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Citrate trisulfonic acid as a novel, recyclable, and heterogeneous organocatalyst for the one-pot synthesis of 4-iminoquinolines

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ABSTRACT

Citrate trisulfonic acid (CTSA), as a novel, heterogeneous and organocatalyst, was applied for an efficient synthesis of 4-iminoquinolines using 2-aminobenzonitrile, active methylenes and orthoesters under solvent-free conditions. CTSA was synthesized via the reaction of trisodium citrate and chlorosulfonic acid in high purity. The catalyst was characterized using FT-IR, NMR and Mass spectra. The present method offers several advantages including high yields, short reaction time, and reusability of the catalyst and simple purification of the products.

1. Introduction

A powerful and efficient synthetic tool in organic chemistry is the multi-component reaction (MCR). From a synthetic point of view, more than two reactants are combined together in a single reaction vessel to give highly selective products [1]. In recent decades, MCRs are developed for the preparation of heterocyclic cores. They have very advantages, including low cost, reduction of energy and time, increase efficiency and green principles. Quinolines are important heterocyclic compounds that produce many natural products with interesting medicinal properties. They present a wide variety of interesting biological and pharmacological activities in synthetic organic chemistry. Derivatives of these compounds have been found to possess anticonvulsant [2], anthelmintic [3], antitumor [4], antibacterial [5], antifungal [6], anti-HIV [7], anticancer [8] and analgesic [9] activity. Furthermore, these compounds are used in the structure of drugs including nifedipine, nicardipine, and amlodipine [10]. Quinoline derivatives could be used as dopants in the polymer-LED materials [11].

Regarding the importance of these compounds in various fields, classical methods such as Skraup [12], Friedlander [13], Pfitzinger [14] and Doebner-von Miller [15] reactions have been frequently utilized for the synthesis of quinoline derivatives. However, these methods cannot make quinolines with wide diversity. Therefore, many efforts have been assigned to develop effective and convenient strategies for preparing of these derivatives.

In recent years, application of catalysts in chemical industries has a prominent role in the economic development. In the presence of the catalyst, reactions can be more efficient and selective thereby reduction and elimination of the amount of hazardous substances and waste residuals. Catalysts also accelerate reactions and reduce energy, time and operation costs. Nowadays, much attention has been focused on the design of high-quality catalysts, including organocatalysts that can eventually reach large scale applications for the synthesis of complex molecules and pharmaceuticals [16,17]. Organocatalysts are generally stable, cheap and easily available, show low toxicity and no sensitivity towards moisture or oxygen [18].

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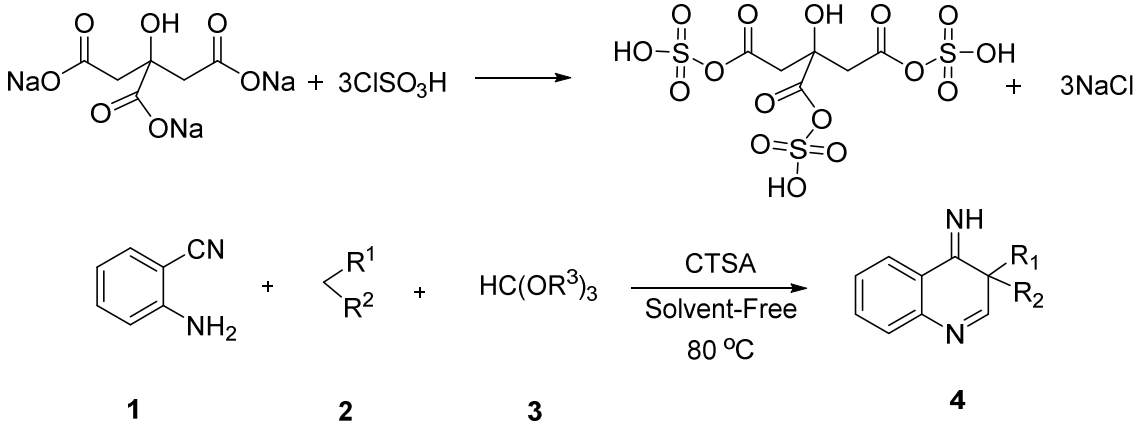
Designing organic reactions in solvent-free conditions possess attractive area in green chemistry. It offers several significant synthetic benefits in term of efficiency, selectivity, economic development and simplicity of the experimental procedure and work up technique. In solvent-free techniques, avoiding the use of solvents that are often toxic and expensive have a prominent role in the chemical reactions.

