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$RuCl_3.xH_2O$ CATALYZED RAPID, FACILE AND AN EFFICIENT SYNTHESIS OF QUINOXALINES IN [bmim] PF6

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ABSTRACT
An efficient and rapid method has been developed for the synthesis of quinoxalines via condensation of 1,2-diketones and 1,2-diamines using $RuCl_3.xH_2O$ as catalyst in [bmim]PF_6 at ambient temperature. This protocol has the features such as mild reaction conditions, readily available starting materials, high yield, simple work-up procedure and recyclable catalyst as well as solvent.
Keywords: Quinoxalines, 1,2-diketones, 1,2-diamines, ruthenium(III) chloride, [bmim]PF_6, recyclable.

INTRODUCTION

Quinoxalines are important class of nitrogen heterocycles and these are the sub-set of a variety of commercially important products such as pharmaceuticals,[1] agrochemicals,[2] dyes,[3] organic semiconductors etc.[4] As their derivatives possess several type of significant biological activities such as anticancer,[5] antiviral,[6] antibacterial,[2(a),7] antitumor,[8] anti-inflammatory,[5] DNA-cleaving[9] and kinase inhibition agents.[10] Quinoxaline ring is also found in clinically used antibiotic molecules such as actinomycin, echinomycin and levomycin.

The simplest way to produce this motif is the condensation of 1,2-aryldiamines and aryl 1,2-diketones[11] rather than other reported methods such as cyclization of α-arylimino oximes with α-dicarbonyl,[12] oxidative coupling of epoxides with ene-1,2-diamines,[13] heteroannulation of nitroketene N,S-aryliminoacetals with $POCl_3$,[14] tandem oxidation of α-hydroxy ketones etc.[15] To fulfill the thrust related to desirable product yields, reduction in reaction time and to keep overall procedure environmentally benign several catalysts such as $Ga(OTf)_3$,[16] I_2,[17] NH_2SO_3H,[18] $CuSO_4.5H_20$,[19] Zn/L-Proline,[20] *p*-TsOH,[21] $InCl_3$,[22] $MnCl_2$,[23] $H_6P_2W_{18}O_{62}.24H_2O$,[24] $Pd(OAc)_2$,[15(a)] IBX,[25] Montmorillonite K-10,[26] and CAN[27] have been employed. Most of these methods have one or more drawbacks such as poor yield, extended reaction time, use of volatile organic solvents and tedious work-up procedure leading to the generation of a large amount of toxic/unwanted waste. There are also a few reports using no catalyst[28] with longer reaction completion time as well as with low in yields. Hence, it is still desirable to search for a facile, efficient and ecofriendly synthetic method to overcome these difficulties. So, we herein report the $RuCl_3.xH_2O$ catalyzed simple method for the synthesis of quinoxalines using IL [bmim]PF_6 certainly, IL are established green solvents of the present times.

The catalytic use of $RuCl_3.xH_2O$ as a mild Lewis acid is of current interest in organic synthesis[29] because of its unique properties like mildness, selectivity and solubility in organic solvents. $RuCl_3.xH_2O$ have been successfully used in well known reactions of chemistry like Biginelli,[30] Prins,[31] Aldol,[32] Strecker,[33] Michael[34] reaction etc. Its utility have also been extended to deoxygenation of organic N-oxides,[35] cleavage of epoxides to yield trans diols[36] and to selective protection of aldehydes as acylals.[37] Use of $RuCl_3.xH_2O$ as an oxidant is reported for Hantzsch dihydropyridines[38] and it is claimed because of its affinity to aerial oxygen.[39] On the other hand, ionic liquids are crowned as green solvents of present century because these are non-volatile, non-flammable, thermally stable, recyclable and they do solubilize inorganic as well as organic compounds and so are superior in comparison to conventional solvents.[40]

Due to these promising applications and other attractive features of this mild Lewis acid authors are prompted to use both $RuCl_3.xH_2O$ and ionic liquids in quinoxalines synthesis.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. Reagent-grade chemicals were purchased from a commercial source and used without further purification. Infrared (IR) spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer. 1H NMR spectra were recorded on a Varian Gemini 300 (300-MHz) spectrometer using tetramethylsilane (TMS) as internal standard. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel G (Merck).

General procedure for the synthesis of quinoxalines

A mixture of 1,2-diamine (1 mmol), 1,2-diketone (1 mmol), $RuCl_3.xH_2O$ (0.05 mmol) and [bmim]PF_6 (2 mL) was stirred at ambient temperature for the appropriate time. After completion of the reaction as indicated by TLC, H_2O (5 mL) was added and the mixture was extracted with diethyl ether (10 mL × 3). The combined organic phases were washed with H_2O and dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by recrystallization from ethanol or by column chromatography eluting with hexane/ethyl acetate of increasing polarity to give the corresponding quinoxaline products. The ionic liquid phase was concentrated and dried under vacuum overnight for reuse. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature.[16-27] The Spectral data for selected products are provided below.

