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Boric Acid: An Efficent Catalyst for The One Pot Synthesis Of Hantzsch Polyhydroquinolines

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Abstract

An efficient multicomponent one-pot synthesis of Hantzsch polyhydroquinoline was achieved by the condensation of aldehyde, dimedone, ethylacetoacetate and ammonium acetate using environmentally benign boric acid as catalyst. The method offers several advantages such as inexpensive, efficient and mild catalyst, less reaction time, simple workup and excellent yield of products.

Keywords: Hantzsch polyhydroquinoline, Boric acid, Dimedone, Multi-component reactions.

1. Introduction

The development of novel synthetic methodologies to facilitate the preparation of specific molecules is an intense area of research. In this regard, efforts have been constantly made to introduce new methodologies that are efficient and more compatible with the environment. One of the most desirable approaches to address this challenge is a search for surrogates for commonly employed organic solvents from various health and environmental reasons[1].
Multicomponent reactions (MCRs) have emerged as an extremely powerful tool in combinatorial chemistry and drug discovery, since they offer significant advantages over conventional linear stepwise syntheses, in terms of improving classical organic reactions, for promoting new reactions and for the development of straightforward synthetic routes to bioactive heterocyclic [2].

The 1,4-dihydropyridine (1,4-DHP) compounds have gained the remarkable importance due to their widespread biological activitie such as, vasodilator, bronchodilator, anti-atherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agent[3-6]. Photocatalytic oxidation of these compounds to pyridine derivatives constitutes the principal metabolic pathway in biological systems [7]. DHPs have found commercial utility as calcium channel blockers as exemplified by therapeutic agents such as Nifedine, Nitrendipine and Nimodipine [8]. Therefore, oxidative aromatization of DHPs has been a subject of great interest of organic and medicinal chemists
Realizing the importance of polyhydroquinoline derivatives, several synthesis methods have been reported using various catalysts, such as $Yb(OTf)_3$[9], $Sc(OTf)_3$[10], $HClO_4$–SiO_2[11], ZnO[12], scolecite[13], nano-Ni[14], GuHCl[15],

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morpholine[16], CuO[17], t-BuOK[18], Mn(III) complex[19], TiO_2,[20] Zn-VCO_3 hydrotalcite[21], magnetic Fe_3O_4 nanoparticles[22], etc. Thus many of the existing strategies suffer from harsh reaction conditions, use of stoichiometric and/or relatively expensive reagents, long reaction time, unsatisfactory yield of products, etc. Some of these methods, for example microwave or ultrasound assisted synthesis [23], require additional equipment such as a microwave oven or a sonication bath. Ionic liquids [24] have also been used for clean chemical reactions replacing volatile organic solvents. But they suffer from inherent problems in separation and tedious workup is often involved.

Herein, we wish to report a novel synthesis of polyhydroquinoline and 1,4-dihydropyridine derivatives using boric acid as catalyst. The advantages of the boric acid catalyst are excellent solubility in alcohol, uncomplicated handling, inexpensiveness and eco-friendly nature. Recently, several synthetically useful organic transformations using boric acid as a catalyst have also been reported in the literature[25-26].

2.Experimental Section

General

All aldehydes were obtained from freshly opened container and used without further purification. The synthesized polyhydroquinoline derivatives were confirmed on the basis of spectral data and comparison of their physical constants to those reported in literature. Melting points were measured in capillaries open at one end and were uncorrected. The progress of reaction was monitored by thin-layer chromatography (TLC) analysis in 30% EA: Hexane. ^{1}H NMR spectra were recorded in $CDCl_3$ on a 400 MHz Varian spectrophotometer using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Shimadzu FTIR spectrometer using KBr pellets. Samples were analyzed for exact mass on a Shimadzu mass analyzer.

General procedure for synthesis of Hantzsch polyhydroquinoline derivatives using boric acid as catalyst.

In a typical condensation reaction, a mixture of aldehyde (1 mmol), dimedone (1 mmol), ethyl acetoacetate (1 mmol), ammonium acetate (1.5 mmol) and boric acid (10mol %) in ethanol (10 mL) was magnetically stirred at reflux temperature for appropriate time as specified in Table 2. After the completion of the reaction as monitored by TLC (EA: Hex 3:7). After completion of reaction conversion, the reaction mixture was cool then crude solid product is obtained. The obtained crude solid product was filtered, dried and crystallized from ethanol.

Spectral data of principal compounds:

Ethyl-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carboxylate (4a):

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.22(t, 3H, CH_3), 4.10 (q, 2H), 2.01–2.21 (m, 4H), 2.5 (s, 3H), 5.13 (s, 1H), 6.12 (brs, 1H, NH), 7.1–7.4 (m, 5H). IR (KBr, cm^{-1}):*v*= 3275, 3062, 2932, 1680, 1609. ES-MS: 339.2 [M^+].

