Asian Journal of Chemistry; *Vol. 23, No. 11 (2011), 5051-5054*

ASIAN JOURNAL OF CHEMISTRY

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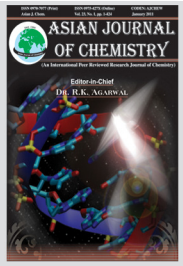

Niobium Pentachloride as a Highly Efficient Catalyst for the Synthesis of Quinoxaline Derivatives

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(*Received*: 25 January 2011; *Accepted*: 27 July 2011) AJC-10208

Niobium pentachloride is found to be an efficient catalyst for the synthesis of quinoxaline derivatives *via* the condensation of aromatic 1,2-dicarbonyl compounds (or unsymmetrical 1,2-diketones or α-hydroxy ketones) with 1,2-diamines. All the reactions were performed at room temperature while using acetonitrile as solvent. The present methodology offers several advantages such as excellent yields, short reaction time and environmentally benign milder reaction conditions.

Key Words: Niobium(V)chloride, 1,2-Diketones, *a*-Hydroxy ketones, 1,2-Diamines, Quinoxalines.

INTRODUCTION

Quinoxaline derivatives are the subject of considerable interest from the point of academic and industrial perspective. Functionalized quinoxalines represent an important class of nitrogen-containing heterocyclic compounds. Those rarely described in nature, quinoxaline derivatives are well known in the pharmaceutical industry[1] and have been shown to possess a diverse of biological activity[2] *viz.,* antiviral, antibacterial, antiinflammatory and as kinase inhibitors[3], which have made them privileged structures in combinatorial drug discovery libraries[4].

Quinoxaline derivatives have been reported for their applications in dyes[5], organic semiconductors[6], efficient electroluminescent materials[7], dehydroannulenes[8], cavitands[9], chemically controllable switches[8], building blocks for the synthesis of anion receptor[10], DNA cleaving agent[11] and were reported as useful intermediates for many target molecules in organic synthesis and also as synthons.

Many synthetic routes have been developed for the synthesis of quinoxaline derivatives[12]. Most common method is the condensation of aromatic 1,2-diamines with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid[13]. However, many improved methods have been reported for the synthesis of quinoxalines using catalytic amounts of various metal precursors such as $Pd(OAc)_2$, $RuCl_2$-$(PPh_3)_3$-TEMPO[14], MnO_2[15] and zeolites[16]. Recently molecular iodine[17], $MnCl_2$[18], copper[19] and bismuth[20] have also been used as catalysts for the synthesis of quinoxaline derivatives. Some of these procedures require stoichiometric amounts of catalyst or even in large excess to effect on complete conversion of the substrate, difficult experimental procedure and harsh reaction conditions with unsatisfactory yields. Therefore, it was thought worthwhile to adopt a convenient method for this condensation.

Niobium pentachloride is less expensive than $InCl_3$ and TMSOTf *etc*. (Aldrich catalog) and the reaction can be run in non-cryogenic temperature. Niobium pentachloride is well known in the literature as mild and efficient catalyst owing to its stability, low hygroscopic characteristic, which is easy to handle and has also been explored as a Lewis acid in promoting various organic transformations[21,22]. The versatility of this reagent encouraged us to study its utility for the synthesis of quinoxaline derivatives. A part of our continuing interest in the development of new synthetic methodologies and the role of transition metal[23-29] as catalyst, herein, we disclose a general rapid and high yielding procedure for the synthesis of a variety of quinoxaline derivatives.

EXPERIMENTAL

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr pellets. ^{1}H NMR and ^{13}C NMR were recorded on a bruker avance spectrospin at 300 and 75 MHz, respectively, using TMS as internal standard. Analytical TLCs were performed on pre-coated Merck silica gel 60 F 254 plates; the spots were detected either under UV light or by placing in iodine chamber. GC/MS mass spectra were recorded in a TOF-mass spectrometer model No. KC 455.

