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Phenyl boronic acid promoted efficient synthesis of perimidine derivatives under mild condition

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Various biologically important perimidines derivatives have been efficiently synthesized in excellent from Napthalene-1,8-diamine and various ketones in presence of a catalytic amount of Phenyl boronic acid. This approach offers many advantages such as good product yield, short reaction time, easy isolation of products and mild reaction conditions.

Capsule Summary: 2,3-dihydo-1H-perimidines derivatives have been synthsized from Napthalene-1,8-diamine and various ketones in presence of a catalytic amount of Phenyl boronic acid as lewis acid with excellent yields and mild reaction conditions.

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INTRODUCTION

Nitrogen containing fused heterocyclic naphthalenes are good candidates for biological, agricultural and medicinal applications (Herbert et al., 1987; Denny et al., 2001; Dhanoa, et al., 1999; Wasulko et al., 1966). Perimidine derivatives serve as ligand scaffolds (Chung et al., 2003; Hocek et al., 2000), stoppers for supramolecules (Chiu et al., 2008), and couplers in hair colorants (Lagrange and Mignon, 2013). Their spiroperimidine derivatives exhibit reversible photochromic and thermochromic properties and thus used in molecular switches, and photochemical memory devices.(Komissarov et al., 1997; Norikane et al., 2009; Tamaoki et al., 2005) Synthesis of 2,3-dihydro-1H-perimidine (Paragamian et al., 1968) comprises reaction of naphthalene-1,8-diamine with various carbonyl functionalities under acidic condition.(Shaabani et al., 2008; Hendrickson et al., 1987; Vanden et al., 1995; Ozeryanskii et al., 2001; Koh et al., 2002). The most frequent approach used for the preparation of dihydroperimidine derivatives is the reaction of naphthalene-1,8-diamine with an aldehyde.

Table 1: Comparison of the effect of solvent for the synthesis of 2,3-dihydo-1H-perimidines catalysed by phenyl boronic acid

Entry	Solvent	Time (hrs.)	Yield[a] (%)
1	$CHCl_3$	2.3	58
2	CH_2Cl_2	2.15	52
3	CH_3CN	2	62
4	C_2H_5OH	1.3	98

[a] Isolated Yield

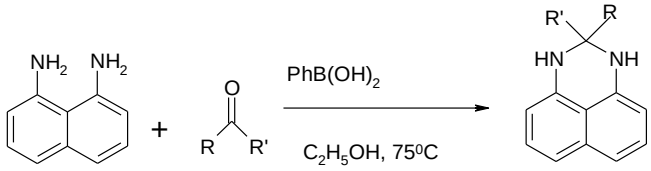
Table 2: Investigation of catalytic effect of anhydr. Phenyl boronic acid on synthesis of 2,3-dihydo-1H-perimidines

Entry	Anhyd. $PhB(OH)_2$	Time	Yield[a]
	mmol	Min	%
1	0.01	45	52
2	0.05	40	58
3	0.1	30	98
4	0.2	29	98

[a] Isolated Yield

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 (Borovlev et al., 2008; Bazgir et al., 2010). 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 $InCl_3$ (Bazgir et al., 2010), $BiCl_3$ (Yoon et al., 1991), $Zn(CH_3COO)_2{\cdot}2H_2O$ (Belmonte et al., 2010) $RuCl_3$ (Zhang et al., 2007) $Yb(OTf)_3$ (Zhang et al., 2008) and HBOB (Shankarling et al., 2012) 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.

Phenyl boronic acid have received considerable attention as an efficient catalyst in synthesis (Zheng et al.2010; Frutos et al.2011; Tale et al.2006; Krokhin et al.2010; Sridhar et al.2005; Debache et al., 2006; Lopez-Ruiz et al., 2011; Tibhe et al., 2012).Herein we describe the use of Phenyl Boronic acid as a lewis acid catalyst for synthesis of 2,3-dihydo-1H-perimidines derivatives. This transformation was performed by condensation reaction of naphthalene-1,8-diamine with various ketones in presence of catalytic amount of Phenyl boronic acid in Ethanol solvent (Scheme 1).



Scheme 1: Synthesis of 2,3-dihydo-1H-perimidines using naphthalene-1,8-diamine and aliphatic ketones using Phenyl borornic acid.

