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A facile one-pot synthesis of dicycloalkenopyridines at ambient temperature conditions

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ABSTRACT

An efficient synthesis of dicycloalkenopyridines was achieved via one-pot three-component condensation of aromatic aldehyde, cyclohexanone, and hydroxylamine hydrochloride using 3-nitrophenylboronic acid as an efficient catalyst under ambient condition. The current methodology offers several advantages such as high yields (78–90%) and simple experimental work-up at ambient temperature conditions.

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Multi-component reactions (MCRs) are of increasing importance in organic and medicinal chemistry, because the strategies of MCR offer significant advantages over conventional linear-type synthesis.[1,2] MCRs leading to interesting heterocyclic scaffolds are particularly useful for the synthesis of drug-like molecules with several degrees of structural diversity, since the combination of three or more building blocks in a single operation leads to a high combinatorial efficiency.[3] The improvement of effective chemical processes for the research of new biologically active molecules constitutes a great challenge for chemists in organic synthesis.

The pyridine ring is a significant structural constituent in natural products and in many synthetic compounds of pharmaceutical interest.[4] Among the successful examples as drugs possessing pyridine ring as a skeleton are streptonigrin, streptonigrone, and lavendamycin as anticancer drugs, and cerivastatin is reported as the HMG-CoA enzyme inhibitor.[5] Substituted pyridines are used as leukotriene B-4 antagonists.[6] Moreover pyridine derivatives are used as chelating ligands in coordination chemistry, building blocks in supramolecular chemistry, as metal-containing polymers, molecular electronics, optoelectronic devices, solar cells, and as photo-activated species.[7] As a result, these facts are significant in developing a new efficient and effective synthetic procedure for the synthesis of pyridines.[8] Many naturally occurring biologically active compounds feature the presence of a cycloalkenopyridine ring as basic skeleton. This observation produced the development of new synthetic protocol to prepare pharmaceuticals and agrochemicals, containing cycloalkenopyridine ring as a significant building block.[9] Substituted pyridines have been synthesized using various methods and two methods have more advantages over other procedures. One of the methods is the two-step Krohnke synthesis[10–12] via condensation of pyridinium salts with α,β-unsaturated ketones in the presence of a mixture of ammonium acetate and acetic acid. The second method is Hantzsch type synthesis via cyclo-condensation of aromatic aldehyde, acetophenone, and a nitrogen derivative such as ammonium acetate or urea.[13]

Recently several new procedures have been developed for the synthesis of pyridine derivatives including solvent-free reactions,[14,15] reactions in aqueous media,[16] one-pot method under microwave irradiation,[17,18] and direct heating of α,β-unsaturated ketones with ammonium acetate in the presence of a catalytic amount of acetic acid.[19] Unfortunately, many of these processes suffer some limitations such as harsh reaction conditions, low yields, tedious work-up, and possibilities of several side reactions.

Organoboron compounds have been effectively used as a Lewis acid catalyst in various organic transformations[20–22] and in one-pot synthetic organic chemistry.[23,24] The phenylboronic acid, particularly those with electron-withdrawing substituent on aromatic ring work as an efficient Lewis acid catalyst. Herein we describe a novel one-pot three-component synthesis of dicycloalkenopyridines starting from aromatic aldehyde, cyclohexanone, and hydroxylamine hydrochloride using 3-nitrophenylboronic acid as catalyst in methanol at room temperature conditions (Scheme 1).

