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Short Communication

A metal free, eco-friendly protocol for the synthesis of 2,3-dihydro-1*H*-perimidines using commercially available Amberlyst 15 as a catalyst

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ABSTRACT

An efficient protocol has been developed to synthesize various dihydro-1*H*-perimidine derivatives using commercially available Amberlyst-15 as a catalyst. Dihydro-1*H*-perimidine derivatives are potential candidates for pharmaceutical and high tech applications. The conspicuous features of this protocol are short reaction time, compared to higher product yield, easy recovery, reusability and regeneration of catalyst. The reaction was successfully scaled up to gram level, which reflects the practicability of the present protocol.

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1. Introduction

Nitrogen containing fused heterocyclic naphthalenes are good candidates for biological, agricultural and medicinal applications [1–4]. Perimidine derivatives serve as ligand scaffolds [5], stoppers for supramolecules [6], and couplers in hair colorants [7]. Their spiroperimidine derivatives exhibit reversible photochromic and thermochromic properties and thus used in molecular switches, and photochemical memory devices [8–10]. The squaraine dyes with 2,3-dihydro-1*H*-perimidine skeleton possess very good photoconductive and semi conductive properties which are found to be useful in various high-tech applications such as organic solar cells, plasma display panels, and optical recording media [11].

Synthesis of 2,3-dihydro-1*H*-perimidine comprises reaction of naphthalene-1,8-diamine with various carbonyl functionalities under acidic condition [12–16]. The most frequent approach used for the preparation of dihydroperimidine derivatives is the reaction of naphthalene-1,8-diamine with an aldehyde. To the best of our knowledge, there are very few reports available on the synthesis of dihydroperimidine derivatives using ketone. In earlier reports, protonic acids are used as catalyst to carry out above transformations with ketones [17,18]. Higher acidity of these catalysts results into the formation of various by-products, which in turn lower the yield of desired product. The metal catalysts such as $InCl_3$ [19], $BiCl_3$ [20], $Zn(CH_3COO)_2 \cdot 2H_2O$ [21], $RuCl_3$ [22], $Yb(OTf)_3$ [23], and HBOB [24] emerged as good alternatives for these conventional protic acids. Though most of these reactions were carried out at ambient temperature, issues such as high cost and commercial availability of catalyst, and longer reaction time (0.5 to 32 h) limit their applicability on commercial scale. Furthermore, most of these metal catalysts are moisture sensitive and get decomposed or deactivated by moisture to form undesirable hazardous products; for example, $BiCl_3$ get decomposed by moisture to form bismuth oxychlorides. Therefore, a cost effective, non-toxic, and commercially available catalyst for the synthesis of 2,3-dihydro-1*H*-perimidines is still in demand.

In the last few decades Amberlyst-15 has gained much attention due to its easy availability, mild and environment friendly nature with high selectivity. It is a macro reticular polymeric resin with cross linked styrene divinyl benzene co-polymer which has high acidity. It has high H + ion exchange capacity (4.2 meq/g) and surface area (42 m^2/g) [25]. Being insoluble in almost all solvents, it is easy to separate the catalyst from the product. Commercial availability has made utilization of this heterogeneous catalyst possible at commercial scale in various important transformations such as quinolone synthesis [26], esterification

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[27], in Prins reaction [28], alkylation [29], halogenation [30], acetalization [31] deprotection [32] in the manufacture of fused homocyclic compounds [33] and in Biginelli reaction [34].

In the present context, we are exploring the heterogeneous catalytic reaction by utilizing commercially available Amberlyst-15 catalyst to synthesize various dihydro perimidine derivatives by reacting naphthalene-1,8-diamine with various ketones. This protocol offers a simple, environmentally benign route for the synthesis of 2,3-dihydro-1*H*-perimidines.

