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Original scientific paper

$B(HSO_4)_3$: An efficient and recyclable catalyst for the Friedländer synthesis of substituted quinolines

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Abstract: Substituted quinolines have been synthesized in the presence of catalytic amounts of boron hydrogen sulfate (BHS) under solvent-free conditions. This methodology offers some advantages, including high yield, short reaction time, low cost of the catalyst, green conditions by avoiding toxic solvents and recoverable catalyst.

Keywords: boron hydrogen sulfate; substituted quinolines; solvent-free conditions; Friedländer reaction.

INTRODUCTION

The presence of quinoline moiety core in several natural compounds, such as cinchona alkaloids, and pharmacologically active substances[1]with a broad range of biological activities, including anti-asthmatic,[2] antibacterial,[3] anti-inflammatory[4] and antihypertensive[5] properties, has raised the interest of organic chemists for finding straightforward routes for the synthesis of these compounds.

Considering the above reports, and due to great importance of quinolines, it is not surprising that many synthetic procedures, such as the Skraup, Doebner von Miller, Conrad–Limpach–Knorr, Pfitzinger, Friedländer and Combes reactions, were developed for the preparation of these compounds.[6,7] Nevertheless, the development of novel synthetic approaches for the synthesis of quinolones remain an active area of research.

Amongst various methodologies reported for the preparation of quinolines, the Friedländer reaction is still one of the simplest and most straightforward protocols. Friedländer synthesis involves a condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone and an aldehyde or ketone possessing α-active methylene groups.[8] While different catalysts have

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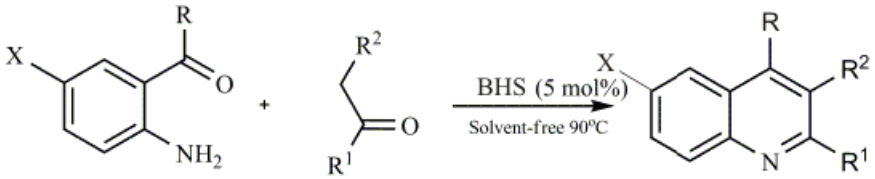
been proposed for Friedländer annulations, it has been shown that acidic catalysts are superior to basic ones.[9] Other than different acidic catalysts, such as Brønsted acids[10–14] and Lewis acids,[15–17] ionic liquids,[18] and other catalysts[19,20] have also been employed to promote this reaction. Friedländer reaction has recently been reviewed.[21]

Uncatalyzed Friedländer syntheses require drastic reaction conditions, with temperatures in the range 150–220 °C. Most of the synthetic protocols for quinolines reported so far suffer from harsh conditions, low yields, prolonged reaction time and the use of hazardous and often expensive catalysts. Moreover, the syntheses of these heterocycles have usually been performed in polar solvents, such as acetonitrile, THF, DMF and DMSO, leading to complex isolation and recovery procedures. These processes also generate waste-containing solvent and catalyst, which have to be recovered, treated and disposed of.

Solid acids have many advantages both in industry and the laboratory, such as simplicity in handling, reduced reactor and plant corrosion problems, and more environmentally safe disposal in chemical processes.[22] Solid acids are employed under heterogeneous conditions and hence can be conveniently handled and removed from the reaction mixture by simple filtration and recovered for reuse. Boron hydrogen sulfate has recently been successfully used as an efficient solid acid catalyst for the preparation of thiocyanohydrins under solvent-free conditions.[23]

In continuation of efforts in the synthesis of new solid acid catalysts, and their application in organic synthesis,[23–25] boron hydrogen sulfate was utilized in the present study as an efficient solid acid catalyst for the preparation of substituted quinolines by Friedländer annulation (Scheme 1).



1a; X=H, R= CH_3
1b; X=H, R= Ph
1c; X=Cl, R= Ph

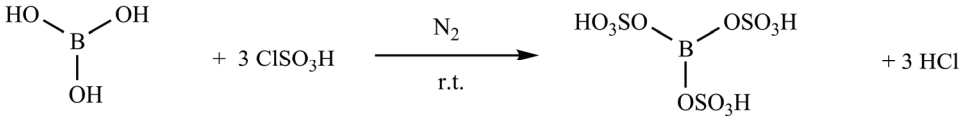
2

3a-o

Scheme 1. Preparation of substituted quinolines in the presence of BHS.

RESULTS AND DISCUSSION

Boron hydrogen sulfate, BHS, was easily prepared by simply mixing boric acid and chlorosulfonic acid in CH_2Cl_2 at room temperature (Scheme 2). This reaction is easy and clean, because the evolved HCl gas leaves the reaction vessel immediately.