In continuation of our interest in the synthesis of heterocycles using organoboron compounds,[25] herein we report for the first time, a simple, mild, and efficient method for the synthesis of

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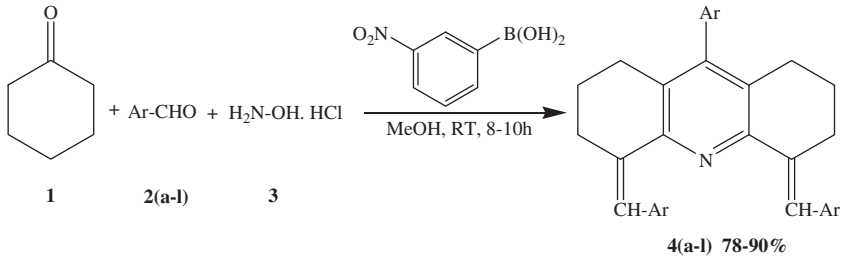
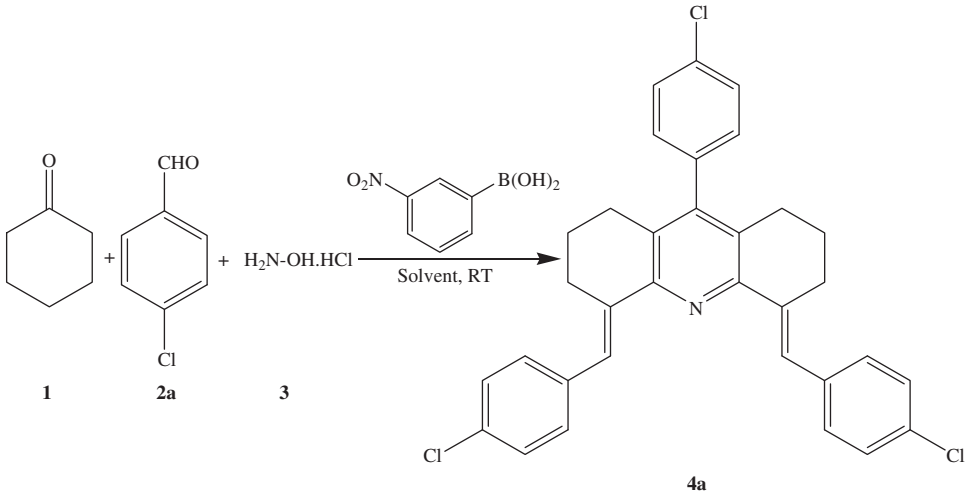


Scheme 1. One-pot multicomponent synthesis of dicycloalkenopyridines.

Table 1
Screening of the solvent in one-pot synthesis of dicycloalkenopyridines[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	Ethanol	15	64
2	**Methanol**	**12**	**78**
3	Chloroform	28	48
4	Dichloromethane	28	50
5	Water	30	38
6	Acetonitrile	22	58

[a] Conditions: 4-Chlorobenzaldehyde (3 mmol), cyclohexanone (2 mmol), and hydroxylamine hydrochloride (3 g), 3-nitrophenylboronic acid (10 mol %) at room temperature. The progress of reaction was monitored by thin layer chromatography.
[b] Isolated yield.

dicycloalkenopyridines using 3-nitrophenylboronic acid as Lewis acid catalyst at ambient temperature conditions in excellent yields.[26]

For initial optimization of the reaction conditions, we studied the solvent effect on the model reaction of 4-chlorobenzaldehyde, cyclohexanone, and hydroxylamine hydrochloride using 10 mol % 3-nitrophenylboronic acid as catalyst at room temperature condition. The polar protic solvents ethanol and methanol were found to be the effective solvent for the reaction, especially methanol. In the solvent methanol, product **4a** was obtained in good yield 78% within 12 h (Table 1, entry 2). In the non-polar solvents like chloroform and dichloromethane, the desired product **4a** was obtained in lower yield with extended reaction time (Table 1, entries 3 and 4, respectively). It was attributed to the less solubility of the catalyst 3-nitrophenylboronic acid in these solvents. Moreover the reaction in the solvents water and acetonitrile afforded 38 and 58% yields, respectively with longer reaction time (Table 1, entries 5 and 6, respectively).

