J IRAN CHEM SOC
DOI 10.1007/s13738-013-0252-2

ORIGINAL PAPER

Zirconium triflate: An efficient catalyst for the synthesis of quinolines and quinoxalines

Eskandar Kolvari · Mohammad Ali Zolfigol · Nadiya Koukabi · Maryam Gilandust · Abdol-Vahid Kordi

Received: 16 November 2012 / Accepted: 17 March 2013

Abstract An environmentally friendly method is described for the preparation of substituted quinoline and quinoxaline derivatives using $Zr(OTf)_4$ as an efficient catalyst. The method is based on using 1,3-diketones, ketones and 2-aminoaryl ketones under solvent-free conditions and also on using 1,2-diketone, 1,2-diamine in $EtOH/H_2O$ at room temperature for quinloine and quinoxaline synthesis, respectively. The advantages in using this method, include its environmental friendliness, simple operating process and good yields.

Keywords Zirconium triflate · Quinolines · Quinoxalines

Introduction

Acid catalysts play a predominant role in organic synthesis and transformations. Many organic reactions, such as alkylation, acylation, isomerization, nitration, esterification, and rearrangements like pinacol, Beckman, etc. are accomplished by acid catalysts. All these acid catalyzed reactions are mostly carried out by employing conventional mineral acids, such as H_2SO_4, HNO_3, and HF or Lewis acids, such as $AlCl_3$ and BF_3. In view of environmental and economical reasons, there is an ongoing effort to replace the conventional catalysts with newer solid acids. This is mainly due to the distinct advantages of solid acid catalysts, such as non-toxicity, non-corrosiveness, ease of handling, and ease to recover and reusability [1]. In this direction, various solid acid systems were introduced which include hetropolyacids, zeolites, and clays. The main disadvantage associated with hetropolyacids is that they are soluble in polar solvents and lose their activity at higher temperatures by losing structural integrity. To prevent this there are some attempts to immobilize them in silica or activated carbon matrix, which, however, limits the accessibility and efficiency of the catalysts. Although clays and zeolites are quite reliable, activities of these materials are much lower than those of the conventional homogeneous acids due to pore blocking and hydration. Considering these reasons, there is an ongoing effort to develop stronger solid acid systems, which are water tolerant, stable at high temperatures and suitable for both liquid and solvent-free media. Metal-based catalysts offer several advantages over zeolite and clay-based catalysts. These are active over a wide range of temperatures and more resistant to thermal excursions. Therefore, comprehensive investigations were undertaken on promoted zirconium (IV) catalysts for organic synthesis and transformation reactions [2].

For many years, synthesis of quinoline and quinoxaline has been of considerable interest in organic and medicinal chemistry since a large number of natural products and drugs contain these heterocyclic nucleuses [3–5]. There are many reported methods for the synthesis of quinoline rings [6], the Friedlander procedure [7, 8] is still one of the

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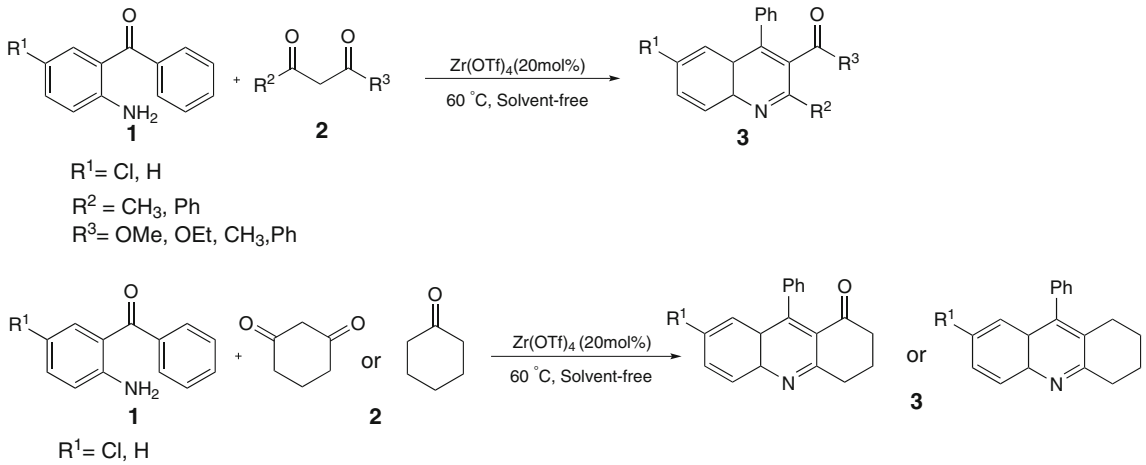
Published online: 09 April 2013



