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Green synthesis of quinoline-4-carboxylic acid derivatives using silica sulfuric acid as an efficient catalyst

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Abstract : Quinoline-4-caboxylic acid derivatives were synthesized in moderate to high yields via one-pot three components Doebner reaction of pyruvic acid, aldehydes and anilines in the presence of silica sulfuric acid as an efficient catalyst, under very mild conditions with excellent yields. The notable advantages of this protocol are work-up procedure is easy and the catalyst can be recovered by simple filtration and reused.

Keywords : Quinoline, Doebner synthesis, Silica sulfuric acid (SSA), Multicomponent reaction (MCR).

Introduction

Quinoline is a heterocyclic scaffold of paramount importance to human race. The utility of quinoline derivatives in the areas of drugs, food, catalyst, dye, materials, refineries[1] and electronics is well established. As a result, the synthesis of quinoline core and its derivatives have been an attractive goal for the synthetic organic and medicinal chemist. Several methods for the synthesis of the quinoline nucleus have been reported in the literature including Skraup[2], Friedlander[3], Pfitzinger[4], Conrad-Limpach and Combes[5]. These classical methods are well known and still frequently used for the preparation of pharmaceutically important materials bearing a quinoline backbone. Which possess diverse types of physiological activities including such as antitumour[6], antimalarial[7a,b], antimicrobial, antifungal[8], analgesic. Furthermore, these compounds find applications in chemistry of nano-structures and meso-structures with enhanced electronic and photonic functions[9]. Among them, the Doebner synthesis is one of the simplest and most frequently used pathways for synthesis of quinoline derivatives that involve a condensation reaction between pyruvic acid, aldehyde as well as aniline derivatives and which were discovered in the late 19th century. In the last few years remarkable improvements have been made through Doebner synthesis.

Owing to such significance, recently sulfuric acid immobilized on silica (HO_3SO-SiO_2)[10] has been introduced as an effective heterogeneous acid catalyst[11] for organic reactions. With the advance of green chemistry, a heterogeneous solid acid catalyst produces little waste with excellent activity and selectivity[12]. Reusability[13] and non-toxicity of these solids organize them as more beneficial industrial catalysts than homogeneous analogs and hence modern processes have turned to the gradual replacing of traditional catalysts with these advantageous recoverable solids. Silica sulfuric acid (SSA) is inexpensive and readily handled solid alternatives to sulfuric acid which have been used as superior catalysts in various heterogeneous organic transformations affording the corresponding products. Although the catalytic applications of solid supported reagents for organic synthesis have been well established, relatively few examples are reported on the use of (HO_3SO-SiO_2). Therefore utilization of such method offers significant advantages such as high conversions, mild reaction conditions, cleaner reaction profiles, high selectivity and low cost of the heterogeneous catalyst.

Results and discussion

A efficient synthesis of quinoline-4-carboxylic acid by using reusable silica sulfuric acid as catalyst. In order to evaluate the feasibility of silica sulfuric acid for Doebner reaction a model reaction (Scheme 1) with a building block ratio of 1.1 : 1 : 1 of aniline, benzaldehyde and pyruvic acid respectively, to give 2-phenylquinoline-4-carboxylic acid (**4a**) was conducted under different con-

ditions both in the absence and in the presence of silica sulfuric acid and results are given in Fig. 1. In the absence of silica sulfuric acid trace amount of product was obtained even after 12 h reflux with recovery of starting material, whereas in the presence of silica sulfuric acid (0.04 g) under the same conditions yield significantly increased. Buildings upon these result further studies were conducted and it was found that (0.10 g) of silica sulfuric acid was optimum for this reaction and gave a product of 82% yield in just 3 h. Duration of yield reached to maximum at 0.10 g and any further increase did not show any benefits (Fig. 1).

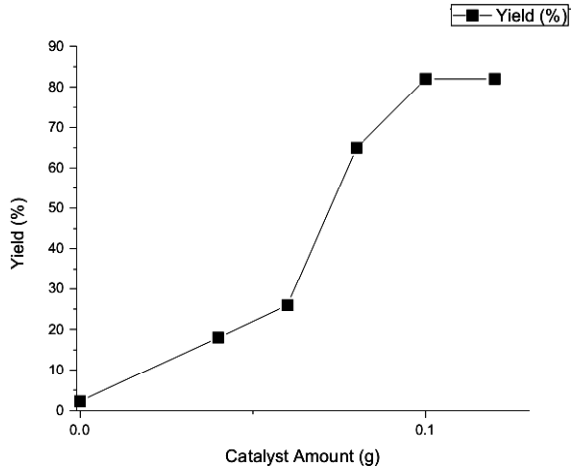


Fig. 1. The effect of amount of silica sulfuric acid the preparation of quinoline carboxylic acids.

Silica sulfuric acid was easily separated from the reaction medium by adding CH_3OH : $CHCl_3$ (6 : 4 v/v) to the stirred reaction mixture followed by filtration for its reusability experiments. The recovered catalyst was dried in oven at 80 °C for 1 h. The recovered catalyst was reused four times under the same reaction conditions for preparation of compound **4a**, as a model reaction, without any significant loose of activity (Fig. 2).

