

HETEROCYCLES, Vol. 83, No. 10, 2011, pp. 2313 - 2320. © 2011 The Japan Institute of Heterocyclic Chemistry
Received, 9th June, 2011, Accepted, 21st July, 2011, Published online, 28th July, 2011
DOI: 10.3987/COM-11-12278

CeCl₃·7H₂O-CATALYZED SYNTHESIS OF QUINOXALINE DERIVATIVES IN LIQUID PEG-400

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Abstract - A mild and efficient route for the synthesis of quinoxaline derivatives utilizing cerium chloride heptahydrate (CeCl₃·7H₂O) as a novel catalyst in poly(ethylene glycol) (PEG-400) under mild conditions was described.

Nitrogen-containing heteroaromatic and heterocyclic compounds are indispensable structural units for both the chemist and the biochemist. Quinoxalines constitute the basis of many insecticides, fungicides, herbicides and anthelmintics, as well as being important in human health and as receptor antagonists.^{1,2} A number of methods have been developed for the synthesis of substituted quinoxalines involving condensation of 1,2-diamines with α -diketones,³ 1,4-addition of 1,2-diamines to diazenylbutenes,⁴ oxidation-trapping of α -hydroxy ketones with 1,2-diamine.⁵ Other recently, reported methods accomplished the synthesis of quinoxaline by the reaction of 1,2-amines with phenacyl bromides in solid-phase,⁶ or using heterogenous catalyst like HClO₄·SiO₂.⁷ Nevertheless, most of these methods suffer from unsatisfactory yields, difficult experimental procedures, expensive and detrimental metal precursors and harsh reaction conditions. Therefore, the development of improved methods for the synthesis of quinoxaline derivatives has acquired relevance to current research.

Poly(ethylene glycol) (PEG),⁸ a biologically acceptable polymer used extensively in drug delivery and in

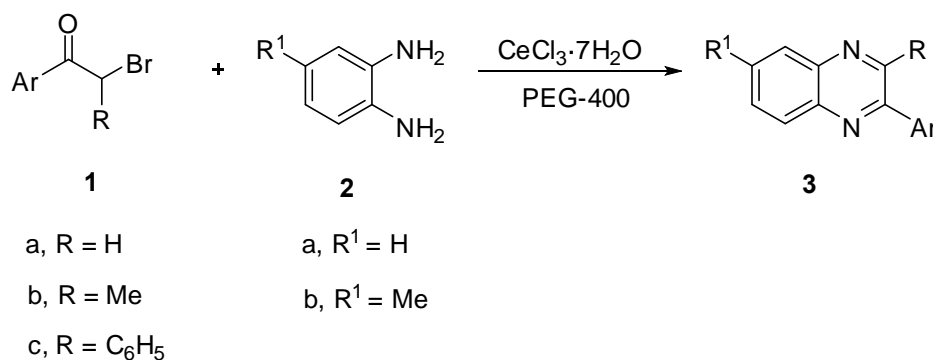
bioconjugates as tools for diagnostics has been used as a solvent medium support for various transformations.⁹ In recent times ionic liquids have been in the forefront of research, and several publications and reviews have already appeared.¹⁰ Even though ionic liquids offer some advantages, the tedious preparation of ionic liquids (and raw materials for ionic liquids) and their environmental safety is still debated. Compared with PEG, however, toxicity and environmental burden data of ionic liquids are for the most part unknown. Furthermore, the cost of ionic liquids is often more expensive than that of PEG.¹¹

Cerium chloride heptahydrate ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) has emerged as a potentially useful Lewis acid imparting high regio- and chemoselectivity in various chemical transformations. It is also a cheap, nontoxic and water-tolerant catalyst.¹²