Scheme 1 Zirconium triflate catalyzed synthesis of quinolines under solvent-free conditions

Table 1 Effect of different solvents for the synthesis of quinolines (A) and quinoxalines (B) catalyzed by $Zr(OTf)_4$

Entry	Solvent	Time (h:min)		Yield (%)[a]	
		A[b]	B[c]	A[b]	B[c]
1	THF	1:00	04:00	90	89
2	Ethanol	04:00	04:00	82	90
3	Methanol	04:00	00:30	50	94
4	CH_3CN	01:00	04:00	92	87
5	H_2O	00:30	04:00	95	85
6	Ether	04:00	04:00	52	87
7	CH_2Cl_2	04:00	04:00	57	80
8	H_2O/Ethanol	01:00	00:10	85	96
9	–	00:30	04:00	98	78

[a] Isolated yield

[b] All reactions were performed on a 1.0 mmol scale using 20 mol %of $Zr(OTf)_4$ in 5 ml of solvent

[c] All reactions were performed on a 1.0 mmol scale using 10 mol %of $Zr(OTf)_4$ in 5 ml of solvent

Table 2 Effect of various amount of $Zr(OTf)_4$ for the synthesis of quinolines (A) and quinoxalines (B)

Entry	$Zr(OTf)_4$ (mol %)	Time (h:min)		Yield (%)[a]	
		A[b]	B[c]	A[b]	B[c]
1	5	01:15	00:20	90	78
2	10	01:00	00:10	93	96
3	15	01:00	00:20	95	90
4	20	00:30	00:20	98	86
5	25	01:30	00:20	94	80
6	–[d]	24:00	24:00	86	73

[a] Isolated yield

[b] All reactions were performed on a 1.0 mmol scale under solvent-free conditions at 60 °C

[c] All reactions were performed on a 1.0 mmol scale in H_2O/Ethanolat R.T.

[d] Without $Zr(OTf)_4$

simplest and straightforward methods for the synthesis of polyfunctional quinolines. Alternatively, this reaction was also investigated using different protic and Lewis acids, such as Nano-Flake ZnO [9], $Bi(OTf)_3$ [10], $FeCl_3$ and $Mg(ClO_4)_2$ [11], AcOH under microwave irradiation [12], HCl [13], PBBS and TBBDA [14]. In addition, a number of synthetic strategies have been developed for the preparation of substituted quinoxalines, such as the bi-catalyzed oxidative coupling reaction [15], via a tandem oxidation process using $Pd(OAc)_2$ or $RuCl_2$–$(Ph_3P)_3$–TEMPO [16], heteroannulation of nitroketene N,S-arylaminoacetals with $POCl_3$ [17], etc [18–21].

However, most of the synthetic protocols reported so far suffer from high temperatures, prolonged reaction times, low yields and the use of hazardous catalysts. Moreover, the synthesis of these heterocyclic compounds has been usually carried out in harmful solvents such as acetonitrile, THF, DMF, and DMSO, leading to difficult product isolation and recovery procedures, thus making these methods unsuitable for scale up in an environmentally benign and economical way. When considering the wide spread applications of the resultant compounds, we felt that a catalyst of choice should be one that is easily available, less toxic, and operable under environmentally friendly conditions so as to fulfil the 'triple bottom line' hilosophy of green chemistry.

Thus to continue our investigation on developing new methodologies in synthesis of heterocyclic compounds [22–25] and to explore the applicability of zirconium in various reactions, we became interested in zirconium-triflate promoted synthesis of quinolines and quinoxalines containing reactive functionalities.