The general efficiency of this protocol was then studied for the synthesis of a variety of quinoline-4-carboxy acids derivatives (Table 1). As it can be seen in Table 1 various aldehyde and aniline reacted efficiently with pyruvic acid to afford the desired quinoline-4-carboxy acid in good yields. Experiment was carried out in a series of aromatic aldehydes and anilines bearing either electron-donating or electron-withdrawing groups on the aromatic ring.

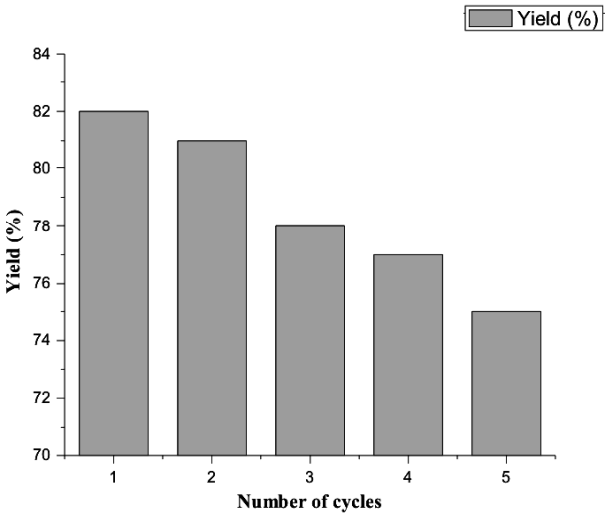


Fig. 2. Repeated use of silica sulfuric acid in Doebner synthesis.

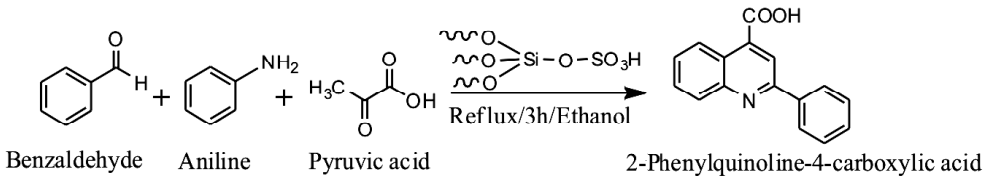
Table 1. Synthesis of quinoline-4-carboxylic acids by SSA catalyzed Doebner reaction

Entry	R_1	R_2	Time (h)	Product	Yield (%)
1	H	H	3	**4a**	82
2	4-CH_3	4-Cl	3	**4b**	84
3	4-CH_3	H	3.5	**4c**	81
4	4-CH_3	4-OMe	3	**4d**	83
5	4-Cl	H	3	**4e**	81
6	4-OMe	H	3	**4f**	80
7	4-NO_2	H	3	**4g**	75
8	H	3-Cl	3	**4h**	68

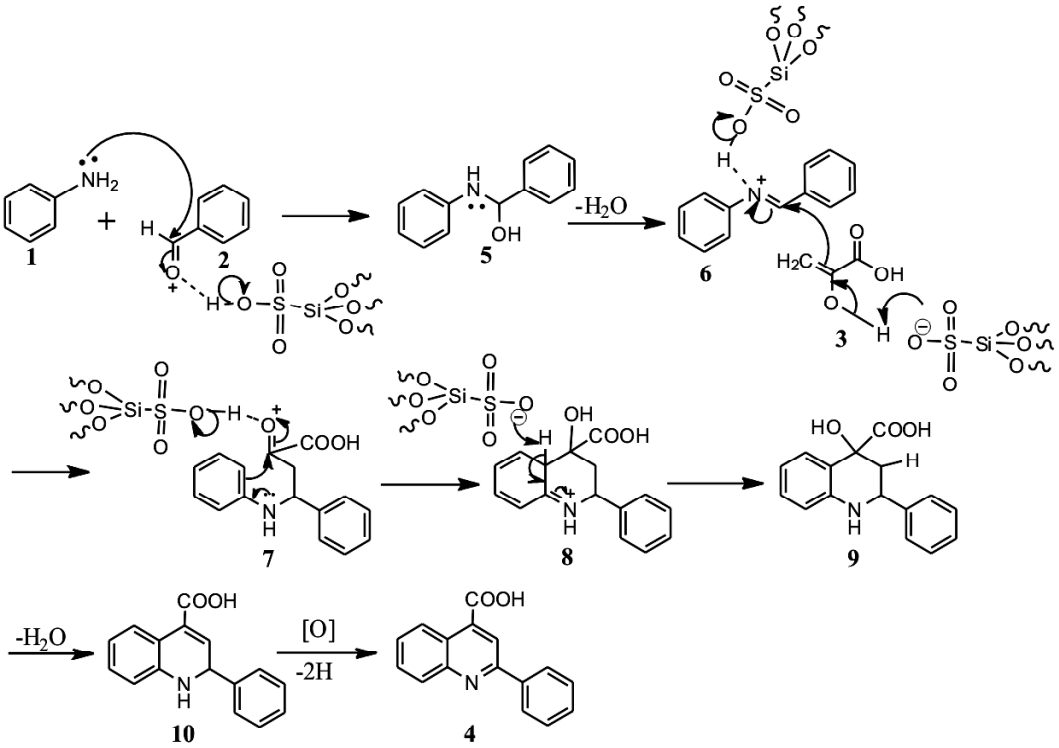
The mechanism of Doebner reaction was studied and explained by many researchers in recent year[14]. The reaction catalyzed by silica sulfuric acid is proposed to involved 1,2-addition of the aniline to aromatic aldehyde to form Schiff's base adducts followed by Mannich reaction with pyruvic acid to form intermediate **7** then dehydrative ring closure and oxidation afforded the final quinoline. Silica sulfuric acid could activate carbonyl group aromatic aldehyde, facilitate the subsequent cyclization and accelerate the reaction (Scheme 2).