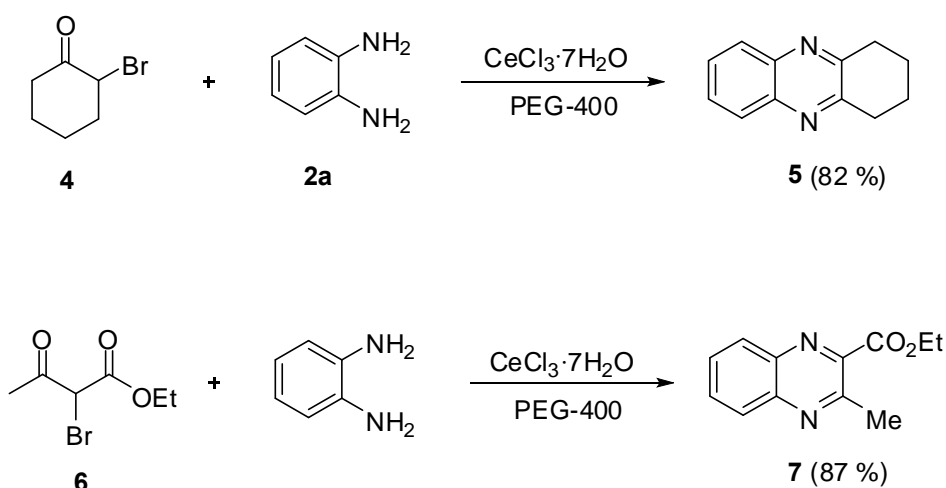
As part of our efforts to develop greener organic reaction procedures, we now report PEG-400 mediated facile and efficient synthesis of quinoxaline derivatives by the reaction of *o*-phenylenediamines with phenacyl bromides in the presence of catalytic amounts of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ under mild reaction conditions (Scheme 1).

Treatment of phenacyl bromide (**1a**) and *o*-phenylenediamine (**2a**) with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as catalyst in PEG-400 at room temperature for 30 min caused cyclodehydration to give 2-phenylquinoxaline (**3a**) in 92% yield. The results are given in Table 1. An array of phenacyl bromides having electron-donating and -withdrawing substituents on the aromatic ring attached to carbonyl carbon reacted with *o*-phenylenediamine (**2a**) to afford 2-aryl substituted quinoxalines (**3b-3g**) in good yields.

The method is equally effective for α -bromo cyclic ketone and α -bromo- β -keto ester such as α -bromo cyclohexanone (**4**) and α -bromo ethyl acetoacetate (**6**) reacted efficiently with *o*-phenylenediamine (**2a**) to give the corresponding substituted quinoxalines (**5**, **7**) (Scheme 2).

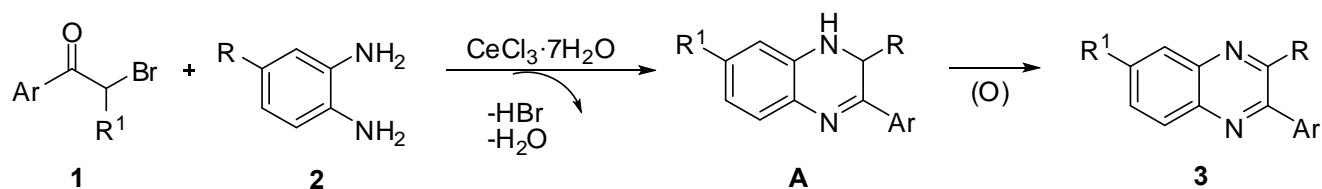


Scheme 1



Scheme 2

The formation of product may be explained by the reaction of phenacyl bromide (**1**) with *o*-phenylenediamine (**2**) and subsequent cyclization to produce **A** which leads to product **3** by oxidation (Scheme 3).



Scheme 3

In conclusion, the PEG-400 was shown to be an effective and useful alternative reaction medium for the preparation of quinoxaline derivatives using $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ as a catalyst. The important features of this procedure are enhanced reaction rate, mild reaction condition, high yields and green aspects such as avoiding hazardous organic solvents and toxic catalysts.