Subsequently, we investigated the influence of catalytic concentration on the model reaction with methanol as solvent. Initially at the catalytic loading of 5 mol % 3-nitrophenylboronic acid, the reaction was sluggish (18 h) and afforded 64% yield of the product **4a** (Table 2, entry 1). The reaction performance improved with the increase in catalytic loading to 12 mol % and 15 mol %, the reaction time was reduced and enhanced yield for the product **4a** was obtained (Table 2, entries 2 and 3, respectively). The best result for the reaction was obtained at the catalytic loading of 20 mol % of

Table 2
Screening of the catalytic loading in one-pot synthesis of dicycloalkenopyridines[a]

Entry	3-Nitrophenylboronic acid (mol %)	Time (h)	Yield[b] (%)
1	5	18	64
2	12	12	76
3	15	11	72
4	**20**	**8**	**89**
5	25	10	72
6	0	36	Trace

[a] Conditions: 4-Chlorobenzaldehyde (3 mmol), cyclohexanone (2 mmol), and hydroxylamine hydrochloride (3 g), methanol (15 ml) at room temperature. The progress of reaction was monitored by thin layer chromatography.
[b] Isolated yield.

Table 3
One-pot synthesis of dicycloalkenopyridines[a]

Entry	Ar	Product **4**	Time (h)	MP	Yield[b] (%)
1	4-Cl	**a**	8	194–196[15]	89
2	4-OCH_3	**b**	8	224–226[15]	82
3	3-NO_2	**c**	9	196–198	88
4	3,4-OCH_3	**d**	10	228–230	79
5	4-F	**e**	10	230–232	86
6	4-NO_2	**f**	9	193–195	89
7	2-Cl	**g**	8	181–183	90
8	3-Br	**h**	10	236–238	88
9	3-OCH_3	**i**	8	>250	84
10	H	**j**	9	157–159[15]	78
11	4-$N(CH_3)_2$	**k**	8	>250[15]	84
12	4-Br	**l**	9	198–199	87

[a] Conditions: Aromatic aldehyde (3 mmol), cyclohexanone (2 mmol), hydroxylamine hydrochloride (3 g), 3-nitrophenylboronic acid (20 mol %), and methanol (15 ml) at room temperature. The progress of reaction was monitored by thin layer chromatography.
[b] Isolated yield.

the catalyst 3-nitrophenylboronic acid. The reaction was completed within 8 h and afforded the product **4a** in excellent yield of 89% (Table 2, entry 4). Further increase in the catalytic loading of 25 mol % did not show significant improvement in the yield even with extended reaction time (Table 2, entry 5).

To check the necessity of the catalyst 3-nitrophenylboronic acid in the reaction, the same reaction was carried out without catalyst. The reaction showed some progress after 36 h but the obtained product was very poor in yield (Table 2, entry 6). Also, at the elevated temperature the reaction showed no significant changes with respect to yield and time in the absence of catalyst.

Under the optimized reaction conditions, various aromatic aldehydes were allowed to react with cyclohexanone and hydroxylamine hydrochloride. All the reactions proceeded well with a wide range of aromatic aldehydes affording good to excellent yield of the corresponding products (Table 3).

From the mechanistic point of view, we propose a plausible mechanism for the synthesis of dicycloalkenopyridines in Scheme 2. The catalyst 3-nitrophenylboronic acid activates the cyclohexanone ring through non-bonding interaction to form enolized six membered intermediate **I**. The carbonyl carbon of aromatic aldehyde was attacked by an electron rich enol form of cyclohexanone to afford intermediate **II**. The intermediate **II** on further reaction with another molecule of aldehyde leads to intermediate **III**. Intermediate **III** and intermediate **II** undergo Michael addition reaction to form intermediate **IV**, which on cyclo-condensation with hydroxylamine hydrochloride gives the final product **4** dicycloalkenopyridines.

In conclusion, we have demonstrated a facile and efficient method for the synthesis of dicycloalkenopyridines using 3-nitrophenylboronic acid as catalyst under mild reaction conditions for the first time. Arylboronic acids are usually crystalline solids, and stable in air and moisture. Such evidence as exists indicates that they are of relatively low toxicity and have low environmental impact. The reaction proceeds smoothly at room temperature. The key advantages of the present method include mild reaction conditions, easy work-up, clean reaction profile, a wide range of substrate applicability, high yields of products, and non-toxicity of the reagents.