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (4b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.09 (s, 3H), 1.21 (t,3H), 4.04 (q, 2H), 2.01–2.21 (m, 4H), 2.4 (s, 3H), 5.11 (s, 1H), 5.61(brs, 1H, NH), 6.21 (s,1H, OH) 7.23–7.29 (d, 2H, J = 8.4 Hz), 7.28–7.32 (d, 2H,J = 8.4 Hz). IR (KBr, cm^{-1}): *v*=3290, 3054, 2923, 1709, 1642 1621. ES-MS: 355.2 [M^+],.

Ethyl 1,4,5,6,7,8-hexahydro-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (4c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.03 (s, 3H), 1.24 (t,3H), 4.01 (q, 2H), 2.01–2.15 (m, 4H), 2.5 (s, 3H), 3.71 (s,3H, OCH_3) 5.11 (s, 1H), 5.61(brs, 1H, NH), 7.31–7.39 (d, 2H, J = 8.4 Hz), 7.18–7.22 (d, 2H,J = 8.4 Hz). IR (KBr, cm^{-1}): *v*=3293, 3024, 2923, 1702, 1632, 1621. ES-MS: 369.2 [M^+],

Ethyl-4-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carboxylate (4e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 3H), 1.09 (s, 3H), 1.23 (t,3H), 4.02 (q, 2H), 2.11–

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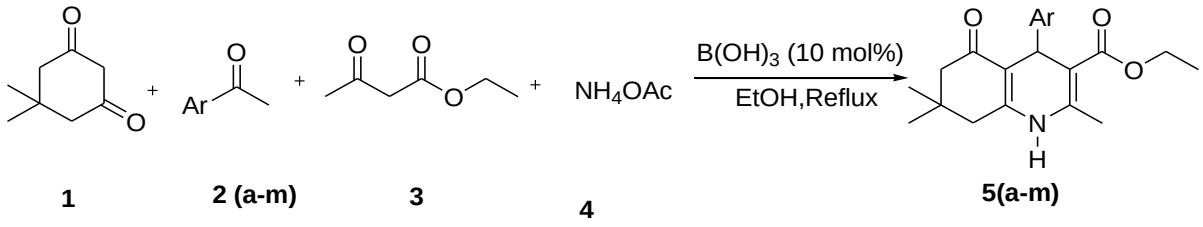
2.33 (m, 4H), 2.5 (s, 3H), 5.13 (s, 1H), 5.61(brs, 1H, NH), 7.13–7.22 (d, 2H, J = 8.4 Hz), 7.21–7.32 (d, 2H,J = 8.4 Hz). IR (KBr, cm^{-1}): *v*=3272, 3076, 2953, 1701, 1644 1601. ES-MS: 373.1 [M^{+}],373.1 [M^{+2}].

3. Results and Discussion

In continuation of our research work on the development of novel synthetic methodologies[27] herein, we would like to report a highly efficient route for the synthesis of polyhydroquinoline catalyzed by an commercially available, inexpensive, mild catalyst boric acid. This protocol is a one-pot four component coupling of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate in ethanol. (**Scheme 1**)



1 **2 (a-m)** **3** **4** **5(a-m)**

Scheme 1. Synthesis of Hantzsch polyhydroquinolines

In our search for the better solvent and the best experimental reaction conditions in the preparation of polyhydroquinoline, in our initial study, reaction of 4-chlorobenzaldehyde, dimedone, ethyl acetoacetate, ammonium acetate and boric acid as catalyst was considered as a standard model reaction

To evaluate the effect of solvent, we have screened different solvents such as Water, Water: Ethanol (1:1), Acetonitrile, Dichloromethane, Tetrahydrofuran, Methanol, water, ethanol: water and ethanol at reflux temperature. Ethanol stand out as the solvent of choice among the solvents tested because of the rapid conversion and excellent yield (91%) of desired product, where as the product formed in lower yields (30-70 %) by using other solvents. (**Table 1, Entry 1-6**)

To determine the optimum concentration of catalyst, we have investigated the model reaction at 5, 7.5, 10 and 12.5 mol% of boric acid in ethanol at reflux temperature. The product was obtained in 70, 82, 95 and 95 % yield respectively. This indicates that the use of 10 mol% of boric acid is sufficient to promote the reaction forward

Table 1. Screening of solvent

Entry	Solvent	Time (hr)	Yield[b] (%)
1	Water	2.5	34
2	Water :ethanol (1:1)	2.5	38
3	Acetonitrile	2.5	48
4	Dichloromethane	2.5	44
5	Tetrahydrofuran	2.5	55
6	Methanol	2.5	70
7	Ethanol	2.5	95

b=Isolated yield.