Scheme 2. Preparation of the catalyst.

One of the informative techniques for an investigation of catalyst formation is FT-IR spectroscopy. Thus, the structure of the catalyst was characterized by FT-IR spectroscopy (Fig. 1). As seen in Fig. 1, the spectrum of $B(HSO_4)_3$ was different from that of boric acid. The FT-IR spectrum of $B(HSO_4)_3$ showed absorption bands at 1400 (ν(S=O) asymmetric stretching), 1200 (ν(S=O) symmetric stretching) and at 650 cm^{-1} corresponding to ν(S–O). Moreover, a broad band from 2700–3400 cm^{-1} corresponds to acidic O–H stretching.

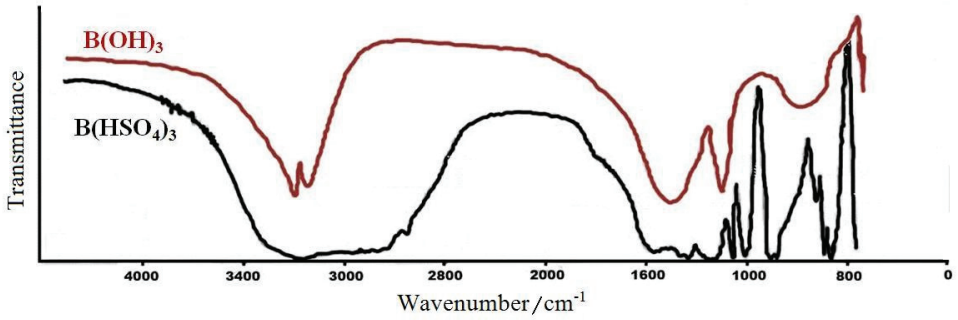
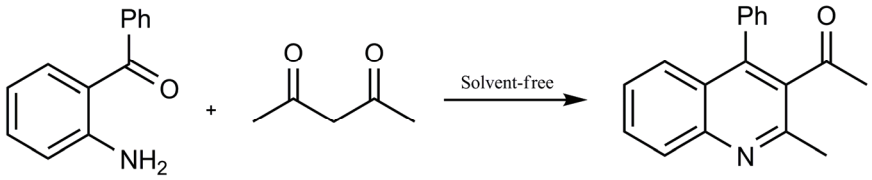


Figure 1. IR spectra of $B(HSO_4)_3$ and $B(OH)_3$.

To evaluate the catalytic activity of BHS in the preparation of substituted quinolines, a model reaction of 2-aminobenzophenone (1 mmol), and acetylacetone (1.2 mmol) under solvent-free conditions at different temperatures and in the presence of variable catalyst loadings was examined (Scheme 3). It was found that in the absence of the solid acid catalyst, only a trace amount of the desired product was observed on the TLC plate even after heating for 2 h. (Table I, Entry 1). When the reaction was performed in the presence of BHS, it proceeded rapidly to give the desired product.



Scheme 3. Optimization of the reaction conditions for 2-aminobenzophenone and acetylacetone as a model reaction.

In order to evaluate the appropriate catalyst loading, the model reaction was performed using 3.5 to 9.5 mol % at different temperatures in the absence of solvent (Table I). It was found that 5 mol % catalyst gave the maximum yield in the minimum time. A higher percentage of loading of the catalyst (7–9.5 mol %) neither increases the yield nor lowers the conversion time substantially. In the next step, the effect of temperature was evaluated for the model reaction. It was observed that the reaction did not proceed at room temperature. Elevating the reaction temperature proved helpful, and the yield of desired product increased considerably. To our satisfaction, the reaction was found to proceed smoothly, and almost complete conversion of product was observed at 90 °C, affording 1-(2-methyl-4-phenylquinolin-3-yl)ethanone (**3f**) in 91 % yield within a short time.

TABLE I. Optimization of the reaction conditions for 2-aminobenzophenone and acetylacetone as a model reaction under thermal solvent-free conditions

Entry	Catalyst amount, mol %	Temperature, °C	Time, min	Yield, %
1	–	r.t.	120	10
2	3.5	r.t.	120	45
3	5	r.t.	120	52
4	5	60	60	65
5	3.5	90	60	68
6	5	90	35	91
7	7	90	34	92
8	9.5	90	45	88

Subsequently, with the optimal conditions in hand, using 1:1.2 molar ratio of a 2-aminoaryl ketone, a carbonyl compound and 5 mol % of BHS at 90 °C under solvent-free conditions, the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of substituted quinolines (Table II). Gratifyingly, a wide range of aromatic aldehydes was well tolerated under the optimized reaction conditions. The time taken for complete conversion (monitored by TLC) and the isolated yields are presented in Table II. All the new compounds were characterized by their satisfactory microanalytical (C, H, N) and spectral (IR, ^{1}H-NMR, ^{13}C-NMR and MS) studies, and known compounds by comparison of their physical and spectral data with those of the authentic samples.