Owing to mentioned points and in green chemistry viewpoint, application of heterogeneous organocatalysts in multicomponent reactions under solvent-free conditions very remains a topic of interest. Therefore, in the present study, we have been continuous efforts to develop the synthesis of a new solid acid organocatalyst (CTSA) via reaction between trisodium citrate and chlorosulfonic acid with 1:3 mol ratio, respectively (Scheme 1). Afterwards, this catalyst was used for the preparation of 4- iminoquinolines 4 via three-component coupling 2-aminobenzonitrile 1, active methylenes 2 and orthoesters 3 (ethyl orthoformate and methyl orthoformate) under solvent-free conditions (Scheme 1).



Scheme 1. Synthesis of citrate trisulfonic acid, and 4- iminoquinolines catalyzed by CTSA

2. Experimental

All reagents and chemicals were purchased from Aldrich, Fluka, and Merck chemical companies**.** FT-IR spectra were recorded using a FT-IR JASCO-680 spectrometer instrument using KBr discs with absorptions in cm^{-1}. NMR spectra were run on a Bruker 400 MHz Ultrashield spectrometer at 400 MHz (1H) and 100 MHz (13C) using TMS as internal standard either $CDCl_3$ or DMSO-d_6 as solvent. Melting points of all synthesis compounds were determined using a Barnstead Electrothermal (BI 9300) apparatus and are uncorrected. The progress of the reactions and purity determination of the substrates were monitored by thin layer chromatography.

2.1. Preparation of citrate trisulfonic acid

Trisodium citrate trihydrate ($Na_3C_6H_5O_7.3H_2O$, MW = 312.07) was dried in an oven at 250 ^oC for 6 h to obtain anhydrous salt. Then, to chlorosulfonic acid (23.1 mL, 0.3 mol, 34.8 g) in a 250 mL round bottom flask, anhydrous trisodium citrate (25.8 g, 0.1 mmol) was gradually added with stirring over a period of 30 min at room temperature. After completion of the addition of trisodium citrate, the mixture was shaken for 30 min. citrate trisulfonic acid (CTSA) was obtained as light brown solid after washing with hot ethanol. Then it was dried and was stored in a capped bottle.

2.1.1. Spectral data of CTSA:

Mp = 190-192 ^oC; IR (KBr, cm^{-1}): 3500, 2921, 2468, 1776, 1724, 1643, 1226, 1060, 873, 592, 439. ^1H NMR (400 MHz, DMSO-d_6): δ_H 12.70 (s, 1H, S-OH), 12.65 (s, 2H, S-OH), 3.87 (br, 1H, OH), 2.88 (d, 2H, J=15.6, CH_2), 2.72 (d, 2H, J=15.6 CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 191.23, 188.32, 79.41, 50.13; MS (*m/z*): 430.4$[C_6H_8S_3O_{16}]^+$, 337.1 $[C_6H_8S_2O_{12}]^+$, 382.2 $[C_6H_6S_3O_{13}]^+$, 175.1 $[C_6H_8O_6]^+$, 351.1 $[C_6H_8S_2O_{13}]^+$, 310.1 $[C_5H_8S_2O_{11}]$, 293.1$[C_5H_8S_2O_{10}]$, 249, 232, 182, 123, 78 [19].

2.2. General procedure for the preparation of compounds 4a-j:

A mixture of 2-aminobenzonitrile (1.0 mmol), active methylenes (1.0 mmol), orthoesters (1.0 mmol) and CTSA (5.0 mol %) was heated with stirring at 80 °C for the suitable time. After completion of the reaction, as indicated by TLC, hot ethyl acetate (5 mL) was added and the obtained mixture was filtered and separated the pure catalyst. Then, the solvent was evaporated and solid products recrystallized from ethyl acetate to afford pure products. The recovered catalyst was dried and recovered for subsequent runs. The products were fully characterized by spectroscopic methods such as IR, ^1H

NMR, ^{13}C NMR and mass spectroscopy. The physical and spectroscopic data of new compounds are shown below:

Butyl 3-cyano-4-imino-3,4-dihydroquinoline-3-carboxylate (4i):

