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3-Nitrophenylboronic acid-catalyzed efficient one-pot synthesis of 1,4-dihydropyridines and polyhydroquinolines

Ramkishan N Adude, Ramkishan M Tigote, Santosh V Goswami and Sudhakar R Bhusare*

Abstract An efficient protocol for the synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives via multi-component coupling reaction of aldehyde, β-keto ester and ammonium acetate at room temperature condition using 3-nitrophenylboronic acid as a catalyst is described.

Keywords: 1,4-dihydropyridines, Hantzsch condensation, Multi-component reactions, 3-nitrophenylboronic acid, Polyhydroquinolines

Background

The multi-component condensation reactions signify an important tool in the organic synthesis as they possess ability of building up the complex molecules with greatest simplicity and brevity [1]. The search of a cleaner and efficient organic process is still sustained by synthetic organic chemists. In addition to the intrinsic atom economy and selectivity underlying such reactions, time and energy saving, as well as environmental friendliness, have led to significant efforts to design and implement multi-component reactions both in academia and industry [2-5]. 1,4-Dihydropyridine derivatives are widely used drugs for the treatment of cardiovascular disease [6-11] and have a broad range of pharmaceutical activities [12-21].

Three-component condensation reaction involving aldehyde, β-keto ester and ammonium acetate, popularly known as Hantzsch pyridine synthesis [6-11], lead to the formation of 1,4-dihydropyridine nucleus. The compounds containing 1,4-dihydropyridine nucleus comprise a large family of medicinally important compounds like nifedipine as Ca^{2+} channel antagonists [12-18]. Moreover, 1,4-dihydropyridine nucleus exhibits several pharmaceutical applications such as neuroprotectant [19], anti-aggregratory agents [20], cerebral and ischemic agents for the treatment of Alzheimer's disease, and as chemo sensitizer in tumor therapy [21], and it is also proven to be a valuable intermediate in the preparation of natural product alkaloids [22].

In the present investigation, various aromatic aldehydes condensed with β-keto ester and ammonium acetate in the presence of the catalyst 3-nitrophenylboronic acid at room temperature yielded 1,4-dihydropyridine and polyhydroquinoline derivatives in good to excellent isolated yield (Schemes 1 and 2).

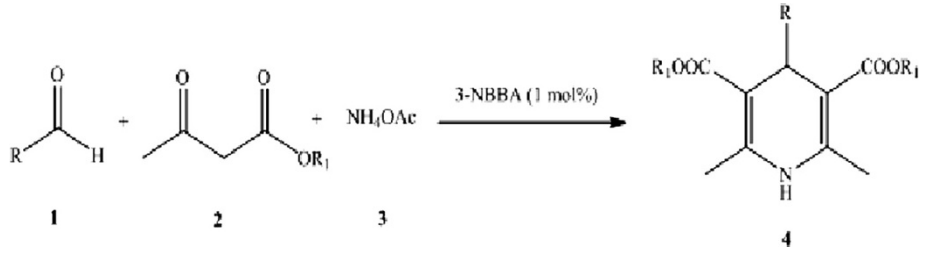
Methods

All chemicals were purchased from Sigma-Aldrich chemical companies (St. Louis, MO, USA). The progress of the reactions was followed by thin layer chromatography TLC using silica gel Merck 60 F254 plates (Merck & Co., Inc., Whitehouse Station, NJ, USA). Melting points were recorded on open capillaries and were not corrected. IR spectra were recorded on Varian FTIR spectrophotometer (Agilent Technologies, Santa Clara, CA, USA) using KBr disks. ^{1}H NMR spectra were recorded on a Varian 300-MHz spectrometer using $CDCl_3$ as solvent. The mass spectra were scanned on a Shimadzu LCMS-2010 EV instrument (Shimadzu, Columbia, MD, USA) at 70 eV.

General procedure for synthesis of 1, 4-dihydropyridines (Scheme 1)

A mixture of aldehyde (2 mmol), β-keto ester (4 mmol) and ammonium acetate (3 mmol) in acetonitrile (20 mL) was added to 3-nitrophenylboronic acid (3.5 mg, 1 mol%), and the resulting mixture was stirred at room temperature for 5 h. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with 10% sodium

* Correspondence: bhusare71@gmail.com
Department of Chemistry, Dnyanopasak College, Parbhani, MS 431401, India



Scheme 1 Synthesis of 1, 4-dihydropyridines.

bicarbonate solution followed by water three times and then dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo* to furnish the products, which were purified by column chromatography using silica gel (100-200 mesh) with ethyl acetate to n-hexane in the ratio of 8:2 as eluent.

General procedure for synthesis of polyhydroquinolines (Scheme 2)

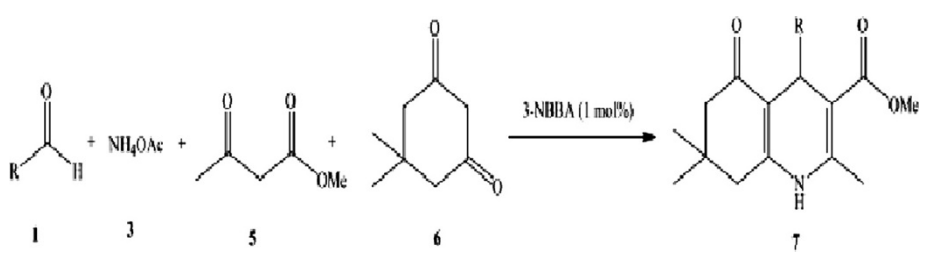
A mixture of aldehyde (2 mmol), β-keto ester (2 mmol), 5,5-dimethylcyclohexane-1,3-dione (2 mmol) and ammonium acetate (3 mmol) in acetonitrile (20 mL) was added to 3-nitrophenylboronic acid (3.5 mg, 1 mol%), and the resulting mixture was stirred at room temperature for 5 h. After completion of the reaction, as indicated by TLC, the reaction mixture was poured on crushed ice, and precipitate was filtered and washed with cold water. The crude product of crystallization with ethyl alcohol gave pure polyhydroquinoline derivatives.