As shown in Table II, the different carbonyl compounds, including ethyl acetoacetate, acetylacetone, cyclohexanone, cyclohexane-1,3-dione and dimedone, were uniformly transformed into the corresponding quinolines in good to excellent yields within 25–62 min.

The reusability of the catalyst in the reaction of 2-aminobenzophenone, and acetylacetone, under solvent-free conditions at 90 °C was evaluated. In this procedure, after completion of each reaction, hot ethanol was added and the catalyst was filtered off. The recovered catalyst was washed with ethanol, dried

and reused six times. A small decrease in the catalytic activity of the catalyst was observed after the 6th time of reuse (Table III).

TABLE II. Preparation of substituted quinolines promoted by BHS under solvent-free conditions at 90 °C

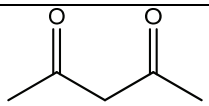
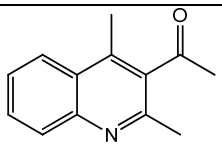
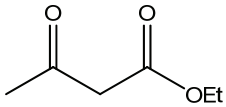
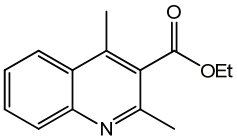
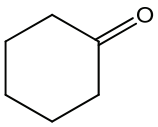
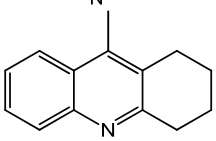
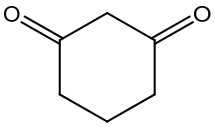
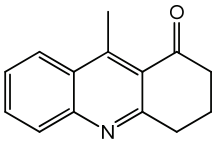
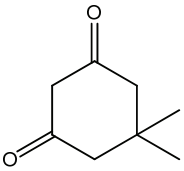
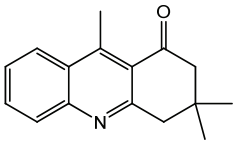
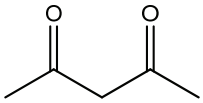
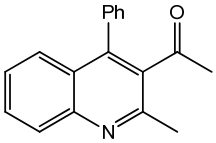
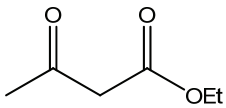
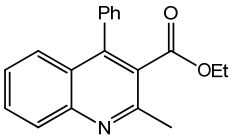
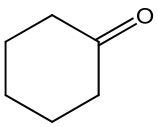
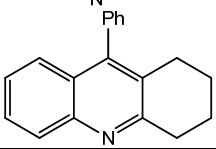
Product	1	2	3	Time, min	Yield, %
3a	**1a**			62	65
3b	**1a**			45	68
3c	**1a**			48	67
3d	**1a**			50	62
3e	**1a**			50	72
3f	**1b**			41	91
3g	**1b**			49	92
3h	**1b**			46	80

TABLE II. Continued

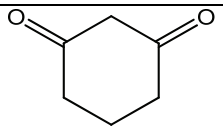
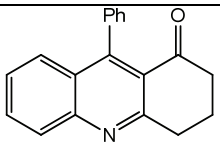
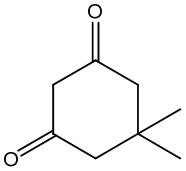
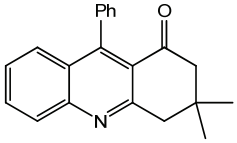
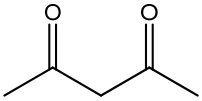
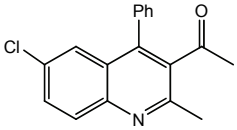
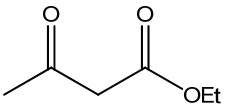
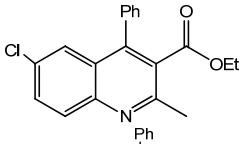
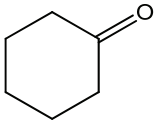
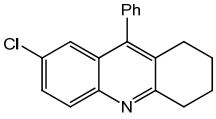
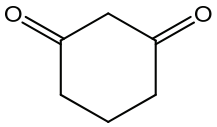
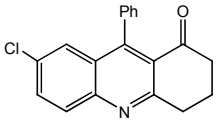
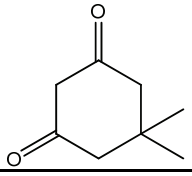
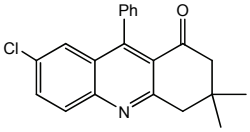
Product	1	2	3	Time, min	Yield, %
3i	**1b**			35	95
3j	**1b**			28	98
3k	**1c**			38	94
3l	**1c**			41	92
3m	**1c**			45	88
3n	**1c**			32	82
3o	**1c**			25	96