Table 3 Synthesis of quinolines derivatives catalyzed by $Zr(OTf)_4$ using different 1,3-diketones,ketones and 2-aminoaryl ketones

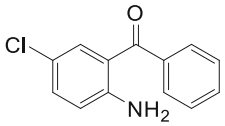
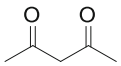
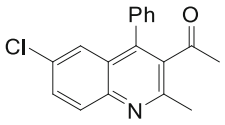
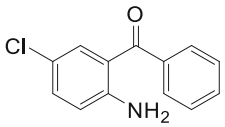
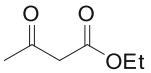
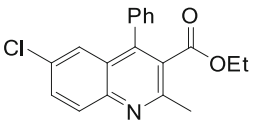
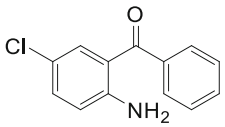
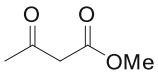
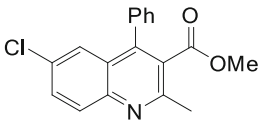
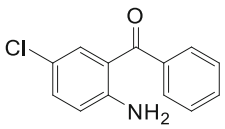
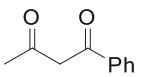
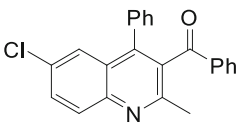
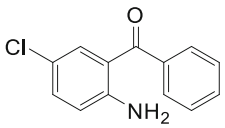
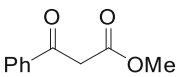
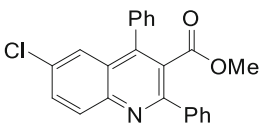
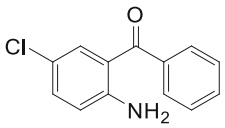
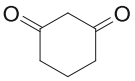
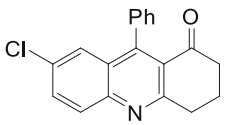
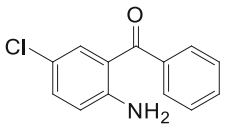
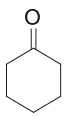
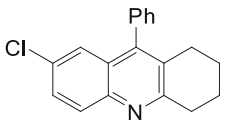
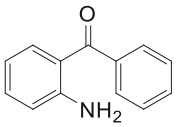
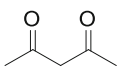
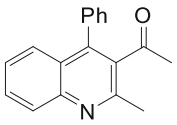
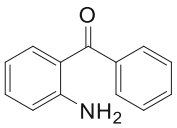
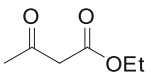
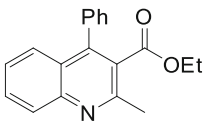
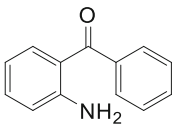
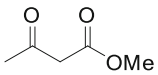
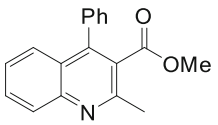
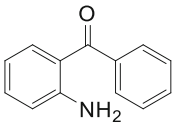
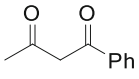
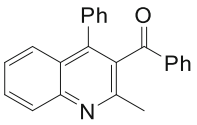
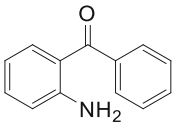
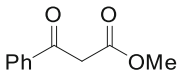
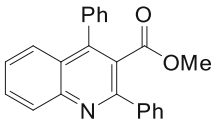
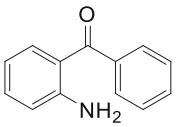
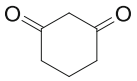
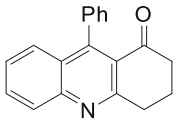
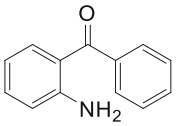
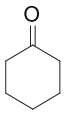
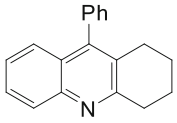
Entry	2-Aminoaryl ketone	1,3-Diketone	Product	MP (°C) Found	Time(min)	Yield (%)[b]
1				157-158	90	97
2				101-102	90	88
3				134-135	30	98
4				217-218	30	89
5				136-138	120	85
6				185-186	60	98
7				165-166	30	90
8				111-113	30	85
9				98-100	30	83
10				106-108	90	80

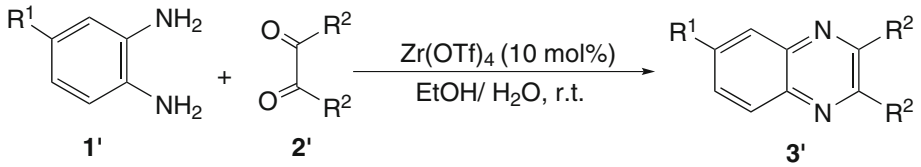
Table 3 continued

Entry	2-Aminoaryl ketone	1,3-Diketone	Product	MP (°C) Found	Time(min)	Yield (%)[b]
11				140-141	30	88
12				130-133	60	93
13				158-160	90	95
14				146-148	120	91