2. Experimental

2.1. Materials and equipments

All the reagents and reactants were purchased from commercial suppliers and were used without further purification. Melting points were uncorrected and recorded on standard melting point apparatus from Sunder Industrial Products, Mumbai. ^{1}H NMR spectra were recorded on 400 MHz Bruker spectrometer using $CDCl_3$ as a solvent and chemical shifts have been expressed in δ ppm using TMS as an internal standard. Infrared spectra were recorded on Jasco-FT/IR 4100 LE ATR PRO450-S spectrometer. Mass spectral data was obtained with micromass-Q-Tof (YA105) spectrometer.

2.2. General procedure for the synthesis of 2,3-dihydro-1H-perimidine

A mixture of naphthalene-1,8-diamine (**1a**) (0.5 g, 3.16 mmol), ketone/ β-keto derivative (**2**) (3.16 mmol) and Amberlyst-15 (20%, w/w) was stirred in ethanol (5 ml) at 80 °C. The progress of reaction was monitored using thin layer chromatography. The catalyst was filtered off and washed with ethanol (3 × 5 ml). Filtrate and all washings were collected and evaporated under vacuum using rotary evaporator to get crude solid mass. The crude product was purified by column chromatography using toluene as an eluting system. The compounds were characterized using spectroscopic techniques (FT-IR, MS, ^{1}H-NMR).

2.2.1. Spectral data of a representative compound

2.2.1.1. 2-Methyl-2-phenyl-2,3-dihydro-1H-perimidine (entry 3a, Table 2). Off white solid. 0.485 g, 97%, m.p. 138 °C (from toluene); IR(KBr): υ_{max}/cm^{-1} 3369, 3283, 1592, 1404, 812, 754, 700 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si) δppm 7.56–7.54 (d, 2H, Ar–H, J = 7.6), 7.29–7.19 (m, 5H, Ar–H), 7.12–7.09 (d, 2H, Ar–H, J = 8.4), 6.51–6.49 (d, 2H, Ar–H, J = 7.6), 4.69 (broad singlet, 2H, N–H), 1.79 (s, 3H, $-CH_3$); MS (EI) 261.1 (M + H), 244.1.

3. Result and discussion

3.1. Reaction condition optimization

The reaction parameters were optimized using naphthalene-1,8-diamine **1a** and acetophenone **2a** as model substrates with 20% (w/w) Amberlyst-15 catalyst. Under solvent free condition, 36% yield of **3a** was obtained after 10 h (Table 1, entry 1). Higher yield was obtained when ethanol was employed as a solvent (Table 1, entry 7). The yield of **3a** was increased exponentially with rise in temperature. At room temperature no product formation was observed (Table 1, entry 8) while the highest yield was obtained at 80 °C (Table 1, entry 7). The catalyst loading was optimized to 20% (w/w) as further rise in catalyst quantity did not show any influence on yield and reaction time (Table 1, entries 7, 14–16). Under catalyst free conditions only starting material was observed on TLC (Table 1, entry 17). When we replaced Amberlyst-15 with other acidic catalyst such as Amberlite IR-120, sulfated zirconia, reaction did not occur (Table 1, entries 18–19) while with Indion-130, poor yield of **3a** was obtained in 10 h (Table 1, entry 20).

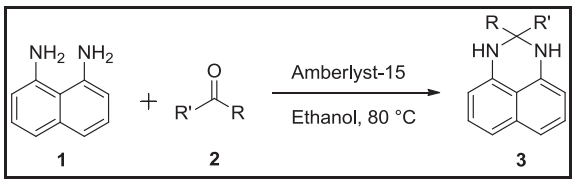
3.2. Reaction of naphthalene-1,8-diamine with various ketones

The optimized reaction conditions were then tested with various ketonic compounds (Scheme 1) and the results obtained were summarized in Table 2. It was found that, the alkyl–aryl ketones with an electron withdrawing group on the aryl ring kinetically favored the reaction as the reaction was completed within a shorter period compared to the corresponding electron donating group. For instance, reaction with 4-nitro acetophenone (**2b)** was observed to be terminated in 45 min to give 90% yield of **3b** (Table 2, entry 2), while reaction with 4-methoxy acetophenone (**2d)** required 2.15 h to give 95% of **3d** (Table 2, entry 4). Compared to aryl–alkyl ketones, dialkyl ketones (Table 2, entries 9–13) showed high reactivity with even shorter reaction time of less than 30 min. The reason for high reactivity of dialkyl ketones over aryl–alkyl ketones could be due to the steric hindrance exerted by phenyl ring. It is also noticeable that, under present reaction conditions, 87% yield of compound **3m** was obtained which was significantly higher than the earlier reported yield (25%) by Yavari et al. [35] in 60 h.

