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Boric acid: A green, mild and efficient catalyst for the synthesis of polyhydroquinoline under solvent-free conditions

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ABSTRACT

Boric acid was found to be an efficient and versatile catalyst for the synthesis of a wide range of polyhydroquinolines via one-pot four component condensation of aldehydes, cyclic 1,3-dicarbonyl compounds and ammonium acetate in good to excellent yields under solvent-free conditions.

KEYWORDS

Green catalysis;
Solvent-free;
Boric acid;
1,4-Dihydropyridines;
Polyhydroquinolines.

INTRODUCTION

Compounds containing 4-aryl-1, 4-dihydropyridine (DHP) nucleus comprise a large family of medicinally important compounds[1]. The most prominent of these is the nifedipine class of Ca^{2+}-channel antagonists and their second generation analogs[2]. In addition, 1,4-dihydropyridines exhibit several important applications in the field of pharmaceuticals such as neuroprotectant, anti-aggregators agent, cerebral antiischemic agent for the treatment of Alzheimer's disease and as chemo sensitizer in tumor therapy[3]. Hantzsch one-pot three component condensation of 1,3-dicrbonyl compounds, aldehyde, and ammonium acetate provides the most efficient access to DHP derivatives[4]. However, the classical Hantzsch synthesis of DHP derivatives generally resulted in low yields. Owing to the biological significance of DHP, there is a renewed interest in Hantzsch reaction and consequently several improved procedures including different catalysts such as molecular iodine, $HClO_4$-SiO_2, organo-catalyst, and expensive metal triflates, $Yb(OTf)_3$, have been reported[5-10]. However, the practical applicability of many of these methods suffer from the limitations such as unsatisfactory yields, harsh reaction conditions, use of expensive/sensitive catalysts (some times even in stiochometric amount) and high temperature. Moreover, till date there is no report on the synthesis of polyhydroquinolines in a truly catalytic process under solvent-free conditions at room temperature. Thus the development of efficient, general and milder protocol for the synthesis polyhydroquinolines in an environmentally benign manner is still highly desired.

Boric acid is inexpensive, commercially available and considered to be "green" compound[11]. Boric acid has been successfully employed in various useful organic transformations[12]. Herein, we wish to report further application of boric acid for the efficient synthesis of polyhydroquinolines via muti-component Hantzsch reaction. The reactions were carried out under solvent-free conditions using inexpensive boric acid in a catalytic quantity.

The four component condensation reaction involving 4-chlorobenzaldehyde, dimedone, ethylacetoacetate and ammonium acetate using 20 mol % of boric acid at room temperature was initially considered as the model reaction. This reaction was carried out under solvent-

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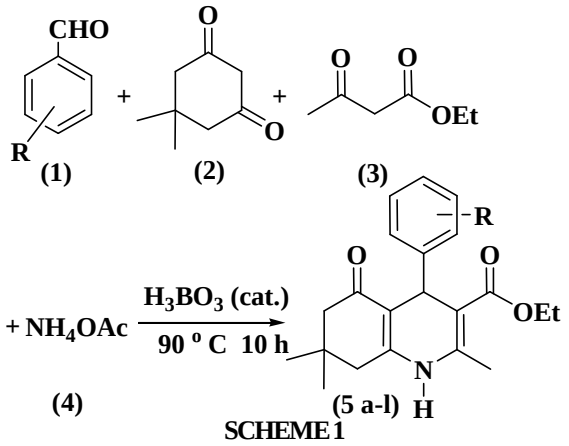
TABLE 1 : Boric acid: A green, mild and efficient catalyst for the synthesis of polyhydroquinolines under solvent-free conditions

Entry	1	Ar	Time (h)	Product	Yield (%)[a]	M.p. (°C) found	M. p. (°C) (Lit.)
1	(1a)	C_6H_5	10	5a	92	202-205	202-204[6]
2	(1b)	4–$MeOC_6H_4$	10	5b	86	252-254	257-259[6]
3	(1c)	3,4,5-$(MeO)_3C_6H_2$	10	5c	87	197-199	199-200[13]
4	(1d)	4–HOC_6H_4	10	5d	90	234-237	232-234[6]
5	(1e)	4–ClC_6H_4	10	5e	87	232-234	230-232[6]
6	(1f)	4–BrC_6H_4	10	5f	81	251-253	253-255[6]
7	(1g)	4–MeC_6H_4	10	5g	83	258-260	260-261[6]
9	(1h)	4–$NO_2C_6H_4$	10	5h	91	241-243	242-244[9a]
10	(1i)	3–$NO_2C_6H_4$	10	5i	84	176-179	177-178[13]
11	(1j)	2- $NO_2C_6H_4$	10	5j	81	208-211	206-208[13]

[a]Isolated yields after crystallization



SCHEME 1

free conditions and the formation of the corresponding polyhydroquinolines (TABLE 1, entry 5e) derivative was realized in 10 h reflux time with 92 % yield. The optimized reaction conditions revealed that the catalyst loading can be reduced to 5 mol % but reaction required longer reaction time up to 28 h to obtain the maximum yield of polyhydroquinolines.

With good result being obtained in the reaction with 4-chlorobenzaldehyde, next, using our optimized reaction conditions the structurally diverse aromatic, heteroaromatic as well as aliphatic aldehydes were converted into corresponding polyhydroquinolines derivatives in good to excellent yields at room temperature (SCHEME 1). The results are presented in TABLE 1. As shown in TABLE 1, the aromatic aledhydes bearing electron releasing as well as electron withdrawing substituents reacted efficiently to afford the corresponding polyhydroquinoline derivatives in high yields. Moreover, heteroaromatic aldehydes such as 2-pyridyl and 2-thieny aldehyde were also underwent Hantzsch condensation smoothly giving high yields of the corresponding product without any unwanted side reaction.

The reaction conditions presented here are extremely mild and products were obtained in high yields and purity under-solvent-free conditions. Moreover, in contrast to many reported procedures, the present methodology relies on the use of catalytic amount of environmentally benign boric acid which makes it an attractive and environmentally benign approach. Thus we have developed general, and high yielding one-pot synthesis of a wide range of polyhydroquinoline derivatives under solvent-free conditions.

EXPERIMENTAL

Synthesis of polyhydroquinoline derivatives

To a mixture of aldehyde, ethylacetoacetate, dimedone and ammonium acetate in the molar ratio of 1:1:1:1.5 was added boric acid (0. 2 mmol) and resulting mixture was heated at 90^{0}C while stirring for 10h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice cold water and solid product was filtered. The crude product was washed with water several time and recrystalised from ethanol.

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