recyclability, product yield and green solvent.
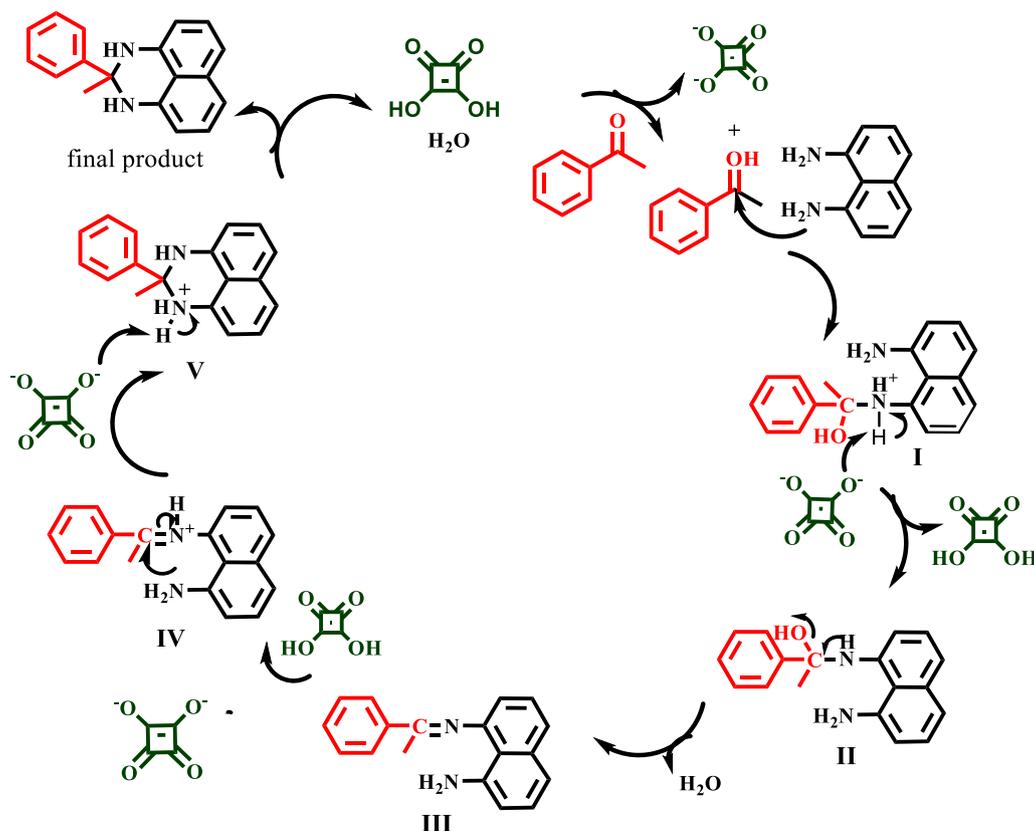
Figure 4. Plausible reaction mechanism for the synthesis of **3g**.

Table 4. Comparison of catalytic activity of squaric acid with reported catalysts for the synthesis of **3g**.

Entry	Catalyst (mol%)	Nature of catalyst	Solvent	Temp.	Time (h)	Yield (%)[a]	Refs.
1	HBOB	Non-metal	Ethanol	Reflux	2	85	[16]
2	BiCl₃	Metal	Ethanol	RT	6	82	[13]
3	MNPs-TBSA	Metal	Water: ethanol	50 °C	24	82	[19]
4	CMK-5-SO₃H	Non-metal	Ethanol	Reflux	7	80	[18]
5	RuCl₃	Metal	Ethanol	RT	24	91	[14]
6	Yb(OTf)₃	Metal	Ethanol	RT	24	82	[15]
7	Amberlyst 15	Non-metal	Ethanol	Reflux	1.30	97	[17]
8	**Squaric acid**	**Non-metal**	**Water**	**80 °C**	**0.45**	**95**	**Present work**

The bold values indicate our catalyst advantages over other reported catalysts
[a]Isolated yield.

4. Conclusions

In summary, we have developed highly efficient and metal-free, a squaric acid-catalyzed methodology for the synthesis of 2,3-dihydro-1H-perimidines in water. Use of green solvent, high recyclability of catalyst, avoidance of column chromatography and good to excellent yields of desired products in shorter reaction time are the key points of this protocol which makes the protocol green, environment-friendly and sustainable. Moreover, easy handling of the catalyst, low catalyst loading, easy workup procedure and good results in gram scale reactions are some of the advantages for this protocol. We hope, the present protocol can be valuable for synthetic and medicinal chemists for academic and industrial purposes.

