$NbCl_5$ as an Efficient Catalyst for Rapid Synthesis of Quinoxaline Derivatives

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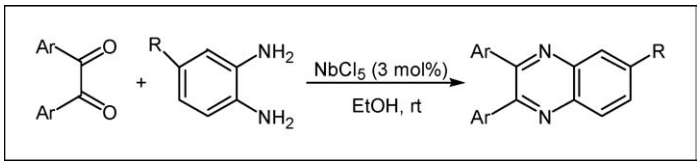

A series of quinoxaline derivatives have been synthesized in excellent yields by the condensation of 1,2-diketones and 1,2-phenylenediamines in the presence of a catalytic amount of $NbCl_5$ at room temperature in short times.

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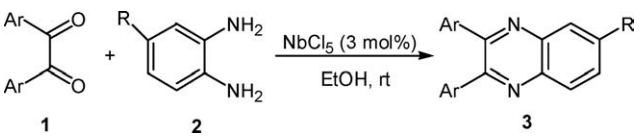
INTRODUCTION

The quinoxaline derivatives are important heterocyclic compounds, which exhibit a diverse range of biological properties, such as antitumor [1], cytotoxic [2], antiviral, antibacterial, anti-inflammatory, and kinase inhibitor properties [3]. They have also been used as dyes, efficient electron luminescent material, organic semiconductors, DNA cleaving agents [4], photoinitiators in UV-cured coatings [5], and donor materials [6]. In addition, the quinoxaline ring is a part of a number of antibiotics, such as echinomycin, levomycin, and actinomycin that are known to inhibit the growth of gram-positive bacteria and are active against various transplantable tumors [7].

Therefore, the synthesis of this type of compounds has attracted considerable attention. Synthetic routes that are common to the preparation of these heterocycles typically involve the reaction of 1,2-diamine and 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid. Various catalysts, such as bismuth(III) triflate [8], metal hydrogen sulfates [9], gallium(III) triflate [10], molecular iodine [11], cerium (IV) ammonium nitrate [12], stannous chloride [7], zirconium tetrakis(dodecyl sulfate) [13], amidosulfonic acid [14], montmorillonite K-10 [15], binary metal oxides supported on Si-MCM-41 mesoporous molecular sieves [4], polyaniline-sulfate salt [16], Wells-Dawson heteropoly acid [17], and ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [18] have been used to promote this transformation. Alternative approaches, such as oxidative cyclization of α-hydroxyketones with *o*-phenylenediamines [19], reaction of *o*-phenylenediamine with α-bromoketonethe [20,21], reaction of α-keto oximes and 1,2-diamines [3], oxidative coupling of epoxides and ene-1,2-diamines [22], the coupling of α-diazoketones with aryl 1,2-diamines [23], reductive cyclization of 1,2-dicarbonyl compounds with 2-nitroanilines [7], heteroannulation of nitroketene *N*,*S*-aryliminoacetals with $POCl_3$ [24], intramolecular cyclizations of dialdimines [25], the reaction of aryl-1,2-diamines and diethyl bromomalonate [26], the reaction of *o*-phenylenediamines and ketones [27], reaction of *o*-phenylenediamines and vicinal-diols [28], and palladium-catalyzed reductive *N*-heteroannulation of enamines [29] have been also developed to prepare functionalized quinoxalines. However, the long reaction time [15], costly catalysts, such as bismuth(III) triflate [8] and gallium(III) triflate [10], requirement of special effect for catalyst preparation [4,16] and a special instrumentation, such as microwave [30], harsh reaction conditions, such as heating at 70°C [21] can not be avoided. Because of the importance of quinoxaline derivatives in organic synthesis, the development of a convenient, efficient and practically useful process for synthesis quinoxaline derivatives is in demand.

In recent years, niobium pentachloride has been considered as mild Lewis acid catalyst for a variety of organic transformations [31], such as one-pot Mannich-type reaction [32], alkoxide rearrangements [33], the intramolecular Friedel–Crafts acylation reaction [34], conversion of aldehydes and ketones to allylic halides [35], cyanosilylation of aldehydes [36], synthesis of α-aminonitriles [37], 1,1-diacetates [38], bis(indol)alkanes [39], and 1,5-benzodiazepine derivatives [40]. However, to the best of our knowledge, there is no report on the synthesis of quinoxaline derivatives using niobium pentachloride as a reagent. As part of our continuing interest in the development of new synthetic methodologies [41–46], we report herein an efficient and convenient

Scheme 1



procedure for the synthesis of quinoxaline derivatives by the condensation of 1,2-diketones and 1,2-phenylenediamines in the presence of a catalytic amount of niobium pentachloride at room temperature (Scheme 1).