All reactions were performed on 1.5 mmol of 1,3-diketone, 1.0 mmol of 2-aminoaryl ketone, 20 mol % of $Zr(OTf)_4$, at 60 °C under solvent-free conditions

[a] Isolated yield of quinolines, confirmed by ^{1}HNMR

Scheme 2 Zirconium triflate catalyzed synthesis of quinoxalines at room temperature



Results and discussion

We initially investigated the effect of different solvents on the reaction rate as well as the yield of product in the synthesis of 6-chloro-3-(methylformato)-2-methyl-4-phenylquinoline from 2-amino-5-chlorobenzophenone and methyl acetoacetate in the presence of $Zr(OTf)_4$ as a model reaction. Screening different solvents, shows H_2O afford the products in good yields and with higher reaction rates but under solvent-free conditions, the reactions proceeded to afford the corresponding product in less time and excellent yield (Scheme 1; Table 1, columns A). We also evaluated the amount of $Zr(OTf)_4$ required for this transformation to improve the yield and optimize the reaction conditions, using a 20 % mol of catalyst is most effective in terms of both time and yield (Table 2, columns A). In the absence of $Zr(OTf)_4$, the reaction takes more than 24 h to complete (Table 2). In an optimized reaction condition, 1,3-diketone (1.5 mmol) and 2-aminoaryl ketones (1.0 mmol) were mixed with $Zr(OTf)_4$ (0.2 mmol) and stirred at 60 °C under solvent-free conditions for 0.5–2 h. After the completion of the reaction (monitored by TLC), a simple work up affords the products in excellent yields.

To evaluate the efficiency of this methodology, a number of 1,3-diketones, ketones and 2-aminoaryl ketones were further subjected to condensation using catalytic amount of $Zr(OTf)_4$ (Table 3). Reactions proceeded very cleanly at 60 °C and no undesirable side reactions were observed.

Subsequently, this catalyst was explored for the synthesis of quinoxalines. A blank reaction was conducted

Table 4 Synthesis of quinoxaline derivatives catalyzed by $Zr(OTf)_4$ using different 1,2-diketones and 1,2-diamines