MATERIAL AND METHODS

Chemical and reagents

All chemical and solvents were purchased from Merck and sigma Aldrich and used without further purification. The reaction was monitored by TLC using 0.25 mm E-Merck silica gel plates, which were visualized in Iodine Chamber. Melting points were taken in open capillaries. ^1H NMR in $d_6$on 300 MHz using TMS as an internal standard ^{13}C NMR spectra was recorded on JOEL EXC-500 spectrometer in $CDCl_3$.

General procedure for synthesis of 2,3-dihydo-1H-perimidines

A mixture of naphthalene-1,8-diamine (1 mmol), ketone (1.2 mmol) and Phenyl boronic acid (0.1 mmol) 0.1 g was stirred in ethanol at 75°C . The reaction progress was monitored by Thin layer Chromatography. After the completion of the reaction, hot ethanol was added to the mixture and the catalyst was filtered off. After drying it was purified by recrystallization from hot ethanol, pure products were obtained. The compounds were characterized using spectroscopic techniques.

RESULTS AND DISCUSSION

The optimum condition for the synthesis of 2,3-dihydo-1H-perimidines derivatives was established by considering a reaction between naphthalene-1,8-diamine and ketone as model reaction. It was performed in the presence of Phenyl boronic acid as a catalyst using ethanol as a solvent (Scheme 1).

Table 3: Synthesis of different perimidine derivatives using naphthalene-1,8-diamine and aliphatic ketones

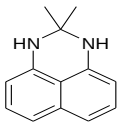
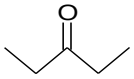
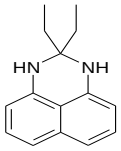
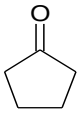
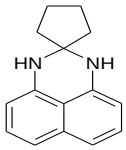
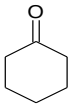
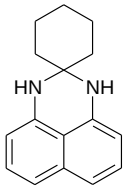
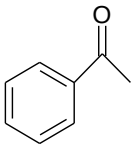
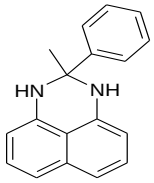
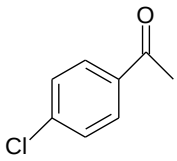
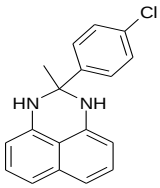
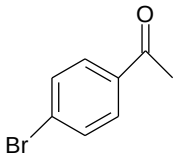
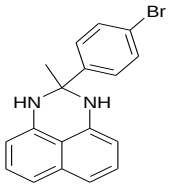
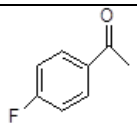
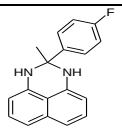
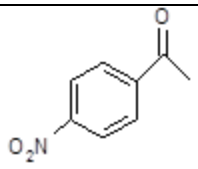
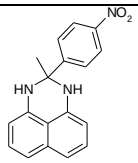
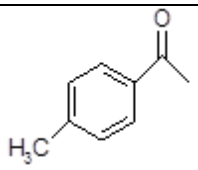
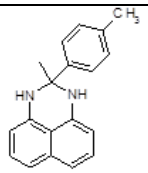
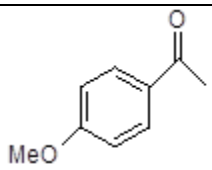
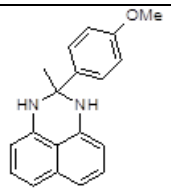
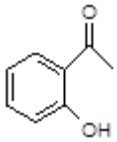
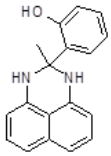
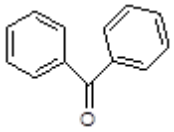
Entry	Ketone[a]	Time (Min)	Product[b]	Yield[c] (%)	M. P. (^{0}C)
1		30 min	 (1a)	86	115-116
2		30 min	 (1b)	87	94-95
3		30 min	 (1c)	90	85-86
4		30 min	 (1d)	92	110-111
5		1.15 h	 (1e)	98	136-138
6		1.45 h	 (1f)	92	129-130
7		1.45 h	 (1g)	91	126-128

Table 3: continue…

Entry	Ketone[a]	Time (Min)	Product[b]	Yield[c] (%)	M. P. (^{0}C)
8		2 h	 (1a)	91	156-158
9		1.15 h	 (1b)	90	193-194
10		1.15 h	 (1c)	95	118-119
11		2.15 h	 (1d)	96	179-180
12		1h	 (1e)	86	191-192
13		12	No reaction	-----	----