Table 1. Synthesis of quinoxalines **3a-n**

Entry	Ar	R	R ₁	Product	Yield (%)
1	C ₆ H ₅	H	H	3a	92
2	4-MeC ₆ H ₄	H	H	3b	88
3	4-MeOC ₆ H ₄	H	H	3c	87
4	4-FC ₆ H ₄	H	H	3d	90
5	4-ClC ₆ H ₄	H	H	3e	86
6	4-BrC ₆ H ₄	H	H	3f	87
7	3,4-Cl ₂ C ₆ H ₃	H	H	3g	90
8	C ₆ H ₅	Me	H	3h	84
9	C ₆ H ₅	C ₆ H ₅	H	3i	91
10	C ₆ H ₅	C ₆ H ₅	Me	3j	93
11	2-Pyridyl	H	H	3k	90
12	2-Furyl	H	H	3l	85
13	2-Thienyl	H	H	3m	92
14	2-Naphthyl	H	H	3n	89

ACKNOWLEDGEMENT

We gratefully acknowledge the National Council Science of Republic of China for financial support of this work.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27 G spectrophotometer. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Unity Plus 400 MHz. Chemical shifts (δ) were measured in ppm with respect to TMS. MS were obtained on a JEOL JMS D-300 instrument.

General procedure for the synthesis of quinoxalines (3)

A mixture of phenacyl bromide (**1**) (1.0 mmol) and *o*-phenylenediamine (**2**) (1.0 mmol) in PEG-400 (2 g) was added CeCl₃·7H₂O (0.05 mmol) and the resultant mixture was stirred at room temperature for 0.5 h to complete the reaction. Subsequently, AcOEt (3×5 mL) was added and the organic phase was separated from PEG-400/catalyst mixture, dried over MgSO₄, and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel using ethyl acetate as eluent to give **3**.

2-Phenylquinoxaline (**3a**)

Mp 74-75 °C (Lit.,¹³ 75-76 °C). IR (KBr) ν : 3119, 1614, 1560, 1076 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.55-7.58 (m, 3H), 7.74-7.82 (m, 2H), 8.11-8.22 (m, 4H), 9.34 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 127.5, 128.5, 129.1, 129.5, 129.6, 130.1, 130.2, 136.8, 141.5, 142.3, 143.3, 151.8; EI-MS m/z (relative intensity) 206 (M⁺), 179, 152.

2-(4-Methylphenyl)quinoxaline (**3b**)

Mp 92-93 °C (Lit.,¹³ 90-91 °C). IR (KBr) ν : 3053, 952, 748 cm⁻¹; ¹H NMR (CDCl₃) δ : 2.46 (s, 3H), 7.38 (dd, J = 0.8, 8.8 Hz, 2H), 7.71-7.80 (m, 2H), 8.09-8.16 (m, 4H), 9.32 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 21.4, 127.4, 129.0, 129.3, 129.5, 129.8, 130.2, 133.9, 140.5, 141.4, 142.3, 143.3, 151.8; EI-MS m/z (relative intensity) 220 (M⁺), 193, 192.

2-(4-Methoxyphenyl)quinoxaline (**3c**)

Mp 97-98 °C (Lit.,¹³ 99-100 °C). IR (KBr) ν : 3057, 2360, 954, 759 cm⁻¹; ¹H NMR (CDCl₃) δ : 3.90 (s, 3H), 7.07 (dd, J = 2.0, 6.8 Hz, 2H), 7.68-7.77 (m, 2H), 8.09 (t, J = 8.0 Hz, 2H), 8.15-8.18 (m, 2H), 9.28 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 55.3, 114.5, 128.9, 129.0, 129.1, 129.3, 130.1, 141.1, 142.2, 143.0, 151.4, 161.4; EI-MS m/z (relative intensity) 236 (M⁺), 221, 209, 193, 166.

2-(4-Fluorophenyl)quinoxaline (**3d**)

Mp 119-120 °C (Lit.,¹³ 120-121 °C). IR (KBr) ν : 3048, 2361, 956, 755 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.22-7.28 (m, 2H), 7.72-7.81 (m, 2H), 8.11-8.14 (m, 2H), 8.18-8.22 (m, 2H), 9.29 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 116.3, 129.1, 129.4, 129.5, 130.3, 132.8, 132.9, 141.4, 142.1, 142.8, 150.7, 165.4; EI-MS m/z (relative intensity) 225, 224 (M⁺), 197, 196.