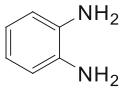
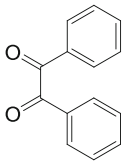
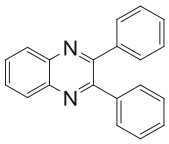
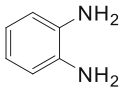
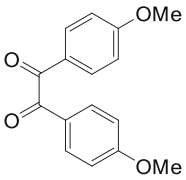
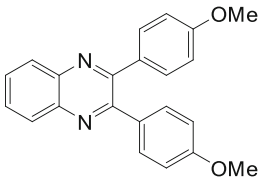
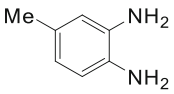
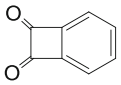
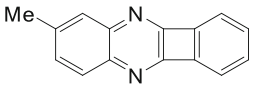
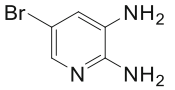
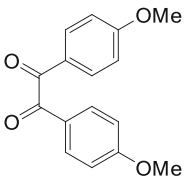
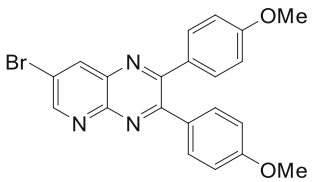
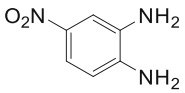
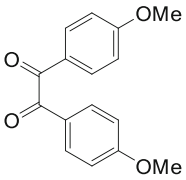
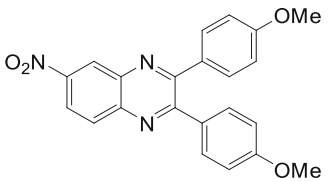
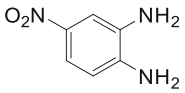
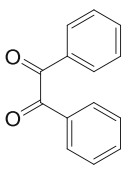
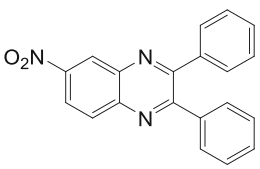
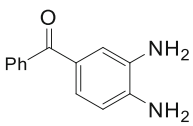
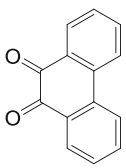
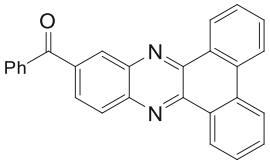
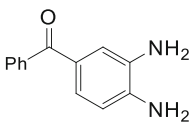
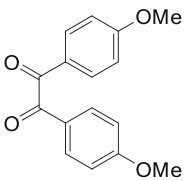
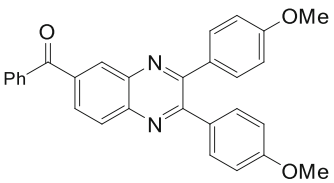
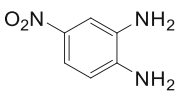
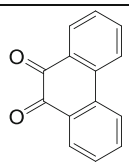
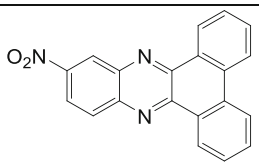
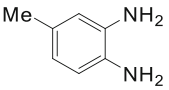
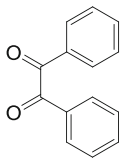
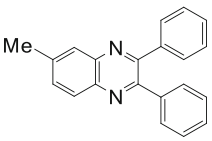
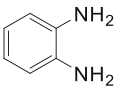
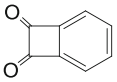
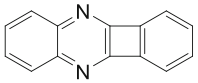
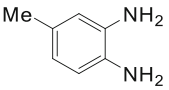
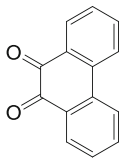
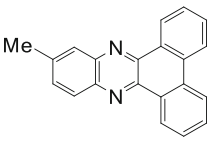
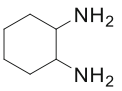
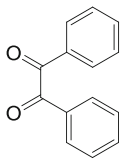
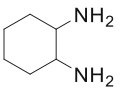
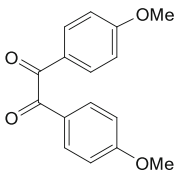
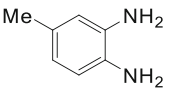
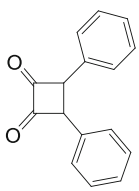
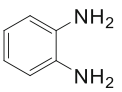
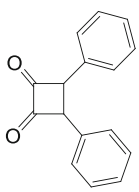
Entry	1,2-Diamine	1,2-Diketone	Product	Mp (°C) Found	Time (min)	Yield (%)[b]
1				124-125	10 (30)[c]	96 (90)[c]
2				151-152	30	87
3				189-192	20	87
4				132-134	30	87
5				189-191	30	94
6				187-189	20	94
7				242-244	30	94
8				198-200	20	94

Table 4 continued

Entry	1,2-Diamine	1,2-Diketone	Product	Mp (°C) Found	Time (min)	Yield (%)[b]
9				240-243	30	96
10				115-117	15	97
11				189-191	20	85
12				205-207	20	95
13			N.R.[d]	----	360	-
14			N.R.[d]	----	360	-
15			N.R.[d]	----	360	-
16			N.R.[d]	----	360	-

Reaction conditions: 1,2-diketone (1.0 mmol), 1,2-diamine (1.2 mmol), Zr)OTf($_4$ (10 mol %) in 5 ml of H_2O/EtOH at R.T.

[a] Isolated yield of quinoxalines

[b] Reaction conditions: 1,2-diketone (1.0 mmol), 1,2-diamine (1.2 mmol), CF_3SO_3H (10 mol %) in 5 ml of H_2O/EtOH at R.T.