General procedure for the synthesis of quinoxaline derivatives: Quinoxaline derivatives 3(**a-t**) and 5(**a-f**) were prepared according to the following general procedure: In a 50 mL round bottom flask, aromatic 1,2-diketones (or unsymmetrical 1,2-diketones or α-hydroxy ketones) (1.2 mmol) and 1,2-diamines (1 mmol) in acetonitrile (5 mL) were mixed followed by addition of catalyst $NbCl_5$ (5 mole %) and stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography. After complete conversion of starting material, as indicated by TLC with time, the solid product was filtered and then washed with cold methanol and dried under vacuum for 10 min to afford the desired product. The crude product was subjected to further purification by flash chromatography using 10 % ethyl acetate in hexane as an eluent to yield the quinoxalines 3(**a-t**) and 5(**a-f**). The structures of all the products were unambiguously established on the basis of their spectral analysis.

Spectral data of done representative products are given below: 2,3-Diphenyl-quinoxaline (Table-3, **3a**): white solid; m.p. 126-127 ºC; IR (KBr, ν_{max}, cm^{-1}): 3056, 2862, 1574, 1408, 1346, 1202, 768, 730, 548; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.21 (dd, *J* = 3.61, 6.30 Hz, 2H), 7.79 (dd, *J* = 3.30, 6.60 Hz, 2H), 7.50-7.53 (m, 4H), 7.31-7.36 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 138.9, 137.8, 133.9, 129.7, 128.9, 128.4, 128.1, 127.4, 126.6. HRMS, *m/z* (found/calc.): 283.1182/283.1157 (M^+, $C_{20}H_{14}N_2$).

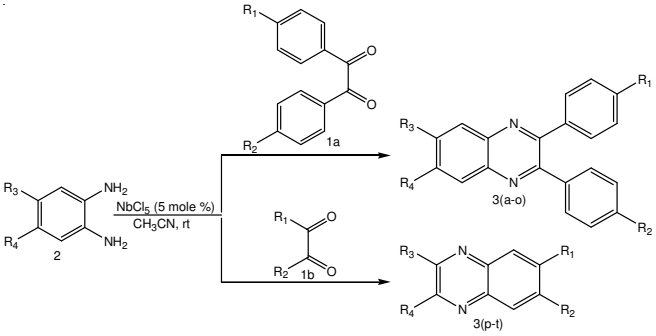
2-Methyl-3-phenylquinoxaline (Table-3, 3p): Orange solid; m.p. 58-59 ºC; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.03 (dd, *J* = 3.18, 7.32 Hz, 2H), 7.77 (dd, *J* = 3.01, 6.84 Hz, 2H), 7.47-7.60 (m, 5H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 152.5, 140.8, 141.1, 138.3, 129.4, 129.3, 128.8, 128.4, 128.2, 128.1, 24.6; IR (KBr, ν_{max}, cm^{-1}): 3100, 2995, 1556, 1320, 1204, 1126, 997, 768, 609, 563. HRMS, *m/z* (found/calc.): 220.1146/220.1000 (M^+, $C_{15}H_{12}N_2$).

2-Phenylquinoxaline (Table-4, 5a): White solid; m.p. 72-73 ºC; IR (KBr, ν_{max}, cm^{-1}): 3421, 2918, 1625, 1550, 1358, 1026, 952, 719, 492; ^1H NMR (300 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.10-8.21 (m, 4H), 7.69-7.72 (m, 3H), 7.17-7.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.8, 144.2, 143.0, 136.8, 130.2, 129.1, 128.3, 127.1, 126.8. HRMS, *m/z* (found/calc.): 206.4318/ 206.0844 (M^+, $C_{14}H_{10}N_2$).

RESULTS AND DISCUSSION

The authors report in this paper, highly efficient synthesis of a variety of quinoxaline derivatives namely substituted 2,3-diphenyl quinoxalines (**3a-o**), 2,3-dialkyl quinoxalines (**3p-t**) and 2-phenyl quinoxalines (**5a-f**) catalyzed by $NbCl_5$ in acetonitrile at room temperature. Reactions were completed in 10-25 min and high yields of the products were obtained by a simple workup.