Results and discussion

We have been engaged in evaluating the catalytic potential of phenylboronic acids, particularly those with electron-withdrawing substituents in organic synthesis. As a part of our ongoing research on 3-nitrophenylboronic acid as efficient catalyst for selective trans-esterification of β-keto esters and acetylation of alcohols under mild and solvent-free conditions [23,24], we report herein the synthesis of 1,4-dihydropyridine and polyhydroquinoline derivatives by Hantzsch pyridine synthesis. Thus, to find out the best reaction conditions and reactivity pattern of different aldehydes in three-component Hantzsch condensation reaction by the use of 3-nitrophenylboronic acid as catalyst for the synthesis of 1,4-dihydropyridines is our objective in the present investigation.

The model reaction involving three-component condensation of 4-chlorobenzaldehyde, ethyl acetoacetate and ammonium acetate in the molar ratio of 2:1:1.5 was performed without any catalyst; the reaction resulted in the low yield of product. However, in the presence of 3-nitrophenylboronic acid, the reaction is proceeded smoothly with the desired product in 94% isolated yield using catalytic amount of catalyst (1 mol%) in a short reaction time. A wide variety of aromatic aldehydes bearing electron-releasing, as well as electron-withdrawing, substituent reacted smoothly to give the corresponding 1,4-dihydropyridines in good to excellent yields. Notably, the aromatic aldehydes possessing highly sensitive functionalities such as 4-benzyloxy benzaldehyde (Table 1, entry 8) also reacted smoothly to give a good yield of the corresponding product. Thus, the present protocol not only preserves the simplicity but also consistently provides the high yield of 1,4-dihydropyridine derivatives under extremely mild conditions, using catalytic amount of the catalyst.

The analogous four-component condensation of aldehyde, β-keto ester, 5,5-dimethylcyclohexane-1,3-dione and ammonium acetate leads to the cyclic 1,4-



Scheme 2 Synthesis of polyhydroquinolines.

Table 1 Synthesis of 1, 4-dihydropyridines (Scheme 1)

Entry	R	R_1	Product[a]	Yield[b] (%)	m. p. (°C)
1.	C_6H_5	Et	4a	93	61
2.	4-Me- C_6H_5	Et	4b	88	67
3.	4-OMe-C_6H_5	Et	4c	90	50
4.	4-Cl-C_6H_5	Et	4d	91	62
5.	3-Cl-C_6H_5	Et	4e	92	63
6.	3-NO_2-C_6H_5	Et	4f	87	114
7.	2-Furyl	Et	4g	79	70
8.	4-Benzyloxy- C_6H_5	Et	4h	81	161
9.	4-Me-C_6H_5	Me	4j	86	297
10.	3-Cl-C_6H_5	Me	4k	82	61

[a]The structures of the products were characterized by spectral analysis (IR, ^{1}H NMR and MS). [b]Isolated yield.

dihydropyridines (polyhydroquinoline). The structural variation on the dihydropyridine nucleus enhances the biological activity of the parent molecule. In view of the above fact, we investigated the four-component condensation reaction involving 4-chlorobenzaldehyde, methyl acetoacetate, 5,5-dimethy-1,3-hexanedione and ammonium acetate carried out under the same reaction conditions. The reaction proceeds smoothly to give corresponding polyhydroquinoline derivative in 81% yield. The above results prompted us to use different aldehydes for the synthesis of polyhydroquinoline using the same reaction conditions (Table 2). Thus, various cyclic analogs of 1,4-dihydropyridines were synthesized efficiently in high yields at great ease under mild conditions.

Conclusion

In summary, a simple and convenient method for the synthesis of 1,4-dihydropyridines and polyhydroquinolines using 3-nitrophenylboronic acid as an efficient catalyst in excellent yield has been developed. The advantages of this method include mild reaction conditions, simple workup and short reaction time with excellent isolated yield.

Table 2 Synthesis of polyhydroquinolines (Scheme 2)

Entry	R	Product	Yield (%)	m. p. (°C)
1.	C_6H_5	7a	87	203
2.	4-Me- C_6H_5	7b	89	261
3.	4-OMe- C_6H_5	7c	92	259
4.	4-Cl- C_6H_5	7d	90	246
5.	3-Cl- C_6H_5	7e	88	230
6.	4-OH- C_6H_5	7f	95	234

[a]The structures of the products were characterized by spectral analysis (IR, ^{1}H NMR and MS). [b]Isolated yield.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RA carried out synthesis of 1, 4-dihydropyridine derivatives. RT carried out synthesis of polyhydroquinoline derivatives. SG participated in the design of the study and performed the spectral analysis. SB conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

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