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Synthesis of Dihydroquinoline Derivatives Using Biodegradable Cellulose Sulfuric Acid as a Solid Acid Catalyst

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Abstract:

Multicomponent protocol for the condensation of malononitrile, 2-naphthol, aldehydesand ammonium acetate in presence of cellulose sulphuric acid using a mortarand pestle at room temperature afforded a wide range of valuable dihydroquinolines in high yields with short reaction times. This approach offers vital improvements for the synthesis of target compounds with regard to yield of products, simplicity in operation, green aspects by avoiding the solvents.

Key words: Multicomponent reaction (MCR); Grinding; dihydroquinoline derivatives; cellulose sulfuric acid; Mechanochemical Reaction.

Introduction:-

Quinoline is one of the heterocyclic scaffolds mostly found in many natural products and pharmaceutically active substances and commonly used as a building block in organic synthesis and material science (1–4) .Organic compounds containing quinoline scaffold have been studied extensively because of their significant applications as bioactive molecules (5–9).

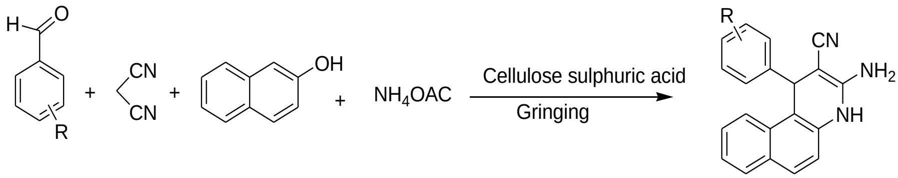
1,4-Dihydroquinoline derivatives have also attracted attention because those comprise a large family of medicinally significant compounds and are used in production of antihypertension, antidiabetic and many other drugs (10–12). Due to their widespread biological activity, a number of synthetic strategies have been developed for the preparation of substituted quinolines (13–16).

However, the scarce availability of starting materials, harsh reaction conditions, and the tedious workup procedures are the main drawbacks of many of these methods. To overcome such difficulties, much competent and convenient synthetic methodology is still desirable.

Cellulose is one of the most abundant natural materials in the world and it has been widely studied during the past several decades because it is a biodegradable material and a renewable resource. Its unique properties make it an alternative to conventional organic or inorganic supports in catalytic applications. Recently, the approach has been shifting more toward eco-friendly and reusable catalysts. Recently, cellulose sulfuric acid has emerged as a solid acid catalyst for acid catalyzed reactions, such as synthesis of a-aminonitriles [17], imidazoazines [18], quinolines [19], xanthenes [20], 3,4-dihydropyrimidine-2(1H)-ones [21], Pechmann condensation [22], thiadiazolobenzimidazoles [23], hexahydroxnthene [24] and quinazolines [25]. Cellulose sulfuric acid can be easily prepared by the reaction of inexpensive cellulose with chlorosulfonic acid.

Result and discussion:-

As a part of our ongoing research devoted to the development of useful synthetic methodologies [26-29], herein wereport an efficient and practical method for the synthesis of dihydroquinoline derivatives using biodegradable cellulose sulfuric acid which makes use of mild catalyst under solvent-free condition (Scheme 1). Herein, we have carried out the reaction



The reactionof malononitrile, 2-naphthol, aldehydesand ammonium acetate in presence of cellulose sulphuric acid has been considered as a standard model reaction.

We also screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of KH_2PO_4, alum, acidic alumina, amberlite-IR 120, sulphamic acid, ammonium metavanadate using mortar and pestle it gave lower yield of product even after prolonged reaction time. However, when the same reaction was conducted using cellulose sulfuric acid as a catalyst it gave excellent yields of product in short reaction time (**Table 1**).

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aldehydes, malanonitrile, 2-naphthol and ammonium acetate in presence of cellulose sulfuric acid as a catalyst using mortar and pestle; the results are shown in Table 2. We have carried out the similar reaction with various aromatic aldehydes containing electron donating or electron withdrawing functional groups at different positions but it did not show any remarkable differences in the yields of product and reaction time. It was observed that the reaction using 2-naphthol is very fast as compared to 1-naphthol. The results obtained in the current method are illustrated in **Table 2.**

In conclusion, cellulose sulfuric acid is an inexpensive and efficient catalyst for the synthesis of dihydroquinoline derivatives. The advantages offered by this method are solvent-free reaction conditions, short reaction times, ease of product isolation, and high yields. We believe that this method is a useful addition to the present methodology for the synthesis of dihydroquinoline derivatives.