2-(4-Chlorophenyl)quinoxaline (**3e**)

Mp 134 °C IR (KBr) ν : 3056, 2360, 955, 760 cm⁻¹; ¹H NMR (CDCl₃) δ : 7.52-7.55 (m, 2H), 7.74-7.82 (m, 2H), 8.11-8.17 (m, 4H), 9.30 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ : 128.7, 129.1, 129.3, 129.5, 129.7, 130.4, 135.1, 136.5, 141.6, 142.1, 142.8, 150.5; EI-MS m/z (relative intensity) 242, 240 (M⁺), 213, 205, 178, 151; Anal. Calcd for C₁₄H₉ClN₂: C, 69.86; H, 3.77; N, 11.64. Found: C, 69.75; H, 3.68; N, 11.78.

2-(4-Bromophenyl)quinoxaline (3f)

Mp 128 °C IR (KBr) ν : 3057, 2359, 955, 760 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.68-7.71 (m, 2H), 7.74-7.82 (m, 2H), 8.07-8.15 (m, 4H), 9.29 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 124.9, 128.9, 129.1, 129.5, 129.7, 130.4, 132.3, 135.6, 141.6, 142.7, 150.6; EI-MS m/z (relative intensity) 287, 286, 285 (M^+), 284, 205, 178, 151; Anal. Calcd for $\text{C}_{14}\text{H}_9\text{BrN}_2$: C, 58.97; H, 3.18; N, 9.82. Found: C, 59.23; H, 3.26; N, 9.74.

2-(3,4-Dichlorophenyl)quinoxaline (3g)

Mp 150-151 °C IR (KBr) ν : 3054, 2360, 963, 757 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.64 (d, $J=8.4$ Hz, 1H), 7.76-7.84 (m, 2H), 8.04 (dd, $J = 2.4, 8.4$ Hz, 1H), 8.14 (ddd, $J = 1.6, 7.0, 7.2$ Hz, 2H), 8.35 (d, $J = 2.0$ Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 128.3, 129.1, 129.3, 129.6, 130.1, 130.6, 131.0, 133.6, 134.6, 136.6, 141.8, 142.5, 149.2; EI-MS m/z (relative intensity) 279, 277, 275 (M^+), 239, 212, 177, 150; Anal. Calcd for $\text{C}_{14}\text{H}_8\text{Cl}_2\text{N}_2$: C, 61.12; H, 2.92; N, 10.18. Found: C, 61.23; H, 2.73; N, 10.26.

2-Methyl-3-phenylquinoxaline (3h)

Mp 55 °C (Lit.,¹⁴ 56 °C). IR (KBr) ν : 3058, 2359, 1558, 1342, 816, 764 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.78 (s, 3H), 7.46-7.54 (m, 3H), 7.63-7.75 (m, 4H), , 8.04-8.12 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 24.3, 128.2, 128.4, 128.8, 128.9, 129.1, 129.6, 138.9, 140.8, 141.1, 152.4, 154.8; EI-MS m/z (relative intensity) 220 (M^+), 219, 179, 151.

2,3-Diphenylquinoxaline (3i)

Mp 123-124 °C (Lit.,¹⁵ 126-127 °C). IR (KBr) ν : 3054, 2922, 1539, 1344, 768, 729 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.32-7.40 (m, 6H), 7.52-7.54 (m, 4H), 7.75 (m, dd, $J = 2.4, 9.2$ Hz, 2H), 8.20 (dd, $J = 2.4, 8.8$ Hz, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 128.2, 128.7, 129.1, 129.7, 129.9, 139.0, 141.1, 153.4; EI-MS m/z (relative intensity) 282 (M^+), 178, 152, 140, 77.

6-Methyl-2,3-diphenylquinoxaline (3j)

Mp 118-119 °C (Lit.,¹⁵ 116-117 °C). IR (KBr) ν : 3055, 2940, 1617, 1199, 1020, 699 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.60 (s, 3H), 7.30-7.33 (m, 6H), 7.49-7.52 (m, 4H), 7.58 (dd, $J = 2.4, 11.2$ Hz, 1H), 8.06 (d, $J = 11.2$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 21.8, 127.9, 128.1, 128.5, 128.6, 129.7, 129.7, 132.2, 139.1, 140.3, 142.2, 152.4, 153.2; EI-MS m/z (relative intensity) 296 (M^+), 192, 165, 89.