TABLE III. The reusability of the catalyst in six cycles for the reaction of 2-aminobenzophenone and acetylacetone under solvent-free conditions at 90 °C

Run	Time, min	Yield, %
1	41	91
2	42	90
3	44	88
4	46	85
5	48	82
6	52	78

To compare the advantage of the use of BHS over other reported catalysts, the model reaction of 2-aminobenzophenone and acetylacetone was considered as a representative example (Table IV). While in most of these cases, comparative yields of the desired product were obtained following the BHS-catalyzed procedure, the reported procedures required high catalyst loading (entry 2 and 4), or long reaction times (entry 1 and 2). These results clearly demonstrate that BHS is an equally or more efficient catalyst for this three-component reaction.

TABLE IV. Comparison of BHS with reported catalysts in the reaction of 2-aminobenzophenone and acetylacetone

Entry	Catalyst/temp., °C	Catalyst loading, mol %	Time, min	Yield, %	Ref.
1	$NaAuCl_4.2H_2O$/80	3	1440	46	19
2	[Hbim]BF_4/100	100	198	94	18
3	Oxalic acid/80	10	120	90	13
4	$HClO_4$–SiO_2/60	0.2 g	150	92	12
5	Sulfamic acid/70	5	45	89	10
6	BHS/90	5	41	91	This work

EXPERIMENTAL

Chemicals and apparatus

All chemicals were purchased from Merck or Fluka. All the synthesized compounds are known and were identified by comparison of their melting points, elemental analyses, mass spectra, IR, ^{1}H- and ^{13}C-NMR data with those of authentic samples. Monitoring of the reactions was accomplished by TLC on silica gel Polygram SIL G/UV 254 plates.

Preparation of boron hydrogen sulfate

A 50 mL suction flask was equipped with a constant pressure, dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution (water) and an alkali trap. Boric acid (1.55 g, 25 mmol) was charged into the flask and chlorosulfonic acid (8.74 g, *ca*. 5 mL, 75 mmol) was added dropwise over a period of 1 h at room temperature. HCl was evolved immediately. After completion of the addition, the mixture was shaken for 1 h, while the residual HCl was eliminated by suction. Then the mixture was washed with diethyl ether to remove the unreacted chlorosulfonic acid. Finally, a grayish solid material was obtained in 85 % yield (6.4 g).[23]

Typical procedure for the preparation of substituted quinolines

A mixture of 2-aminoaryl ketone (1 mmol), a carbonyl compound (1.1 mmol), and BHS (5 mol %) was heated at 90 °C for 10 min. Completion of the reaction was indicated by TLC (*n*-hexane/ethyl acetate, 4:1). After completion of the reaction, the insoluble crude product was dissolved in hot ethanol and boron hydrogen sulfate was filtered. The crude product was purified by recrystallization in ethanol to afford the pure product.

CONCLUSION

In summary, a simple and facile protocol was proposed for the synthesis of substituted quinolines by Friedländer quinoline synthesis using boron hydrogen sulfate as a novel environmentally safe heterogeneous solid acid catalyst under

solvent-free conditions. The method offers several advantages, including high yields, application of an inexpensive catalyst, short reaction times, easy workup and performing the reaction under solvent-free conditions that is considered relatively environmentally benign.

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ИЗВОД

$B(HSO_4)_3$: ЕФИКАСАН И РЕЦИКЛАБИЛАН КАТАЛИЗАТОР ЗА ФРИЛЕНДЕРОВУ СИНТЕЗУ ХИНОЛИНА

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Извршена је синтеза супституисаних хинолина употребом каталитичких количина бор-хидроген сулфата (BHS), без присутног растварача. У поређењу са другим методама, описани поступак нуди предности, као што су висок принос, кратко реакционо време, ниска цена катализатора, еколошки прихватљиви реакциони услови, избегавање токсичних растварача и катализатор који може да се рециклира.

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