Yellow solid, M.P: 216-218 °C; [IR (KBr) cm^{-1}]: 3436, 2958, 2206, 1654, 1629, 1544, 1498, 1137, 1022, 937, 838. ^1H NMR (400 MHz, DMSO-d_6): δ_H 14.66 (s, 1H, NH), 7.85 (s, 1H, N=CH), 7.59 (d, 1H, J= 7.6 Hz, aromatic CH), 7.51-7.53 (m, 2H, aromatic CH), 7.31 (d, 1H, J= 7.6 Hz, aromatic CH), 4.28 (t, 2H, J=6.6 Hz, CH_2), 1.61-1.69 (m, 2H, CH_2), 1.36-1.47 (m, 2H, CH_2), 0.96 (t, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 165.96, 162.20, 162.11, 148.86, 133.77, 131.84, 126.33, 125.39, 117.22, 113.28, 64.40, 51.90, 30.83, 19.13, 14.10; MS (*m/z*): 269.1 $[C_{15}H_{15}N_3O_2]^+$, 244.1 $[C_{14}H_{16}N_2O_2]^+$, 144.1 $[C_9H_8N_2]^+$, 170.1 $[C_{10}H_8N_3]^+$, 219.2 $[C_{13}H_{17}NO_2]^+$, 247.1, 230.1, 118.1, 96.8.

1,1'-(4-imino-3,4-dihydroquinoline-3,3-diyl)diethanone (4j):

Yellow solid, M.P: 191-194 °C; [IR (KBr) cm^{-1}]: 3432, 2960, 1627, 1585, 1496, 1286, 1035, 931, 790. ^1H NMR (400 MHz, DMSO-d_6): δ_H 14.70 (s, 1H, NH), 7.97 (s, 1H, N=CH), 7.89 (d, 1H, J= 8.0 Hz, aromatic CH), 7.78-7.82 (m, 2H, aromatic CH), 7.37 (d, 1H, J= 8.0 Hz, aromatic CH), 2.42 (s, 3H, CH_3), 2.37 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 196.21, 196.03, 163.00, 161.59, 150.87, 133.83, 132.24, 126.57, 125.70, 118.19, 63.43, 32.02, 31.98; MS (*m/z*): 228.1 $[C_{13}H_{12}N_2O_2]^+$, 204.1 $[C_{12}H_{12}NO_2]^+$, 143.1 $[C_9H_7N_2]^+$, 120.1 $[C_8H_{10}N]^+$, 128.1 $[C_6H_9NO_2]^+$, 213.1, 171.1, 112.1, 102.1.

3. Results and Discussion

3.1. Characterization of CTSA

Some techniques such as IR, ^{13}C NMR and ^1H NMR and mass spectroscopy were used to characterize CTSA. FT-IR spectroscopy is an efficient tool, which determines some important changes in the structure of molecular species in a system. In the infrared spectra of trisodium citrate the vibration bands are assigned as follows (Fig. 1a): The band found at 3394 cm^{-1} is assigned for stretching vibration of OH group. The bonds at 1606 cm^{-1} and 1585 cm^{-1} are attributed to carbonyl groups. The peaks in the region of 1068-1442 cm^{-1} related to the stretching vibration of C-O and bending vibration of O-H group.

For citrate trisulfonic acid, the infrared vibration bands are attributed as follows (Fig. 1b): The broad peaks at 3500-2468 cm^{-1} and 1643 cm^{-1} are assigned to the stretching and bending vibrations of OH groups, respectively. The bonds at 1776 cm^{-1} and 1742 cm^{-1} are attributed to carbonyl groups. The absorption peaks found at 1226 cm^{-1} and 1060 cm^{-1} are assigned to stretching vibration of S-OH and asymmetric stretching vibration of S=O of the sulfonic acid bonds.

The ^1H NMR spectrum of CTSA showed two doublets identified as methylene groups (δ= 2.72 and δ= 2.88 ppm), a broad OH of the alcohol (δ= 3.87 ppm), two singlets corresponded to the OH groups of acid (δ= 12.65 and δ= 12.70 ppm). The proton-decoupled ^{13}C NMR spectrum of CTSA exhibited 4 distinct resonances in agreement with the proposed structure.