Supplementary Information (SI)

H-NMR and CNMR data is available at www.ias.ac.in/chemsci.

References

1. Zhang H J, Wang X Z, Cao Q, Gong G H and Quan Z S 2017 Design, synthesis, anti-inflammatory activity, and molecular docking studies of perimidine derivatives containing triazole *Bioorg. Med. Chem. Lett.* **27** 4409

2. Braña M, Garrido M, Rodriguez M L, Morcillo M, Alvarez Y and Valladares Y 1990 Synthesis, structure and cytostatic activity of a series of 2-substituted perimidines *Eur. J. Med. Chem.* **25** 209

3. Wasulko W, Noble A C and Popp F D 1966 Synthesis of potential antineoplastic agents. XIV. Some 2-Substituted 2, 3-Dihydro-1H-perimidines *J. Med. Chem.* **9** 599

4. Arya K and Dandia A 2007 Regioselective synthesis of biologically important scaffold spiro [Indole- Perimidines]: An antitumor agents *Lett. Org. Chem.* **4** 378

5. Farghaly T A, Abdallah M A and Muhammad Z A 2015 New 2-heterocyclic perimidines: Synthesis and antimicrobial activity *Res. Chem. Intermed.* **41** 3937

6. Kim S H, Kim J H, Cui J Z, Gal Y S, Jin S H and Koh K 2002 Absorption spectra, aggregation and photofading behaviour of near-infrared absorbing squarylium dyes containing perimidine moiety *Dye. Pigm.* **55** 1

7. Ernst S, Mistol J, Senns B, Hennig L and Keil D 2018 Synthesis and characterization of a new class of unsymmetrical squaraines with 2, 3-dihydro-1H-perimidine terminal groups *Dye. Pigm.* **154** 216

8. Malherbe R F 1983 2,3-Dihydroperimidines as antioxidants for lubricants *U. S. Patent.* US 4,389,321. Jun. 21

9. Kharlanov V A 1999 Photophysics of photochromic spiroperimidinecyclohexadienone *J. Photochem. Photobiol. A Chem.* **122** 191

10. Alici B, Özdemir I, Karaaslan K, Çetinkaya E and Çetinkaya B 2005 Synthesis and catalytic properties of 1-alkylperimidineruthenium(II) complexes *J. Mol. Catal. A Chem.* **231** 261

11. Azam M, Warad I, Al-Resayes S I, Alzaqri N, Khan M R and Pallepogu R 2013 Synthesis and structural characterization of Pd(II) complexes derived from perimidine ligand and their in vitro antimicrobial studies *J. Mol. Struct.* **1047** 48

12. Hsueh S Y, Cheng K W, Lai C C and Chiu S H 2008 Efficient solvent-free syntheses of [2]- and [4] rotaxanes *Angew. Chem. -Int. Ed.* **47** 4436

13. Zhang J and Zhang S 2007 Bismuth (III) chloride—Promoted efficient synthesis of perimidine derivatives under ambient conditions *Synth. Commun.* **37** 2615

14. Zhang J, Zhang S L and Zhang J M 2007 Ruthenium (III) chloride as an efficient catalyst for the synthesis of perimidine derivatives under mild conditions *Chin. Chem. Lett.* **18** 1057

15. Zhang S L and Zhang J M 2008 Ytterbium (III) triflate as an efficient catalyst for the synthesis of perimidine derivatives under mild conditions *Chin. J. Chem.* **26** 185

16. Phadtare S B, Vijayraghavan R, Shankarling G S and MacFarlane D R 2012 Efficient synthesis of 2,3-dihydro-1H-perimidine derivatives using HBOB as a novel solid acid catalyst *Aust. J. Chem.* **65** 86

17. Patil V V and Shankarling G S 2014 A metal-free, eco-friendly protocol for the synthesis of 2,3-dihydro-1 H - perimidines using commercially available Amberlyst 15 as a catalyst *Catal. Commun.* **57** 138