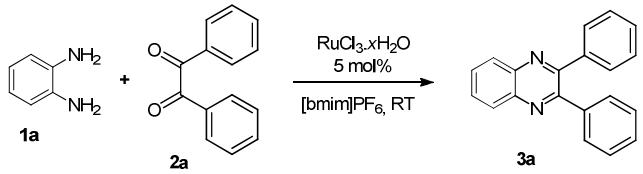
2,3-Bis(4-chlorophenyl)quinoxaline (Table-1, entry 8): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.15 (dd, 2H, J_1 = 3.4 Hz, J_2 = 6.6 Hz, ArH), 7.81-7.73 (dd, 2H, J_1 = 3.4 Hz, J_2 = 6.4 Hz, ArH), 7.51-7.32 (m, 8H, ArH).

2,3-Di(furan-2-yl)quinoxaline (Table-1, entry 9): ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17-8.09 (dd, 2H, J_1 = 3.7 Hz, J_2 = 6.6 Hz, ArH), 7.85-7.71 (dd, 2H, J_1 = 3.5 Hz, J_2 = 6.4 Hz, ArH), 7.67-7.60 (m, 2H, furan-H), 6.69-6.52 (m, 4H, furan-H).

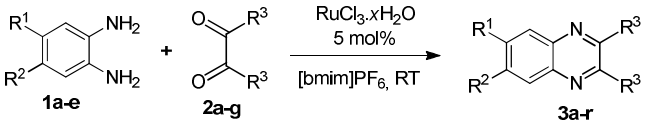
2,3-Di(furan-2-yl)-6-methylquinoxaline (Table-1, entry 15): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14-7.97 (d, 1H, J =8.8Hz, ArH), 7.91-7.85 (s, 1H, ArH), 7.65-7.60 (m, 2H, furan-H), 7.58-7.53 (dd, 1H, J_1 = 1.9 Hz, J_2 = 8.6 Hz, ArH), 6.78-6.69 (m, 4H, furan-H), 2.60-2.55 (s, 3H, CH_3).

RESULTS AND DISCUSSION

In a general experimental procedure, the stirred mixture of o-phenyldiamine (1 mmol) **1a**, benzil (1 mmol) **2a** and 5 mol% $RuCl_3.xH_2O$ in [bmim]PF_6 (2 mL) afforded 2,3-Diphenyl-quinoxaline **3a** in 98% yield in 2 min at ambient temperature (Scheme 1). Similarly, a variety of *o*-phenyldiamine (*o*-PDA) **1a-e** were condensed with aromatic **2a-e**, aliphatic **2g** and heterocyclic **2f** diketones in presence of 5 mol% $RuCl_3.xH_2O$ using ionic liquid as solvent to provide quinoxalines in excellent yields (Scheme-2). Aromatic diketones **2a-e** afforded excellent yields in shorter reaction time (Table-1, entry 1-9, 11-14, 16-17), whereas heterocyclic **2f**, and aliphatic **2g** diketones gave good yields in slightly long reaction time (Table-1, entry 10, 15, 18).



Scheme-1: Synthesis of 2,3-Diphenyl-quinoxaline employing $RuCl_3.xH_2O$

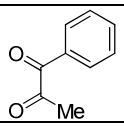


1a: R^1=H **2a:** R^3=C_6H_5 **2f:** R^3= furyl-2-yl
1b: R^1=Me **2b:** R^3=p-Me-C_6H_4 **2g:** R^3=CH_3
1c: R^1=NO_2 **2c:** R^3=p-MeO-C_6H_4
1d: R^1=Cl **2d:** R^3=p-Cl-C_6H_4
1e: R^2=Me **2e:** R^3=p-Br-C_6H_4

Scheme-2: Synthesis of quinoxalines employing $RuCl_3.xH_2O$

For this investigation, firstly we optimize the amount of catalysts, for this a set of reactions of *o*-phenyldiamine **1a** and benzil **2a** was carried out by varying amount of catalyst and keeping other reaction conditions constant (Table 2); the amount of catalyst was optimised to 5 mol%, increasing the amount of catalyst (upto 20 mol %) did not show significant influence on the rate of reaction as well as yield.

Table-1: $RuCl_3.xH_2O$ catalyzed synthesis of various quinoxalines in [bmim]PF_6.