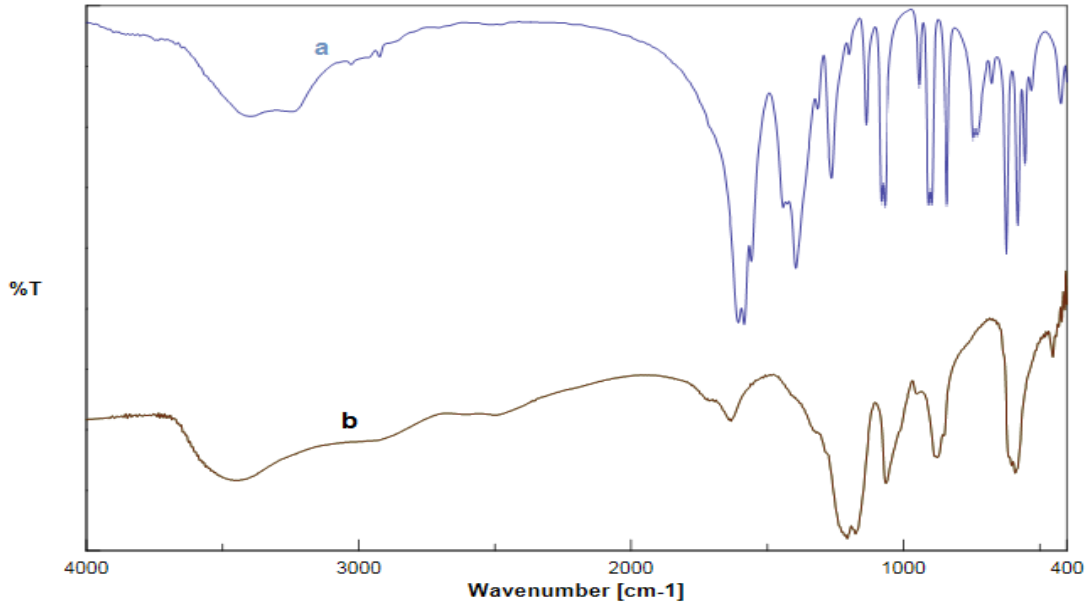


Fig. 1. FT-IR spectra of (a) trisodium citrate; (b) citrate trisulforic acid.

3.2. Recovering and reusing of the catalysts

The recoverability is one of the great characteristics of heterogeneous catalysts. The main disadvantage some catalysts are that they are destroyed in the reaction or work-up procedure and cannot be recovered. It is noteworthy that the CTSA was simply reused by washing with ethyl acetate. After completion of the model reaction of maloninitrile, 2-aminobenzonitrile, ethyl orthoformate and CTSA for the preparation of compound **4a,** the separated catalyst could be recovered after washing with ethyl acetate and drying at 70 °C for 2 h. The catalytic system worked well up to four catalytic runs without a significant decrease in the product yield and its catalytic activity (Fig. 2).