18. 18. Ordered S, Carbon N, An A S and Solid E 2013 Sulfonated ordered nanoporous carbon as an efficient solid catalyst for the synthesis of perimidine derivatives *J. Chil. Chem. Soc.* **3** 1840

19. Ali M, Sajad B and Zahra A 2016 (Triazinediyl) bis sulfamic acid- functionalized silica- coated magnetite nanoparticles: Preparation, characterization and application as an efficient catalyst for synthesis of mono-, bis-, tris- and spiro- perimidines *J. Iran. Chem. Soc.* **14** 365

20. Bayat S, Salleh A B, Malek E A, Yousefi S and Rahman M B A 2015 Design of simple organocatalysts for asymmetric direct Aldol reactions in aqueous medium *Catal. Lett.* **145** 1750

21. Malamiri F and Khaksar S 2014 Pentafluorophenylammonium triflate (PFPAT): A new organocatalyst for the one-pot three-component synthesis of α-aminophosphonates *J. Chem. Sci.* **126** 807

22. Dam B, Saha M and Pal A K 2015 Magnetically recyclable nano-FDP: A novel, efficient nano-organocatalyst for the one-pot multi-Component synthesis of pyran derivatives in water under ultrasound Irradiation *Catal. Lett.* **145** 1808

23. Oliveira V, Cardoso M and Forezi L 2018 Organocatalysis: A brief overview on its evolution and applications *Catalysts* **8** 605

24. Raj M and Singh V K 2009 Organocatalytic reactions in water *Chem. Commun.* 6687

25. Gaunt M J, Johansson C C, McNally A and Vo N T 2007 Enantioselective organocatalysis *Drug Discov. Today* **12** 8

26. Grondal C, Jeanty M and Enders D 2010 Organocatalytic cascade reactions as a new tool in total synthesis *Nat. Chem.* **2** 167

27. Guajardo N, Müller C R, Schrebler R, Carlesi C and Domínguez D M P 2016 Deep eutectic solvents for organocatalysis, biotransformations, and multistep organocatalyst/enzyme combinations *Chem. Cat. Chem.* **8** 1020

28. Lee K S, Kweon J J, Oh L H and Lee C E 2012 Polymorphic phase transition and thermal stability in squaric acid (H_2C_4O4) *J. Phys. Chem. Solids* **73** 890

29. Robert W and Powell D L 1963 New aromatic anions. III. Molecular orbital calculations on oxygenated anions *J. Am. Chem. Soc.* **85** 2577

30. Azizi N, Davoudpour A, Eskandari F and Batebi E 2012 Squaric acid catalyzed simple synthesis of N-substituted pyrroles in green reaction media *Monatsh. Für Chem. – Chem. Mon.* **144** 405

31. Azizi N, Gholibeghlo E and Manocheri Z 2012 Green procedure for the synthesis of bis (indolyl) methanes in water *Sci. Iran.* **19** 574

32. Azizi N and Davoudpour A 2011 Squaric acid catalyzed highly efficient three-component Mannich-type reaction *Catal. Lett.* **141**1506

33. Azizi N, Saki E and Edrisi M 2011 Squaric acid as an impressive organocatalyst for Michael addition in water *C. R. Chim.* **14** 973

34. Tian Y, Liu Q, Y Q Liu, Zhao R, Li G and Xu F 2018 Catalyst-free Mannich-type reactions in water: Expedient synthesis of naphthol-substituted isoindolinones *Tetrahedron Lett.* **59** 1454

35. Muthusamy S and Gangadurai C 2018 "On water" cascade synthesis of benzopyranopyrazoles and their macrocycles *Tetrahedron Lett.* **59** 1501

36. Tanaka C, Nakamura K and Nishikata T 2017 Copper-catalyzed reductive borylations on water *Tetrahedron* **73** 3999

37. Shaabanin A, Sepahvand H, Boroujeni M B and Faroghi M T 2017 A green one-pot three-component cascade reaction: the synthesis of 2-amino-5, 8-dihydro-3H-pyrido [2, 3-D] pyrimidin-4-ones in aqueous medium *Mol Divers.* **21** 147

38. Esmaielzade Rostami M, Gorji B and Zadmard R 2018 Green synthesis of imidazo [1,2-a]pyridines using calix[6]arene-SO$_3$H surfactant in water *Tetrahedron Lett.* **59** 2393