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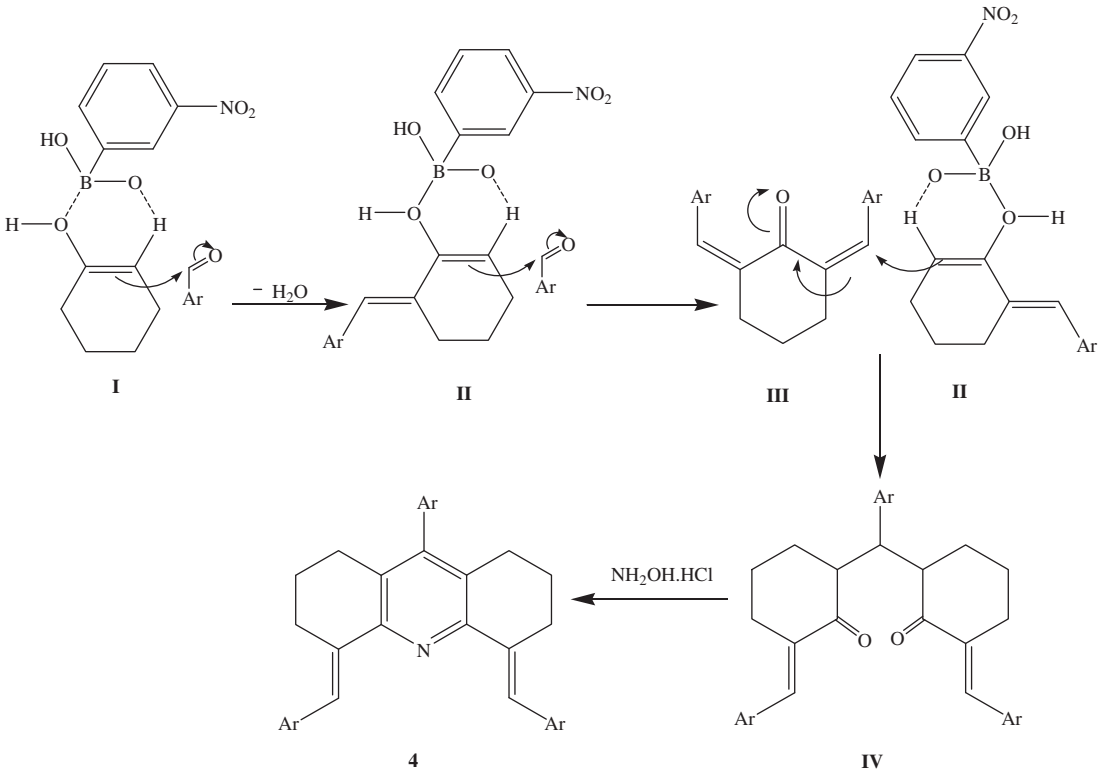

Scheme 2. Mechanistic pathway for the synthesis of dicycloalkenopyridines.

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26. *General procedure for the synthesis of dicycloalkenopyridines:* A mixture of aromatic aldehyde (3.0 mmol), cyclohexanone (2.0 mmol), hydroxylamine hydrochloride (3.0 g), and 3-nitrophenylboronic acid (20 mol %) as catalyst was added in methanol (15 ml) solvent and the reaction mixture was stirred at room temperature for appropriate time (Table 3). After completion of the reaction as indicated by thin layer chromatography (pet ether: ethyl acetate 8:2), the reaction mixture was diluted with 50 ml of water and extracted with ethyl acetate (3 × 20 ml). The organic layer was dried over anhydrous Na_2SO_4, concentrated, and the obtained product was purified by column chromatography using silica gel mesh 80–120 to afford the pure product (**4a–l**).