RESULTS AND DISCUSSION

At the onset of the research, we investigated the model reaction between 1,2-phenylenediamines and benzil in EtOH in the presence of a catalytic amount of $NbCl_5$ (3 mol%) at room temperature. To our delight, the product **3a** was formed and the complete conversion with 95% isolated yield was observed after 2 min. Further studies showed that EtOH was the best solvent among the solvents (MeOH, MeCN, THF, DMF, DMSO, CH_2Cl_2, and $CHCl_3$). Next, the amount of the catalyst was examined and we found that 3 mol% $NbCl_5$ was sufficient to drive the reaction completely in 95% yield. The less amount gave low yield even after a prolonged reaction time, and the more amount could not cause the obvious increase for the yield of product and could not shorten the reaction time. It is noteworthy to mention that the reaction gave only a 60% yield in the absence of $NbCl_5$ after 4 h.

To evaluate the generality of this method, we next investigated the scope and limitation of this reaction under optimized conditions (EtOH, 3 mol% of $NbCl_5$, RT) and the results are illustrated in Table 1. As shown in Table 1, a variety of structurally diverse 1,2-phenylenediamines and a wide of 1,2-diketones underwent the condensation reaction smoothly to afford the corresponding quinoxaline derivatives in excellent yields. The electronic property of the substituents on the aromatic ring of 1,2-phenylenediamines had an obvious effect on reaction time under the above optimal reaction conditions. It was observed that electron-withdrawing groups (Table 1, entries **i–o**) associated with 1,2-phenylenediamines decreased the reactivity of the substrate and long reaction times were required. It is worth noting that the reaction of 4-nitrobenzene-1,2-diamine with benzil failed to give the desired product. On the other hand, the effect of electronic factors associated with aromatic 1,2-diketons is opposite. For example, 4,4′-dibromolbenzil could react with 4-nitrobenzene-1,2-diamine to afford the corresponding product (**3o**) in 92% yield. Besides this, when 2,2′-furil and acenaphthylenequinone were subjected for condensation reaction, the corresponding products were obtained with excellent yields. All of the quinoxaline derivatives have been characterized by ^1H NMR, ^{13}C NMR, and IR spectra, and the known compounds were confirmed by comparison of their spectral data and melting points with those reported in the literature.

In conclusion, we have developed a simple, rapid, and efficient methodology for the synthesis of quinoxaline derivatives by the condensation 1,2-diketones and 1,2-phenylenediamines at room temperature using $NbCl_5$ as a novel catalyst. Simplicity of operation, high yields, short reaction time, and good substrate generality are the key advantages of this method.

EXPERIMENTAL

Melting points were determined using an X-4 apparatus and are uncorrected. IR spectra were obtained using a Bruker-

Table 1

Synthesis of quinoxaline derivatives catalyzed by $NbCl_5$.

Entry	1,2-Diketones	R	Time (min)	Yield (%)[a]	Mp (°C)	Lit. Mp (°C)
a	Benzil	H	2	95	120–121	124–125 [14]
b	4,4′-Dimethylbenzil	H	3	93	141–142	142–143 [7]
c	4,4′-Dibromolbenzil	H	1.5	94	190–192	190–191 [7]
d	Acenaphthylenequinone	H	2	93	243–244	242–245 [8]
e	2,2′-Furil	H	2	94	130–131	129–130 [12]
f	Benzil	4-Me	2	95	113–114	112–113 [7]
g	4,4′-Dibromolbenzil	4-Me	2	94	183–184	184–185 [18]
h	Acenaphthylenequinone	4-Me	2	93	234–236	
i	Benzil	4-Cl	4	92	116–117	118–119 [7]
j	4,4′-Dibromolbenzil	4-Cl	3	93	167–168	166–167 [7]
k	Acenaphthylenequinone	4-Cl	4	95	227–228	
l	Benzil	4-PhC=O	20	93	152–153	140–142 [10]
m	4,4′-Dibromolbenzil	4-PhC=O	5	94	203–204	
n	Acenaphthylenequinone	4-PhC=O	4	95	255–256	
o	4,4′-Dibromolbenzil	4-NO_2	20	92	187–189	188–190 [18]

[a] Isolated yields after column chromatography.

TENSOR 27 spectrometer instrument. NMR spectra were taken with a Bruker DRX-500 spectrometer using TMS as internal standard. Elemental analyses were carried out on a Vario EL III CHNOS elemental analyzer.