Entry	*o*-PDAs	1,2-diketones	Product[a]	Time (min)	Yield[b] (%)
1.	1a	2a	3a	2	98
2.	1b	2a	3b	3.5	97
3.	1c	2a	3c	4	95
4.	1d	2a	3d	10	89
5.	1e	2a	3e	3	94
6.	1a	2b	3f	5	93
7.	1a	2c	3g	6.5	94
8.	1a	2d	3h	4	96
9.	1a	2e	3i	5	92
10.	1a	2f	3j	9	90
11.	1a	2g	3k	8	85
12.	1b	2b	3l	4.5	90
13.	1b	2c	3m	5	89
14.	1b	2e	3n	7	92
15.	1b	2f	3o	10	87
16.	1d	2b	3p	10	85
17.	1d	2e	3q	7.5	87
18.	1b		3r	9	86

[a]Reaction conditions: *o*-PDA (1 mmol), 1,2-diketone (1 mmol), $RuCl_3.xH_2O$ (5 mol%), stirred in [bmim]PF_6 (2 mL) at rt. The products were characterized by spectral techniques like IR, ^{1}H NMR, ^{13}CNMR, mass. [b]Isolated yields after recrystallization.

To study the effect of solvent, the above reaction was examined in different solvent systems (Table-3). Initially, reaction of *o*-PDA **1a**, benzil **2a** in presence of $RuCl_3.xH_2O$ was carried out using no solvent at room temperature but after 1h (Table-3, entry 1) we did not observe the formation of any end product. The enhanced reaction rates, improved yields and high selectivity are the features obtained in [bmim]PF_6 (Table-3, entry 5). However, the same reaction in other solvents did not give satisfactory results even in longer reaction time (Table-3, entry 2-4, 6-8). Therefore, by employing the optimized conditions 1,2-diamine (1 mmol), 1,2-diketone (1 mmol), $RuCl_3.xH_2O$ (5 mol%), and [bmim]PF_6 (2mL) for the synthesis of quinoxalines, provide variously substituted quinoxalines in excellent yields.

These condensation reactions proceeded efficiently at ambient temperature and no undesired side product was observed This method is equally effective with 1,2-diamines bearing electron withdrawing **1c-d** as well as electron donating substituents **1b,1e** in the aromatic ring and also with symmetrical **2a-f** and unsymmetrical (Table-1, entry 18) 1,2-diketones.

Table-2: Condensation of *o*-PDA, benzil employing different amount of $RuCl_3.xH_2O$.[a]

Entry	Catalyst (mol%)	Time (min)	Yield[b]
1	No catalyst	25	65
2	2	5	83
3	5	2	98
4	10	2	98
5	20	2	95

[a]Reaction conditions: *o*-PDA (1 mmol), 1,2-diketone (1 mmol), $RuCl_3.xH_2O$, stirred in $[bmim]PF_6$ (2 mL) at rt. [b]Isolated yield.

Table-3: Condensation of *o*-PDA and benzil in different solvents.[a]

Entry	Solvent	Time (min)	Yield[b]
1	No solvent	60	--
2	CH_2Cl_2	10	90
3	THF	12	88
4	$[bmim]BF_4$	4	98
5	$[bmim]PF_6$	2	98
6	H_2O	20	55
7	EtOH	10	85
8	MeCN	10	85

[a]Reaction conditions: *o*-PDA (1 mmol), 1,2-diketone (1 mmol), $RuCl_3.xH_2O$ (5 mol%), stirred in solvent (2 mL) at rt. [b]Isolated yield.

Table-4: Reusability study of the catalyst-solvent system.[a]

Entry	Run	Time (min)	Yield[b]
1	1	3	91
2	2	3	88
3	3	5	85
4	4	7	80
5	5	7	73

[a]Reaction conditions: *o*-PDA (1 mmol), 1,2-diketone (1 mmol), $RuCl_3.xH_2O$ (recovered), stirred in $[bmim]PF_6$ (recovered) at rt. [b]Isolated yield.

Next, the recyclability of the catalyst as well as solvent was studied by using **1a** and **2a** as the model substrate. We observed that $RuCl_3.xH_2O/[bmim]PF_6$ could be reused for a new set of reaction after the IL phase was extracted with diethyl ether (5 mL X 3) and dried under vacuum. The recovered catalyst-solvent system was recycled and reused for five runs, the results were shown in Table-4.

CONCLUSION

In summary, we have generated a simple, rapid, convenient, environmentally benign and effective method for the synthesis of quinoxalines in the absence of any toxic and corrosive catalysts or organic solvents. However, the beauty of this method is its milder reaction condition, reduced reaction time, excellent yields, recyclable catalyst/solvent, and mild nature of $RuCl_3.xH_2O$, which will have wide scope in organic

synthesis. $RuCl_3.xH_2O$ in $[bmim]PF_6$ shows an excellent catalytic activity. In addition, the catalytic system could be reused up to five times.

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