Table 1
Optimization of reaction parameters.[a]

Entry	Solvent	Catalyst	Cat. conc^n (%, w/w)	Temp (°C)	Time (h)	Isolated yield (%)
1	Neat	Amberlyst-15	20	80	10	36
2	Water	Amberlyst-15	20	80	10	No reaction
3	Acetonitrile	Amberlyst-15	20	80	10	No reaction
4	DES[b]	Amberlyst-15	20	80	10	No reaction
5	DMF	Amberlyst-15	20	80	10	Traces
6	1,3-Dioxane	Amberlyst-15	20	80	10	52
7	Ethanol	Amberlyst-15	20	80	2.15	97
8	Ethanol	Amberlyst-15	20	rt	15	No reaction
9	Ethanol	Amberlyst-15	20	50	10	62
10	Ethanol	Amberlyst-15	20	60	10	68
11	Ethanol	Amberlyst-15	20	70	3	78
12	Ethanol	Amberlyst-15	15	80	10	75
13	Ethanol	Amberlyst-15	17	80	10	84
14	Ethanol	Amberlyst-15	23	80	2.15	96
15	Ethanol	Amberlyst-15	25	80	2.15	97
16	Ethanol	Amberlyst-15	30	80	2.00	97
17	Ethanol	No catalyst	–	80	10	No reaction
18	Ethanol	Amberlite 120	20	80	10	No reaction
19	Ethanol	Sulfated zirconia	20	80	10	No reaction
20	Ethanol	Indion-130	20	80	10	18

rt: room temperature (30–32 °C).
[a] Reaction conditions: naphthalene-1,8-diamine (0.2 g, 1.26 mmol), acetophenone (1.26 mmol), Amberlyst-15 (20%, w/w), ethanol (3 ml).
[b] DES–choline chloride–urea.



Scheme 1. Synthesis of dihydroperimidine derivatives using Amberlyst-15.

Further, the reaction of naphthalene-1,8-diamine with β-keto amide was found to be selective for acyl group over benzoyl. It was found that the perimidine formation occurs easily when acyl substituent was present. The reaction of N-(2-chlorophenyl)-3-oxobutanamide **4a** with naphthalene-1,8-diamine gave compound **5a** in 1.45 h (Table 2, entry 14). Whereas, we carried out reactions with sterically hindered ketonic groups such as benzophenone (diaryl ketone) (Table 2, entry 15) and N-(2-chlorophenyl)-3-oxo-3-phenylpropanamide (Table 2, entry 16) no product formation was observed even after 10 h. This is

Table 2
Reaction with various ketones.[a]

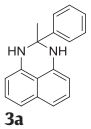
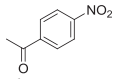
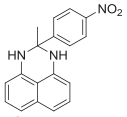
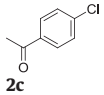
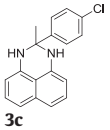
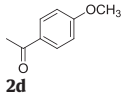
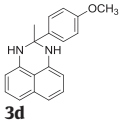
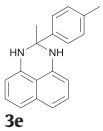
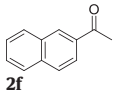
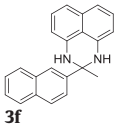
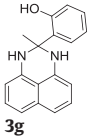
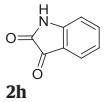
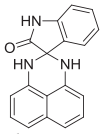
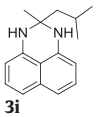
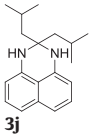
Entry	Substrate	Product	Reaction time	Isolated yield [%]	M.P. (°C)	
					Reported	Observed
1	 **2a**	 **3a**	1.30 h	97	137–138 [24]	136–138
2	 **2b**	 **3b**	45 min	90	192–193 [24]	193–194
3	 **2c**	 **3c**	2.00 h	91	129–130 [20]	129–130
4	 **2d**	 **3d**	2.15 h	95	178–180 [24]	179–180
5	 **2e**	 **3e**	2.00 h	94	117–119 [24]	118–119
6	 **2f**	 **3f**	30 min	92	–	81–82
7	 **2g**	 **3g**	1.15 h	85	193 [24]	191–192
8	 **2h**	 **3h**	1.00 h	97	244–246 [24]	242–244
9	 **2i**	 **3i**	30 min	90	105 [24]	105–107
10	 **2j**	 **3j**	30 min	90	140–142 [24]	142–143
11			30 min	86	95–97 [20]	96–97