Inspired with the catalytic potential of $NbCl_5$, we examined first the catalytic role of $NbCl_5$ in the synthesis of 2,3-diphenyl quinoxalines *via* the condensation of 1,2-dicarbonyl compounds (**1a**) and 1,2-diamines (**2**). The reaction of benzil (1.2 mmol) and *o*-phenylenediamine (1 mmol) was carried out in the presence of varying amounts of $NbCl_5$ at room temperature. It was observed that the use of 5 mole % $NbCl_5$ as a catalyst in CH_3CN yielded the desired product, to afford 2,3-diphenyl quinoxaline in 97 % yield in 10 min (**Scheme-I**, Table -3, entry 1). When this reaction was reported in the absence of catalyst, low yield of product was observed even after 5 h.



Scheme-I. $NbCl_5$-catalyzed synthesis of quinoxalines

In order to optimize the reaction conditions and to evaluate the catalytic activity of $NbCl_5$, we screened the different amount of $NbCl_5$ to catalyze the synthesis of quinoxalines. To increase the yield of the product, various concentrations of the catalyst were employed and it was found that 5 mol % of $NbCl_5$ is suitable to perform the reaction. To study the feasibility of different reported catalysts such as I_2[17], $MnCl_2$[18], $CuCl_2$[19], CuCl[19] and Bi[20] with $NbCl_5$ for the synthesis of quinoxalines, $NbCl_5$ was found to be the most effective catalyst for this condensation. The results with different catalysts are given in Table-1.

TABLE-1
CATALYTIC ACTIVITY OF LEWIS ACIDS IN THE SYNTHESIS OF QUINOXALINES[a]

Entry	Catalyst	Mole (%)	Time	Yield (%)[b]
1	$CuCl_2$	5	3 h	94
2	CuCl	5	3 h	54
3	$MnCl_2$	10	17 min	94
4	Bi	5	5 h	62
5	I_2	10	30 min	90
6	$NbCl_5$	2	1 h	85
7	$NbCl_5$	5	10 min	97
8	$NbCl_5$	10	10 min	97
9	$NbCl_5$	-	3 h	15

[a]Reaction conditions: benzil (1.2 mmol), *o*-phenylenediamine (1 mmol), catalyst, solvent CH_3CN (5 mL), rt. [b]Isolated yields.

The nature of reaction media has an important role to obtain improved yields in the presence of $NbCl_5$ (5 mole %). Among the various solvents investigation, acetonitrile and methanol showed outstanding performance for catalyst and was the solvent of choice, whereas dichloromethane and carbon tetrachloride afforded lower yields. However trace of product was formed in THF (Table-2).

Therefore, the reaction of diversely substituted aromatic 1,2-diketones were attempted with 1,2-diamines in CH_3CN at room temperature in the presence of 5 mole % of $NbCl_5$. All the reactions yielded corresponding quinoxalines (Table-3, entries 3a-o) in excellent yields. In order to broaden the scope of the present method, the use of various functional groups such as methyl, methoxy, chloro and nitro groups present in the substrate. It has been observed that the synthesis of quinoxalines containing electron donating groups in the diamines facilitate the reaction when compared with electron withdrawing group containing systems but in case of 1,2-dicarbonyl compounds the effect is opposite (Table-3). To our

delight, the reaction underwent successful condensation under similar reaction conditions, to afford the corresponding quinoxaline derivatives in high yields (Table-1, entry **3a-o**). Reactions were also attempted by replacing 1,2-dicarbonyl compounds with unsymmetrical substituted 1,2-diketones (**1b**). The components underwent successful condensation to give quinoxalines (Table-3, entries **3p-t**) in excellent yields (**Scheme-I**).

TABLE-2
$NbCl_5$-CATALYZED SYNTHESIS OF QUINOXALINE IN DIFFERENT SOLVENT[a]

Entry	Solvent	Yield (%)[b]
1.	CH_3CN	97
2.	CH_3OH	95
3.	CH_2Cl_2	60
4.	CCl_4	54
5.	THF	Trace

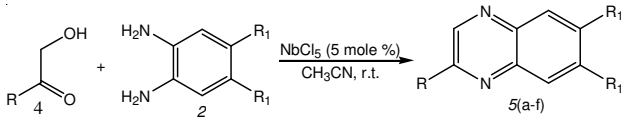
[a]Reaction conditions: benzil (1.2 mmol), *o*-phenylenediamine (1 mmol), $NbCl_5$ (5 mole %), solvent (5 mL), rt. [b]Isolated yields