Experimental

Analytical grade chemicals were used and distilled prior to their use. Melting points were determined on a quality digital melting point apparatus. The IR spectra were recorded on Shimadzu FT-IR spectrometer. ^1H and ^{13}C NMR spectra recorded on a Bruker Avance-400 MHz spectrometer using DMSO-d_6 as a solvent. Chemical shifts



Scheme 1

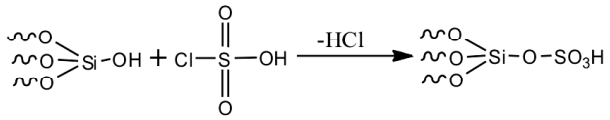


Scheme 2

(ppm) were referenced to the initial standard tetramethylsilane (TMS). Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer. Reactions were monitored by thin layer chromatography using silica gel 60F254 aluminum sheets (Merck).

Preparation of silica sulfuric acid (SSA) :

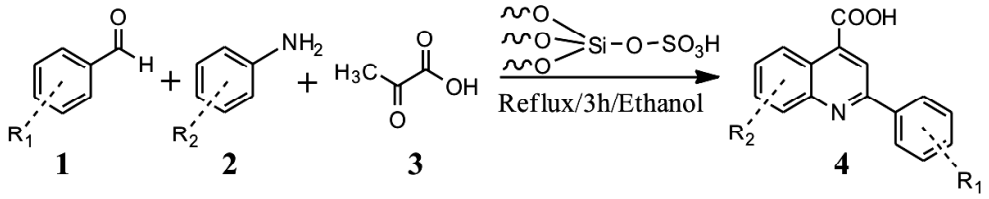
Silica sulfuric acid (SSA) was prepared by literature method with slight modification[15]. A 500 mL suction flask equipped with a constant-pressure dropping funnel and a gas inlet tube for conducting of HCl gas over an adsorbing solution (i.e. water) was used. It was charged with silica gel 60 (230–400 mesh) for column chromatography (60.0 g) in 150 mL chloroform as solvent. Chlorosulfonic acid (23.3 g, 0.2 mol) was added dropwise over a period of 30 min at room temperature. HCl gas immediately evolved from the reaction vessel. After the addition was completed the mixture was stirred for 30 min until all HCl was removed from reaction vessel. The mixture was then filtered, washed with chloroform (20 mL) and dried at room temperature to give the light brown solid of silica sulfuric acid (76.0 g) was obtained (Scheme 3).



Scheme 3

Synthesis of quinoline-4-carboxylic acid (**4**) :

A mixture of aniline (1.1 mmol), benzaldehyde (1



Scheme 4. Synthesis of quinoline-4-carboxylic acids from anilines, aldehydes and pyruvic acid in molar ratio (1.1 : 1 : 1) respectively.

mmol) and silica sulfuric acid in ethanol (10 mL) were refluxed for 10 min, pyruvic acid (1 mmol) in ethanol was then added to this reaction mass and reaction mixture was further refluxed for 3 h. When the reaction was completed as monitored by TLC, the reaction crude product was filtered and washed with water and recrystallized using hot ethanol. Purity of compound **4a** was checked by melting point and TLC.

2-Phenylquinoline-4-carboxylic acid (**4a**) :

Yield : 82%, m.p. 213 °C; IR (KBr, cm^{-1}) : ν 1255, 1589, 1697, 3028, 3423; ^{1}H NMR (DMSO, 400 MHz) δ : 13.8 (1H), 8.45 (1H), 8.7 (1H), 7.8 (H), 7.7 (1H), 8.17 (1H), 8.27 (2H), 7.5 (3H, m); FAB-Mass *m/z* 250.1 (M+1).

2-(4-Chlorophenyl)-6-methylquinoline-4-carboxylic acid **(4b)** :

Yield : 84%, m.p. 213 °C; IR (KBr, cm^{-1}) : ν 813, 1389, 1516, 1670, 3025, 3329; ^{1}H NMR (DMSO, 400 MHz) δ : 10.52 (1H), 8.19 (1H), 7.82 (1H), 7.46 (1H), 7.28 (1H), 7.02–7.25 (4H); FAB-Mass *m/z* 297.2 (M+1).

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