Table 2 *(continued)*

Entry	Substrate	Product	Reaction time	Isolated yield [%]	M.P. (°C)	
					Reported	Observed
	2k	**3k**				
12	**2l**	**3l**	30 min	88	85–86 [24]	84–85
13	**2m**	**3m**	30 min	87	227–228 [35]	226–227
14	**2n**	**3n**	1.45 h	88		150-151
15	**2o**	No reaction	10 h	–	–	–
16	**2p**	No reaction	10 h	–	–	–

[a] Reaction conditions: naphthalene-1,8-diamine (0.5 g, 3.16 mmol), ketone/ β-keto amide (3.16 mmol), Amberlyst-15 (20%, w/w), ethanol (5 ml).

an added advantage in the present protocol, as dihydroperimidine will form selectively with dialkyl or aryl alkyl ketones than diaryl ketones.

3.3. Recyclability and scale up studies

The recyclability study was carried out on 2 g scale. After completion of reaction, the catalyst was filtered off and washed with ethanol. It was then treated with 0.1 N HCl solution and dried at 65 °C for 30 min before used for further runs. The catalyst remained effective till the last cycle studied here (Fig. 1). The reaction was scaled up to 5 g which gives 96% yield of **3a** in 2.30 h. In all, the catalyst can be used over several runs without affecting its activity and also feasible on large scale.

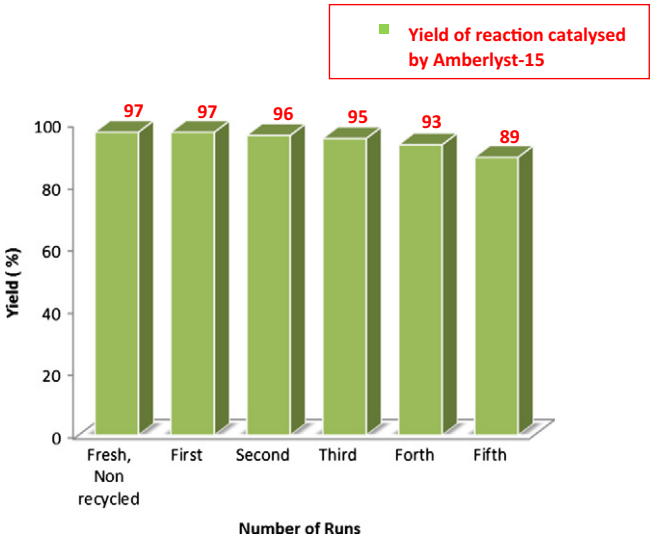


Fig. 1. Studies in recycling of Amberlyst-15 in the synthesis of dihydroperimidine derivative **3a**.

4. Conclusion

In conclusion, we have developed a clean, cost effective and environmentally benign metal free route for the synthesis of various substituted 2,3-dihydro-1*H*-perimidine derivatives. The catalyst, Amberlyst-15 can be easily separated and regenerated thus can be recycled for several reactions. The present protocol was found to be selective for dialkyl and aryl alkyl ketones while sterically hindered ketone remains unaffected under the present reaction conditions. Further study with β-keto amide shows that, dihydroperimidine was selectively obtained when acyl group was present at β-position with respect to amide than the benzoyl group.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2014.08.024. These data include MOL files and InChiKeys of the most important compounds described in this article.

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