TABLE-3
$NbCl_5$-CATALYZED SYNTHESIS OF QUINOXALINE DERIVATIVES USING DIFFERENT AROMATC 1,2-DIKETONES/UNSYMMETRICAL 1,2-DIKETONES WITH DIAMINES[a]

Entry	R_1	R_2	R_3	R_4	Compound (3)	Time (min)	Yield (%)[b]
1.	H	H	H	H	**a**	10	97
2.	H	H	CH_3	H	**b**	10	94
3.	H	H	Cl	Cl	**c**	25	86
4.	OCH_3	OCH_3	CH_3	H	**d**	20	89
5.	CH_3	CH_3	CH_3	H	**e**	20	94
6.	OCH_3	OCH_3	Cl	H	**f**	25	88
7.	OCH_3	OCH_3	H	H	**g**	10	90
8.	CH_3	CH_3	H	H	**h**	10	95
9.	H	H	NO_2	H	**i**	25	85
10.	OCH_3	OCH_3	NO_2	H	**j**	15	90
11.	F	F	H	H	**k**	10	95
12.	F	F	CH_3	H	**l**	10	94
13.	F	F	NO_2	H	**m**	15	88
14.	OCH_3	OCH_3	Cl	Cl	**n**	20	87
15.	H	H	CH_3	CH_3	**o**	15	95
16.	Ph	CH_3	H	H	**p**	15	92
17.	Ph	CH_3	CH_3	H	**q**	10	87
18.	CH_3	Ph	CH_3	H	**r**	25	87
19.	Ph	CH_3	Cl	H	**s**	20	83
20.	CH_3	Ph	Cl	H	**t**	20	82

[a]Reaction conditions: aromatic 1,2-diketones/unsymmetrical 1,2-diketones (1.2 mmol), 1,2-diamines (1 mmol), $NbCl_5$ (5 mole %), solvent CH_3CN (5 mL), rt. [b]Isolated yields.

Encouraged by these results, we attempted the present protocol for condensation of 1,2-diamines with α-hydroxy ketones in place of 1,2-diketones also underwent successful condensation under similar conditions, to afford a series of 2-phenyl quinoxaline derivatives in high yields (Table-4, entries **5a-f**).



Scheme-II: $NbCl_5$-catalyzed synthesis of quinoxalines using α-hydroxy ketones (**4**)

TABLE-4
$NbCl_5$-CATALYZED SYNTHESIS OF QUINOXALINES USING DIFFERENT α-HYDROXY KETONES AND *o*-PHENYLENEDIAMINE[a]

Entry	R	R_1	Compound (5)	Time (min)	Yield (%)[b]
1.	Ph	H	a	10	97
2.	Ph	CH_3	b	10	91
3.	$C_6H_4CH_3$	CH_3	c	25	90
4.	$C_6H_4CH_3$	H	d	20	82
5.	C_6H_4F	H	e	20	92
6.	$C_6H_4OCH_3$	H	f	25	80

[a]Reaction conditions: α-hydroxy ketones (1.2 mmol), α-diamine (1 mmol), $NbCl_5$ (5 mole %), solvent CH_3CN (5 mL), room temperature. [b]Isolated yields

Conclusion

In summary, we have shown that the present methodology describes a simple, convenient and efficient procedure for the synthesis of quinoxalines with different types of ketones *via* condensation of 1,2-diamines using a catalytic amount of $NbCl_5$. The notable features of this procedure are mild reaction conditions, cleaner reaction profiles, improved yields, enhanced reaction rates and simplicity in operation, which makes it a useful process for the synthesis of quinoxaline derivatives. The highly catalytic nature of $NbCl_5$ and its wide applicability should make this protocol an alternative over existing methods.

ACKNOWLEDGEMENTS

The authors express sincere thanks to Dean Research, University of Delhi for providing R & D financial assistance. Neeraj Kumar Mishra, Divya Bhatnagar and Anwar Jahan thank to CSIR and UGC, New Delhi, India for the grant of Senior and Junior Research Fellowships.

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