General procedure for the synthesis of dihydroquinolines:-

Place a solution of freshly distilled benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), 2-naphthol (1.0 mmol) andammonium acetate (2.5 mmol). in a pestle. Add to it cellulose sulphuric acid (10 mol %) as a catalyst. After the starting material was completely consumed, the solid deposit was collected by the filtration and was washed with water and dried. The crude product was recrystallized from ethanol to offer pure product

Table 1. Screening of catalysts on the model reaction[a]

Entry	Catalysts	Time (min)	Yield[b] (%)
1	KH_2PO_4	15	20
1	Alum	15	60
2	Acidic alumina	15	42
3	Amberlite IR-120	15	53
4	Sulphamic acid	15	54
5	Ammonium metavanadate	15	70
6	Cellulose sulfuric acid	15	92

[a]Reaction of benzaldehyde, malononitrile, 2-naphtholand ammonium acetate using mortar and pestle.
[b]Isolated yield.

Table 2 Synthesis of dihydroquinoline derivativescatalysed by Cellulose sulphuric acid.

Entry	RCHO	Naphthol	Time (min)	Yield[b](%)
5a	H	α	6	94
5b	4-Cl	α	6	92
5c	4-Br	α	8	88
5d	4-OH	α	7	90
5e	2-Cl	α	8	87
5f	H	β	7	75
5g	4-Cl	β	9	74

5h	4-Br	β	10	70
5i	4-OH	β	10	67
5j	2-Cl	β	12	73

[a]Reaction Condition: **1 (a-j)**benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), α/ β -naphthol (1.0 mmol) and ammonium acetate (2.5 mmol). cellulose sulphuric acid (10 mol %) by gringing method [b]Isolated yield. All the products obtained were fully characterized by spectroscopic methods.

Spectral data of Compounds:-

Compound 5a: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.30 (1H, s), 6.97 (2H, s, −NH_2), 7.12–7.30 (5H, m), 7.42–7.62 (3H, m), 7.56 (1H, s, −NH), 7.82–7.94 (3H, m); ^{13}C NMR (100 MHz, DMSO-d6): δ 39.0, 59.8, 115.6, 116.9, 119.4, 123.5, 125.8, 126.5, 126.9, 127.0, 128.4, 128.8, 129.4, 130.1, 130.7, 144.6, 146.7, 160.6; IR (KBr, cm^{-1}): 3428, 3342, 2182; Mass spectra, m/z = 320 (M+1).

Compound 5b: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.45 (1H, s), 6.98 (2H, s,−NH_2), 7.15–7.29 (4H, m), 7.41–7.56 (3H, m), 7.59 (1H, s, −NH), 7.80–7.97 (3H, m); ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.3, 57.0, 112.2, 116.8, 120.5, 123.4, 124.5, 125.1, 126.3, 127.8, 128.4, 128.7, 129.8, 130.1, 130.7, 145.4, 146.9, 159.6; IR (KBr, cm^{-1}): 3425, 3338, 2187; Mass spectra, m/z = 332 (M+1).

Compound 5c:^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.40 (1H, s), 6.98 (2H, S, −NH^2), 7.14–7.28 (4H, m), 7.41–7.50 (3H, m), 7.55 (1H, s, −NH), 7.80–7.96 (3H, m); ^{13}C NMR (100MHz, DMSO-d_6): δ 39.1, 57.3, 114.5, 118.8, 120.6, 123.2, 124.4, 126.0, 127.2, 127.9, 128.4, 128.7, 129.6, 130.2, 132.6, 145.4, 148.8, 159.6; IR (KBr, cm^{-1}): 3420, 3326, 2179; Mass spectra, m/z = 377 (M+1).

Compound 5d: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.30 (1H, s), 6.96 (2H, s,−NH_2), 7.14–7.29 (4H, m), 7.38–7.49 (3H, m), 7.52 (1H, s, −NH), 7.81–7.95 (3H, m), 9.65 (1H, s, −OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.2, 59.1, 115.0, 118.7, 120.4, 123.1, 125.2, 126.2, 126.8, 127.7, 128.6, 128.8, 129.4, 130.4, 132.8, 145.3, 147.7, 159.6; IR (KBr, cm^{-1}): 3442, 3321, 3290, 2188; Mass spectra, m/z = 336 (M+1).

Compound 5e: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.80 (1H, s), 6.97(1H, t, J = 8.8 Hz), 7.06 (2H, s, $-NH_2$), 7.19–7.96 (10H, m, Ar−H & −NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.0, 57.1, 114.7, 118.7, 119.8, 123.6, 125.0, 127.4, 127.9, 128.4, 128.6, 129.5, 129.8, 130.02, 130.05, 130.7, 131.0, 142.5, 147.1, 159.8; IR (KBr, cm^{-1}): 3460, 3348, 2178; Mass spectra, m/z = 332 (M +1)

Conclusion

In conclusion the Cellulose Sulphuric Acid was found to be mild and effective catalyst for synthesis of dihydroquinoline derivatives by the condensation of malononitrile, 2-naphthol, aldehydes and ammonium acetate using a mortar and pestle at room temperature. We believed that, synthesis of dihydroquinoline derivatives will be a valuable contribution in the field of Heterocyclic chemistry as compared to the existing processes.

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