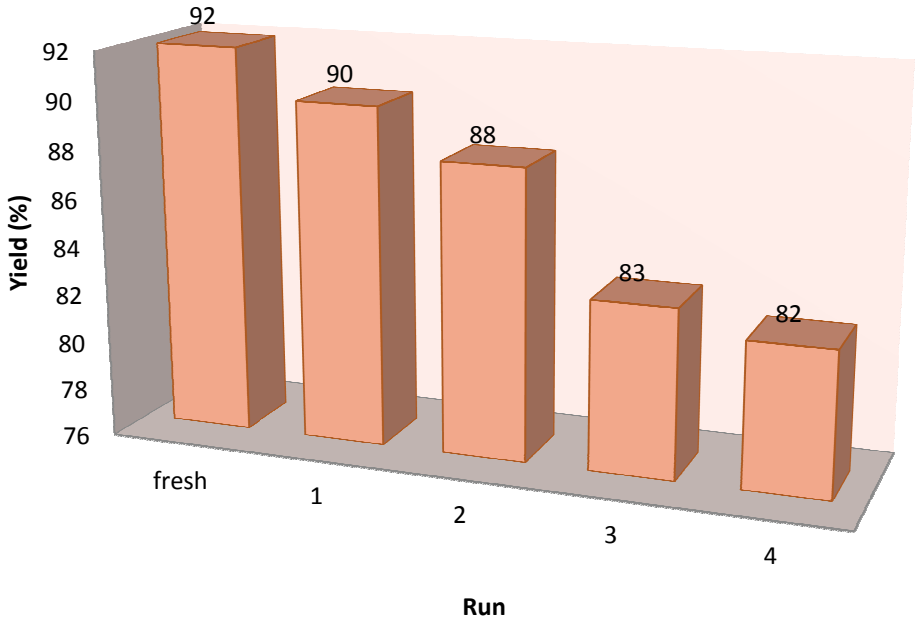


Fig. 2. Catalytic recyclability of CTSA

Fig. 3 indicates the FT-IR spectra of the fresh citrate trisulfonic acid (Fig. 3a) and used citrate trisulfonic acid (Fig. 3b). Both the fresh catalyst and that recovered after fourth use showed similar FT-IR spectra, indicating that the structure and morphology of the catalyst remained the same after recycling.

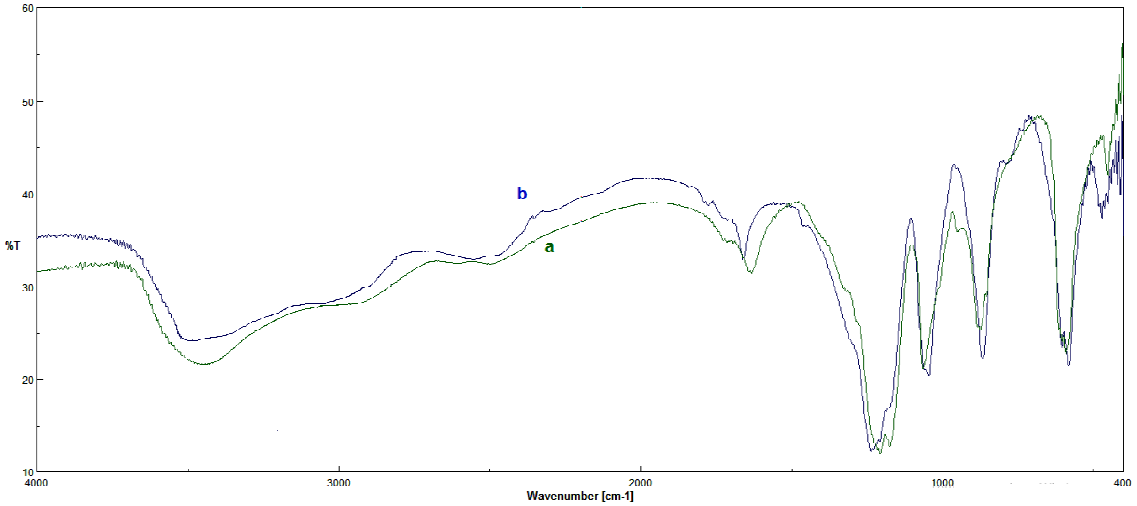


Fig. 3. FT-IR spectra of citrate trisulfonic acid (a) before use and (b) after reuse four times

3.3. Catalytic synthesis of 4-iminoquinoline compounds

In order to optimize the experimental conditions such as amount of the catalyst, solvent, and temperature for the synthesis of 4-iminoquinolines, the condensation between of malononitrile, 2-aminobenzonitrile, and triethyl orthoformate was selected as a model reaction.

As shown in table 1, reaction was screened in ethanol, dichloromethan, methanol, chloroform and a solvent-free system, and the best result was obtained after 35 min in the solvent-free conditions in 92 % yield.

Thereafter, the amount of the catalyst was evaluated in the model reaction and it was found that a quantitatively increase in catalyst amount of CTSA from 2 to 5 mol % causes higher product yields (Table 1, entries 1-3). It is to be noted that further increases in the amount of catalyst did not lead to any improvements in the reaction rate or yield.

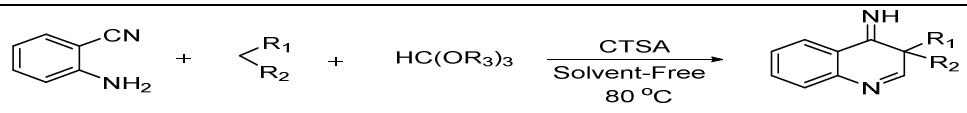
After optimization of catalyst amount and solvent, to improve yield and decrease the reaction time, the effect of temperature was studied. The result indicated that increase temperature to 80 °C leads to improvements in the reaction time and yield, while at temperatures over 80 °C (Table 1, entry 11) the reaction preceded smoothly.