[c] No reaction was observed

Table 5 Reuse of $Zr(OTf)_4$ for the synthesis of 6-chloro-3-)methyl-formato(-2-methyl-4-phenylquinoline (A) and 2,3-diphenylquinoxaline (B)

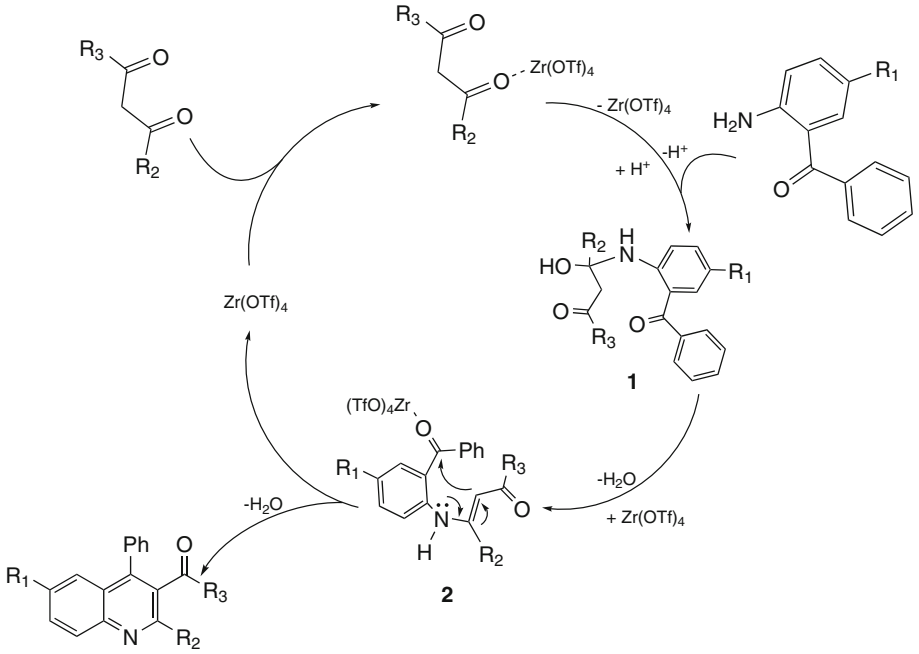
Run	1		2		3	
	A[a]	B[b]	A[a]	B[b]	A[a]	B[b]
Yield (%)[c]	98	96	97	94	94	93

[a] Reaction conditions: 2-amino-5-chlorobenzophenone (1.0 mmol), methyl acetoacetate (1.5 mmol), and $Zr(OTf)_4$ (0.20 mmol), under solvent-free conditionsat 60 °C

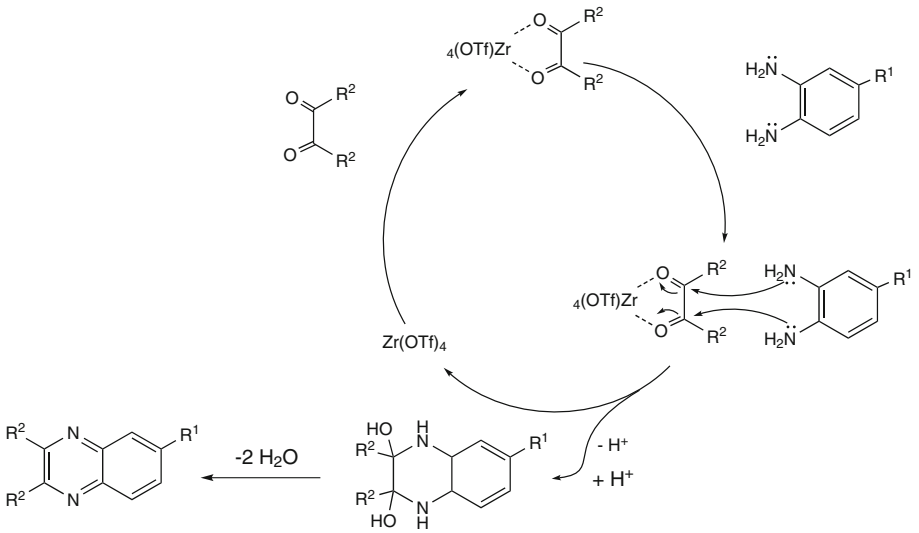
[b] Reaction conditions: *o*-phenylenediamine (1.2 mmol), benzyl (1.0 mmol), and $Zr(OTf)_4$ (0.10 mmol) in $EtOH/H_2O$ at room temperature

[c] Isolated yield of the quinolone and quinoxaline

using benzil and *o*-phenylenediamine, for initial optimization of the reaction conditions and the identification of the best solvent, and amount of catalyst. The mixture of $EtOH/H_2O$ was found to be more effective when compared with the other solvent tested (Table 1, Entry 8, column B). Among different amounts of catalyst used, 10 mol % gave the optimum yield (Table 2, Entry 2, column B). In summary, the optimal conditions for the zirconium-triflate catalyzed quinoxaline synthesis involved a combination of $Zr(OTf)_4$ (10 mol %), 1,2-diketone (1.0 mmol) and 1,2-diamine (1.2 mmol) and $EtOH/H_2O$ as solvent at room temperature. Encouraged by these results, a number of 1,2-diketones and 1,2-diamines were further subjected to