2-(2-Pyridyl)quinoxaline (3k)

Mp 110-111 °C (Lit.,¹⁶ 113-114 °C). IR (KBr) ν : 3048, 2923, 1589, 1401, 805, 770 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.38-7.41 (m, 1H), 7.74-7.81 (m, 2H), 7.86-7.91 (m, 1H), 8.13-8.17 (m, 2H), 8.57-8.60 (m, 1H), 8.77-8.78 (m, 1H), 9.96 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 121.9, 124.5, 139.2, 129.6, 129.9, 130.0, 137.0, 141.7, 142.4, 144.0, 149.3, 150.0, 154.4; EI-MS m/z (relative intensity) 207 (M^+), 179, 105,

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2-(2-Furanyl)quinoxaline (3l)

Mp 99-100 °C (Lit.,¹³ 97-98 °C). IR (KBr) ν : 3117, 2364, 961, 755 cm^{-1} ; ^1H NMR (CDCl_3) δ : 6.64 (dd, $J = 2.0, 3.6$ Hz, 1H), 7.33 (d, $J = 3.2$ Hz, 1H), 7.69-7.78 (m, 3H), 8.09 (ddd, $J = 1.6, 8.0, 12.8$ Hz, 2H), 9.25 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 111.7, 112.4, 126.9, 130.4, 130.8, 141.2, 142.0, 143.8, 144.2, 145.0, 151.5; EI-MS m/z (relative intensity) 196 (M^+), 169, 168, 141, 140, 114.

2-(2-Thienyl)quinoxaline (3m)

Mp 118-119 °C (Lit.,¹⁶ 120-121 °C). IR (KBr) ν : 3052, 2360, 927, 756 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.20 (ddd, $J = 0.4, 4.0, 4.8$ Hz, 1H), 7.54 (dd, $J = 0.4, 4.4$ Hz, 1H), 7.67-7.76 (m, 2H), 7.85 (d, $J = 3.6$ Hz, 1H), 8.05-8.07 (m, 2H), 9.23 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 126.9, 128.4, 129.0, 129.1, 129.7, 130.3, 141.3, 142.0, 142.1, 142.2, 147.3; EI-MS m/z (relative intensity) 212 (M^+), 211, 185, 141.

2-(2-Naphthyl)quinoxaline (3n)

Mp 141-142 °C (Lit.,¹³ 140-142 °C). IR (KBr) ν : 3054, 2355, 1541, 1358, 825, 743 cm^{-1} ; ^1H NMR (CDCl_3) δ : 7.55-7.59 (m, 2H), 7.74-7.83 (m, 2H), 7.91-7.93 (m, 1H), 8.01-8.04 (m, 2H), 8.15 (dd, $J = 1.2, 8.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H), 8.37 (d, $J = 0.8, 8.4$ Hz, 1H), 8.66 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 124.4, 126.6, 127.2, 127.4, 127.7, 128.8, 129.0, 129.1, 129.5, 129.5, 130.3, 133.3, 134.0, 134.0, 141.5, 142.3, 143.4, 151.6; EI-MS m/z (relative intensity) 256 (M^+), 202, 153, 126.

1,2,3,4-Tetrahydrophenazine (5)

Mp 89-90 °C (Lit.,¹³ 91-92 °C). IR (KBr) ν : 3057, 2930, 1605, 1492, 1248, 736 cm^{-1} ; ^1H NMR (CDCl_3) δ : 2.01-2.08 (m, 4H), 3.13-3.20 (m, 4H), 7.64-7.69 (m, 2H), 7.95-7.80 (m, 2H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 23.2, 33.6, 128.7, 129.3, 141.6, 154.5; EI-MS m/z (relative intensity) 184 (M^+), 169, 156, 129, 118.

Ethyl 3-methyl-quinoxaline-2-carboxylate (7)

Mp 63-64 °C (Lit.,¹⁷ 65-66 °C). IR (KBr) ν : 2971, 2926, 1717, 1314, 1269, 1079, 768 cm^{-1} ; ^1H NMR (CDCl_3) δ : 1.50 (t, $J = 4.8$ Hz, 3H), 2.96 (s, 3H), 4.57 (q, $J = 4.8$ Hz, 2H), 7.76-8.20 (m, 4H); EI-MS m/z (relative intensity) 216 (M^+), 172, 144, 116, 102, 75.

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