Table 1. Catalytic activity evaluation and effect of temperature and solvent on the synthesis of multi-substituted imidazoles[a]

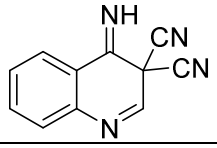
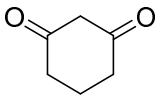
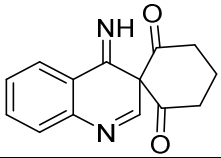
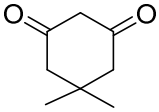
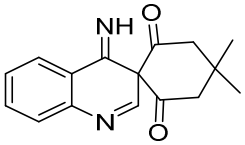
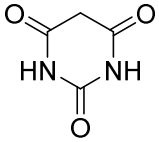
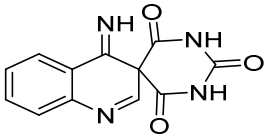
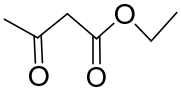
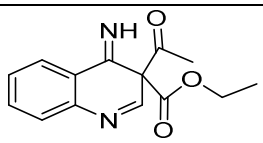
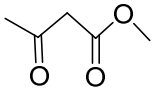
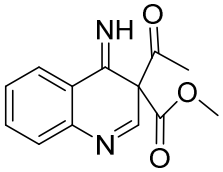
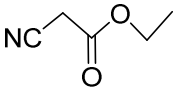
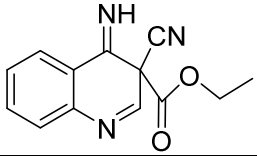
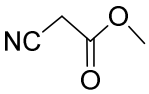
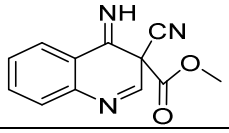
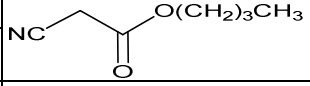
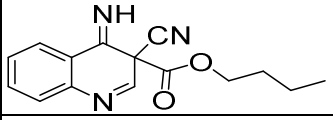
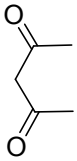
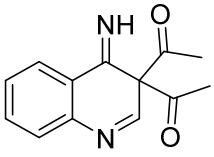
Entry	Catalyst (mol %)	Temp.	Solvent	Yield (%)[b]	Time (min)
1	2	80	-	80	58
2	3	80	-	82	50
3	**5**	**80**	**-**	**92**	**35**
4	10	80	-	91	40
5	5	Reflux	EtOH	71	68
6	5	Reflux	CH_2Cl_2	55	95
7	5	Reflux	CH_3OH	35	115
8	5	Reflux	$CHCl_3$	30	140
9	5	40	-	80	90
10	5	60	-	90	70
11	5	90	-	88	38

Table 2 shows results of the synthesis of the 4-iminoquinoline compounds in the presence of CTSA as a new, recyclable and heterogeneous organocatalyst. As shown, these compounds were prepared under solvent-free conditions with good to excellent yields. The main advantage of this reaction is that the percentage of byproducts was low and the recrystallization was also much easier.

Table 1. Synthesis of 4-iminoquinoline compounds in the presence of CTSA under solvent-free conditions.