General procedure for the synthesis of quinoxaline derivatives (3). A mixture of 1,2-phenylenediamine (1 mmol), 1,2-diketone (1.0 mmol), and $NbCl_5$ (0.03 mmol) in EtOH (3 mL) was stirred at room temperature. The progress of reaction was monitored by TLC. After completion, water was added and the product was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure to afford the crude product. The crude product was subjected to column chromatography over silica gel using hexane/ethyl acetate as eluent to obtain pure product.

9-Methylacenaphtho[1,2-b]quinoxaline (3h). This compound was obtained as yellow needles; IR: 3053, 1635, 1616, 1483, 1434, 1419, 1299, 1212, 1099, 983, 829, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.63 (s, 3H), 7.59 (dd, J = 8.5, 2.0 Hz, 1H), 7.83 (td, J = 8.5, 2.0 Hz, 2H), 7.99 (s, 1H), 8.08–8.10 (m, 3H), 8.41 (t, J =7.0 Hz, 2H); *Anal*. Calcd. for $C_{19}H_{12}N_2$: C, 85.05; H, 4.51; N, 10.44. Found: C, 84.89; H, 4.70; N, 10.62.

9-Chloroacenaphtho[1,2-b]quinoxaline (3k). This compound was obtained as yellow platelets; IR: 1635, 1616, 1419, 1298, 1101, 983, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, J = 8.0, 2.5 Hz, 1H), 7.86 (td, J = 8.0, 2.5 Hz, 2H), 8.13–8.16 (m, 3H), 8.21 (d, J = 2.5 Hz, 1H), 8.42–8.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.1, 122.3, 128.6, 128.7, 129.7, 129.9, 130.0, 130.1, 130.6, 131.4, 131.5, 134.8, 136.7, 139.7, 141.6, 154.2, 154.8; *Anal*. *Calcd*. for $C_{18}H_9ClN_2$: C, 74.88; H, 3.14; N, 9.70. Found: C, 75.02; H, 3.32; N, 9.55.

(2,3-Diphenyl-quinoxalin-6-yl)phenylmethanone (3l). This compound was obtained as brown solid; IR: 1660, 1639, 1616, 1598, 1446, 1402, 1346, 1265, 1197, 1056, 1022, 891, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.42 (m, 6H), 7.51–7.57 (m, 6H), 7.64 (t, J = 7.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H), 8.27 (dd, J = 8.5, 2.0 Hz, 1H), 8.29 (d, J = 9.0 Hz, 1H), 8.54 (d, J = 2.0 Hz, 1H); *Anal*. Calcd. for $C_{27}H_{18}N_2O$: C, 83.92; H, 4.69; N, 7.25. Found: C, 84.10; H, 4.50; N, 7.08.

[2,3-Bis(4-bromo-phenyl)-quinoxalin-6-yl]phenyl-methanone (3m). This compound was obtained as pale yellow solid; IR: 1683, 1652, 1616, 1598, 1334, 1074, 1010, 977, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.51–7.55 (m, 6H), 7.66 (dd, J = 8.5, 2.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 2H), 8.27 (t, J = 8.5 Hz, 2H), 8.51 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.1, 124.3, 128.5, 129.7, 130.1, 130.3, 131.3, 131.4, 131.8, 132.3, 132.5, 132.9, 137.0, 137.2, 137.3, 138.7, 140.2, 142.9, 153.0, 153.6, 195.6; *Anal*. *Calcd*. for $C_{27}H_{16}Br_2N_2O$: C, 59.59; H, 2.96; N, 5.15. Found: C, 59.75; H, 3.16; N, 4.98.

Acenaphtho[1,2-b]quinoxalin-9-yl-phenyl-methanone (3n). This compound was obtained as pale brown needles; IR: 1683, 1647, 1616, 1596, 1436, 1317, 1301, 1263, 1101, 983, 713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.56 (t, J = 7.5 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.87–7.95 (m, 4H), 8.18 (t, J = 7.5 Hz, 2H), 8.27 (dd, J = 7.5, 1.5 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.45 (d, J = 7.0 Hz, 1H), 8.51 (d, J = 7.0 Hz, 1H), 8.60 (d, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 122.2, 122.5, 128.5, 128.8, 129.3, 129.8, 130.0, 130.1, 130.2, 131.3, 131.4, 132.7, 132.8, 136.9, 137.4, 137.6, 140.3, 143.7, 155.0, 155.6, 195.8; *Anal*. *Calcd*. for $C_{25}H_{14}N_2O$ C, 83.78; H, 3.94; N, 7.82. Found: C, 83.95; H, 4.13; N, 7.68.

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