Scheme 3 Suggested mechanism pathway for synthesis of quinolines catalyzed by zirconium triflate



Scheme 4 Suggested mechanism pathway for zirconium triflate catalyzed synthesis of quinoxalines

condensation using catalytic amount of $Zr(OTf)_4$ (Scheme 2; Table 4). Reactions proceed very cleanly at room temperature and no undesirable side reactions were observed.

The possibility of recycling the catalyst was examined. For this reason, the reaction of 2-amino-5-chlorobenzophenone and methyl acetoacetate at 60 °C under solvent-free conditions and the reaction of *o*-phenylenediamine and benzil in $EtOH/H_2O$ at room temperature in the presence of $Zr(OTf)_4$ was studied. When the reaction was completed, solvent was evaporated in vacuum, ethyl acetate was added and organic materials were extracted and $Zr(OTf)_4$ was saved for the next reaction. The recycled catalyst could be directly reused. We have found that $Zr(OTf)_4$ is a reusable catalyst and even after three runs for the synthesis of quinoline and quinoxaline, the catalytic activity of $Zr(OTf)_4$ was almost the same as that of the freshly used catalyst (Table 5).

The mechanisms for these reactions are shown in Schemes 3, 4. The nucleophilic attack of 2-aminoaryl ketone to ketone take place to give intermediate **1** in the presence of Lewis acid $Zr(OTf)_4$ (Scheme 3). The dehydration of **1** gives another intermediate **2** which is further activated by Lewis acid $Zr(OTf)_4$ and serves as an electrophile. An intramolecular attack of α-carbon of enamine on the activated carbonyl group of 2-aminoaryl ketone then occurs to give the cyclization product, followed by dehydration, forming the desired quinoline product. On the other hand, the condensation reaction of 1,2-diamine with 1,2-dicarbonyl compounds follows the regular mechanism of acid-catalyzed condensation reactions [2], we assumed that the step involve the complexation of $Zr(OTf)_4$ with the diketone by acting as an acid, followed by nucleophilic attack of 1,2-diamine on the resulting intermediate. Following dehydration, the products obtained, as shown in Scheme 4.

Experimental

General experimental procedure for the preparation of quinolines

A mixture of 1,3-diketone (1.5 mmol) and 2-aminoaryl ketones (1.0 mmol) were mixed with $Zr(OTf)_4$ (0.2 mmol) and stirred at 60 °C under solvent-free conditions. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate (15 ml) was added. Organic materials were extracted and the solvent evaporated under reduced pressure to afford the crude product, which was recrystallized by suitable solvent-like ethanol to obtain pure quinoline.

General experimental procedure for the preparation of quinoxalines

A mixture of 1,2-diketone (1.0 mmol), 1,2-diamine 2 (1.2 mmol) and $Zr(OTf)_4$ (0.1 mmol) in $EtOH/H_2O$ (3:2 ml) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuum. To separation of catalyst "$Zr(OTf)_4$", ethyl acetate (15 ml) was added to the reaction mixture. Organic materials were dissolved in ethyl acetate and insoluble $Zr(OTf)_4$ was separated by simple filtration and saved for the next reaction. The solvent evaporated under reduced pressure to afford the crude product, which was recrystallized by suitable solvent like ethanol to obtain pure quinoxaline.

All of the obtained quinolines and quinoxalines are known compounds and identified by ^{1}H-NMR and melting point when compared with the literature values.

Conclusion

In this article, we have successfully developed a new, and easy catalytic protocol for the preparation of various quinolines and quinoxalines, using catalytic amounts of $Zr(OTf)_4$ under solvent-free conditions and at room temperature, respectively. The use of non-toxic $Zr(OTf)_4$ as catalyst for the synthesis of quinolines in moderate to excellent yields is also significant under the aspect of environmentally benign process.

Acknowledgments The authors acknowledge to Bu-Ali Sina University Research Council and Center of Excellence in Development of Chemical Methods (CEDCM) and national foundation of elites (BMN) for support of this work.

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