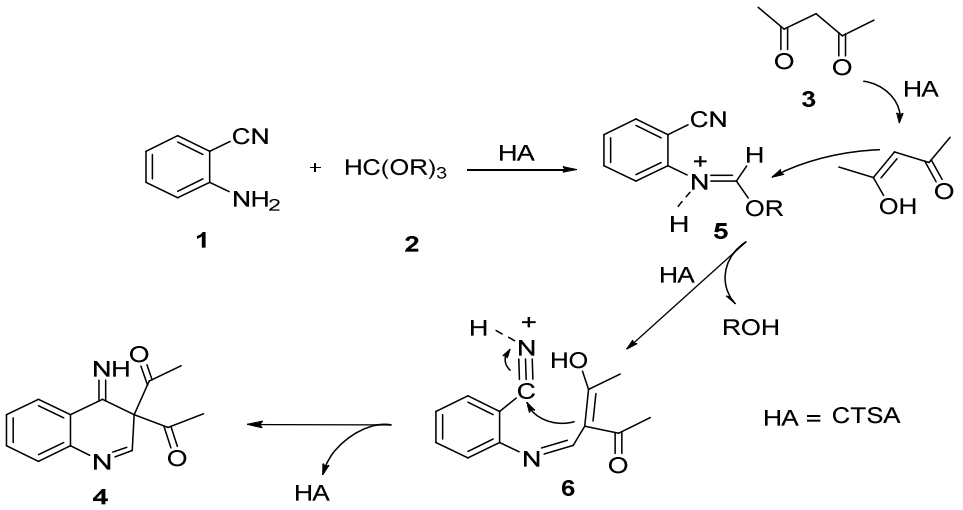


1 2 3 4

Entry	R^3	Active Methylene	Product	Time (min)	Yield [a] (%)	Mp (°C)
4a	Et			35	92	Decomp.
	Me			41	90	Decomp.
4b	Et			30	89	201-203
	Me			40	85	201-204
4c	Et			45	72	235-237
	Me			53	74	235-237
4d	Et			132	94	> 350
	Me			158	91	> 350
4e	Et			90	86	215-217
	Me			110	77	215-217
4f	Et			100	87	197-199
	Me			116	76	198-200
4g	Et			125	84	222-224
	Me			13	75	222-224
4h	Et			130	81	228-229
	Me			157	75	227-229
4i	Et			144	79	216-218
	Me			160	76	215-218
4j	Et			60	81	191-194
	Me			68	78	193-195

According to the above table, it was observed that both triethyl orthoformate and trimethyl orthoformate were utilized for the preparation of 4-iminoquinoline compounds. Indeed, the yield products from trimethyl orthoformate were less than those from triethyl orthoformate, and also the reaction time for trimethyl orthoformate was longer than triethyl orthoformate. Therefore, trimethyl orthoformate proved to be less active than triethyl orthoformate.

A probable mechanism for this conversion was depicted in scheme 2. The first step in this reaction involves the CTSA-catalyzed formation of imidic ester **5** stabilized by H^+, from the reaction of 2- aminobenzonitrile **1** with orthoesteres **2**. The imidic ester **5** that is very prone to react with an active methylene, leading to the formation of intermediate **6**. Then, intermediate **6** activated by CTSA and following intermolecular cyclization of intermediate **6** the product **4** was produced.



Scheme 2. Possible reaction mechanism for CTSA-catalyzed synthesis of 4-iminoquinolines

3.4. Comparative results

In order to show the ability of titled catalyst and condition in comparison with other catalysts and conditions, the three-component reaction of malononitrile, 2-aminobenzonitrile, and triethyl orthoformate as a model reaction was run in the presence of various catalysts under both heterogeneous and homogeneous conditions and then the product yields(%) and reaction times were evaluated as listed in table 2 as compared with titled catalyst. According to the table 2, it was understood that in comparison with other catalysts, the yield and time of the model reaction in the presence of CTSA under heterogeneous conditions especially in the absence of solvent is better or comparable with the other results [19,20].

Table 2. Comparison of efficiency of various catalysts in the synthesis of 4-iminoquinoline derivatives.

Entry	Catalyst	condition	Time (min)	Yield (%)
1	PTSA (Ethanol/Reflux)	homogeneous	110	54
2	Tungstosilicic acid (TSA) (Ethanol/Reflux)	homogeneous	130	50
3	$AlCl_3$ (Ethanol/Reflux)	heterogeneous	150	55
4	Fe_3O_4 (Ethanol/Reflux)	heterogeneous	125	58
5	TiO_2 (Ethanol/Reflux)	heterogeneous	130	64
6	VSA(Ethanol/Reflux)	heterogeneous	80	60
7	Fe_3O_4@APTES-MAH NPs (Ethanol/Reflux)	heterogeneous	92	63
8	CTSA (Ethanol/Reflux) (Current work)	heterogeneous	68	71
9	CTSA(Solvent-free) (current work)	heterogeneous	35	92

4. Conclusions

In conclusion, we have found an efficient one-pot multicomponent method for the synthesis of 4-iminoquinoline derivatives by the condensation reaction of 2-aminobenzonitrile, active methylenes and orthoesters under solvent-free conditions using the catalytic amount of the reusable and environmentally benign citrate trisulfonic acid (CTSA) as a novel solid acid organocatalyst. This catalytic system has very advantages such as high yields, simple workup, inexpensive and recoverability of the catalyst, solvent-free condition, short reaction time and simple purification of the products.

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