To generalize this methodology, we subjected a series of other aldehydes having electron-donating as well as electron withdrawing substituent to obtain the corresponding polyhydroquinoline derivatives under the optimized reaction conditions (**Table 2**). As Table 2 shows yields are good to excellent in most cases.

A reasonable pathway for the formation of polyhydroquinoline in the presence of boric acid is presented by **Scheme 2.**

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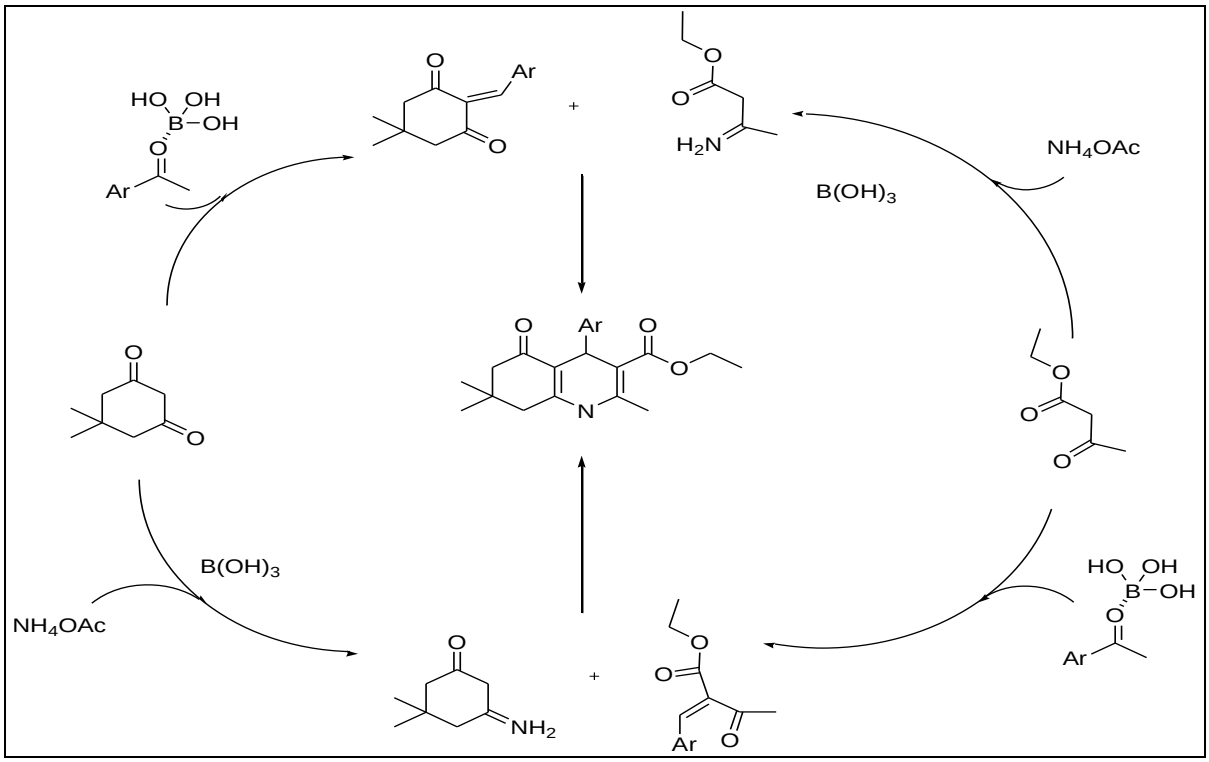
Table 2. Synthesis of polyhydroquinolines catalysed by boric acid

Entry	Ar-	Time(hr)	Yield (%)[b]	M.P.(°C)
4a	C_6H_5	2	88	204-205
4b	4-HO-C_6H_4	2.5	92	231-233
4c	4-MeO-C_6H_4	2	87	257-259
4d	4-Me-C_6H_4	3.5	89	261-263
4e	4-Cl-C_6H_4	2.5	95	245-247
4f	4-F-C_6H_4	2.5	90	186-188
4g	3-HO-C_6H_4	2	88	220-222
4h	4-NO_2-C_6H_4	3	95	242-244
4i	3-NO_2-C_6H_4	2	84	176-177
4j	4-$(CH_3)_2N$-C_6H_4	2.5	92	232-233
4k	4-Br-C_6H_4	2.5	89	252-254
4l	2-Thienyl	3.5	87	239-241

b=Isolated yield.



Scheme 2: Proposed mechanism of boric acid catalyzed synthesis of polyhydroquinoline

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CONCLUSIONS

In conclusion, we have described a general and highly efficient procedure for the synthesis of polyhydroquinolines derivatives using commercially available inexpensive boric acid as catalyst in ethanol. The remarkable advantage of this protocol is mild reaction conditions, excellent yields of product, operational and experimental simplicity. We believe that, this methodology will be a valuable addition to the existing methods of the synthesis of polyhydroquinolines

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