*4,5-Bis(4-chlorobenzylidene)-9-(4-chlorophenyl)-1,2,3,4,5,6,7,8-octahydro-acridine (**4a**):* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (s, 2H), 7.30 (d, 4H, J = 7.6 Hz), 7.21–7.17 (m, 8H), 2.65 (t, 4H, J = 6.2 Hz), 2.32 (t, 4H, J = 6.6 Hz), 1.72 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 152.7, 148.2, 141.2, 140.1, 135.3, 133.5, 131.97, 131.0, 128.4, 128.2, 128.0, 126.1, 125.2, 121.5, 120.1, 28.3, 27.6, 22.7; GC–MS, *m*/*z*: 541 (M+); Elemental Analysis: Anal. Calcd for $C_{33}H_{26}Cl_3N$: C, 73.00; H, 4.83; N, 2.58%. Found C, 73.03; H, 4.88; N, 2.60%.

*4,5-Bis(3-nitrobenzylidene)-1,2,3,4,5,6,7,8-octahydro-9-(3-nitrophenyl)acridine (**4c**):* ^{1}H NMR(300 MHz, $CDCl_3$): δ 8.12 (s, 2H), 7.90 (d, 4H, J = 8.2 Hz), 6.92 (d, 2H, J = 8.2 Hz), 6.86–6.80 (d, 6H, J = 8.0 Hz), 2.81 (t, 4H, J = 6.4 Hz), 2.40 (t, 4H, J = 6.0 Hz), 1.68 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 159.5, 155.2, 144.9, 144.0, 140.4, 139.8, 136.2, 133.6, 129.9, 129.5, 129.0, 120.8, 120.5, 116.6, 115.0, 29.2, 27.9, 23.6; GC–MS, *m*/*z*: 574 (M+); Elemental Analysis: Anal. Calcd for $C_{33}H_{26}N_4O_6$: C, 68.98; H, 4.56; N, 9.75%;. Found: C, 68.94; H, 4.61; N, 9.79%.

*4,5-Bis(4-fluorobenzylidene)-9-(4-fluorophenyl)-1,2,3,4,5,6,7,8-octahydroacridine (**4e**):* ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 2H), 7.42–7.38 (d, 6H, J = 6.8 Hz), 7.28–7.25 (d, 4H, J = 7.4 Hz), 6.95 (d, 2H, J = 7.4 Hz), 2.74 (t, 4H, J = 6.4 Hz), 2.38 (t, 4H, J = 6.4 Hz), 1.79 (m, 4H); ^{13}C NMR(300 MHz, $CDCl_3$): δ 159.8, 155.4, 146.2, 141.6, 140.8, 139.2, 136.7, 133.1, 129.8, 126.9, 126.1, 123.7, 122.4, 116.0, 115.1, 29.1, 28.4, 23.2; GC–MS, *m*/*z* 493 (M+); Elemental Analysis: Anal. Calcd for $C_{33}H_{26}F_3N$: C, 80.30; H, 5.31; N, 2.84%; Found: C, 80.32; H, 5.34; N, 2.86%.

*4,5-Bis(3-bromobenzylidene)-9-(3-bromophenyl)-1,2,3,4,5,6,7,8-octahydroacridine (**4h**):* ^{1}H NMR(300 MHz, $CDCl_3$): δ 7.82 (s, 2H), 7.40 (d, 4H, J = 7.8 Hz), 6.88 (d, 2H, J = 7.8 Hz), 6.76–6,71 (m, 6H), 2.78 (t, 4H, J = 7.0 Hz), 2.32 (t, 4H, J = 7.0 Hz), 1.68 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 160.1, 158.9, 151.3, 135.4, 133.9, 130.6, 129.8, 126.6, 115.1, 114.2, 55.6, 29.4, 28.7, 22.5; GC–MS, *m*/*z*: 676 (M+); Elemental Analysis: Anal. Calcd for $C_{33}H_{26}Br_3N$: C, 58.61; H, 3.88; N, 2.07%; Found: C, 58.66; H, 3.84; N, 2.11%.