A proper solvent for the reaction was selected by investigating the effect of different solvents on reaction time and yield of product for model reaction. We observed that the reaction time was long and yield of the corresponding product was low when the reaction was performed in solvents of low polarity (Table 1, Entries 1 and 2). Even in CH_3CN the reaction time and yield were not satisfactory (Table 1, Entry 3). The reaction gave maximum yield of product in short time period when it was performed in polar solvent such as C_2H_5OH (Table1, Entry-4)

The efficiency of Phenyl boronic acid as a catalyst was determined with respect to its amount to be loaded in reaction mixture. There was no improvement in yield with increment in loading amount of catalyst from 0.01 mmol to 0.05 mmol. A satisfactory yield in short reaction time was obtained with 0.1 mmol of catalyst. There was no appreciable improvement in yield even if loading amount was increased to 0.2 mmol.

Thus, the most appropriate loading amount for anhydrous $PhB(OH)_2$ as a catalyst was found to be 0.1 mmol as per results summarized in Table 2.

To evaluate the scope and generality of this methodology, a number of aromatic and aliphatic ketones were further subjected to reaction using catalytic amount of Phenyl boronic acid. In general, with aliphatic ketones, the reactions showed better product yields and higher rate than aromatic ketones (Table 3 entries 1-4). Aromatic ketones, such as acetopheneone, the conjugating factor of the phenyl

ring, played a key role in affecting the rate of reaction, and the reaction requires a longer time than aliphatic ketones. Moreover, various aromatic ketones containing either electron donating (Table 3 entries 6-8,10-12) or electron withdrawing substituents (Table 3 entries 9) at different position worked well under present reaction condition. In benzopheneone, perhaps because of the conjugation effect of two phenyl rings and the steric hindrance, the reaction showed no reaction (Table 3 entries 13). This proved the wide scope and generality of the present protocol. The results are summarized in Table 3.

The categorization data of various (1H NMR, Infrared and Mass spectroscopy) achieved for various representative compounds are given below.

2,2-Dimethyl-2,3-dihydro-1H-perimidine (entry 1a, Table 3)

^{1}H NMR (400 MHz; $CDCl_3$) δ ppm 7.24–7.16 (M, 4H), 6.52 (d, 2H, J = 7.2 Hz), 4.21 (br s, 2H), 1.52 (s, 6H), ^{13}C NMR ($CDCl_3$, 100MHz): δ 140.72, 135.04, 127.47, 117.52, 113.36, 106.35, 65.00, 29.28.

2-Methyl-2-phenyl-2,3-dihydro-1H-perimidine (entry 1e,Table 3)

^{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).

2-Methyl-2-(4-nitrophenyl)-2,3-dihydro-1H-perimidine (entry 1i,Table 3)

^{1}H NMR (400 MHz; $CDCl_3$) δ ppm 8.02 (d, 2H. j=8.8 Hz), 7.64 (d, 2H, j=8.8 Hz), 7.25-7.14 (m, 4H), 6.59 (d, 2H,j=7.2 Hz), 4.86 (br s, 2H), 1.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100MHz): δ 1.54.65, 147.50, 139.73, 135.00, 127.57, 124.20, 118.74, 114.74, 107.50, 107.29, 68.46, 30.35.

2-Methyl-2-p-tolyl-2,3-dihydro-1H-perimidine (entry 1j, Table 3).

^{1}H NMR (400 MHz; $CDCl_3$) δ ppm 7.47 (d, 2H. j=7.6 Hz), 7.24-7.08 (m, 6H), 6.55 (d, 2H, j=6.8 Hz), 4.85 (br s, 2H), 2.27 (s, 3H), 1.83 (s, 3H), ^{13}C NMR ($CDCl_3$, 100MHz): δ 143.42, 140.73, 137.86, 135.05, 129.59, 127.45, 126.32, 117.73, 113.91, 106.37, 68.45, 29.71, 21.42.

CONCLUSIONS

In conclusion, 2,3-dihydo-1H-perimidines derivatives were synthesized via one pot two component addition reaction using phenyl boronic acid as lewis acid. This synthetic method is simple because no special apparatus is required. This synthesis is also advantageous in terms of atom economy and is devoid of any hazardous chemicals. This transformation was successfully studied for different range of ketones. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields.

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