Green and Efficient Synthesis of Quinoxaline Derivatives *via* Ceric Ammonium Nitrate Promoted and *in Situ* Aerobic Oxidation of α-Hydroxy Ketones and α-Keto Oximes in Aqueous Media

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The direct conversion of α-hydroxy ketones and α-keto oximes into quinoxaline derivatives in the presence of a catalytic amount of ceric ammonium nitrate *via* metal-catalyzed aerobic oxidation followed by *in situ* trapping with aromatic 1,2-diamines in water as a green and efficient reaction media, is reported.

Key words quinoxaline; aerobic oxidation; α-hydroxy ketone; ceric ammonium nitrate; diamine

The methodology for heterocyclic synthesis represents a powerful approach for the rapid build-up of molecular complexity from potentially simple starting materials.[1] Nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties.[2] Quinoxaline derivatives as an important class of nitrogen-containing heterocycles are known to exhibit a wide range of biological activities such as antiviral, antibacterial, antiinflammatory and kinase inhibitor properties.[3—10] The echinomycin[11] and the triostins[12] are well known as antibiotic families of quinoxaline derivatives.

A number of synthetic strategies have been reported for the synthesis of quinoxaline derivatives.[2,13] The most common method is the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing acetic acid for 2—12 h giving 34—85% yields[14] or in high boiling point solvent such as dimethylsulfoxide (DMSO)[15] in the presence of catalytic amounts of molecular iodine.

Recently, the synthesis of quinoxaline derivatives with condensation of *o*-phenylenediamine and a 1,2-dicarbonyl compound in MeOH/AcOH[16] under microwave irradiation at 100 °C has been reported, but requires special instrumentation. In addition, improved methods have been developed for the synthesis of quinoxaline derivatives including the Bi-catalyzed oxidative coupling of epoxides and ene-1,2-diamines,[17] and the cyclization of α-arylimino oximes of α-dicarbonyl compounds under reflux conditions in acetic anhydride.[18] Moreover, Taylor and his co-worker[19,20] have shown that quinoxalines can be produced in one-pot process commencing from α-hydroxy ketones using a manganese dioxide-mediated or aerobic oxidation palladium acetate-catalyzed tandem oxidation process with *in situ* trapping of α-dicarbonyls with aromatic 1,2-diamines. These oxidation and condensation reactions into a single operation provide a significant improvement to existing procedure. However, in the case of manganese dioxide, the requirement for an excess of it (usually 10 equiv) detracts from commercial attractiveness and green credentials of this process and with palladium acetate-catalyzed aerobic oxidation the reaction requires long times (24 h) for completion at ambient temperature in toluene as a toxic solvent. It is important to note that the yield of reaction with palladium acetate is only trace after 1 h.

In recent years, water as an environmentally benign solvent has attracted interests because of its favorable properties and a variety of catalytic reactions which have been successfully carried out in aqueous medium.[21—24] The solvophobic properties of water are able to generate an internal pressure and promote the association of the reactants in a solvent cavity during the activation process and accelerate a reaction. These properties of water are very efficient for condensation reactions in which the entropy of reaction decreases in the transition state.

During the course of our studies towards the development of new routes to the synthesis of heterocyclic compounds using green reaction mediums[25—27] and new catalysts,[28,29] we wish to report the direct conversion of α-hydroxy ketones **1** and α-keto oximes **2** into quinoxaline derivatives **4a**—**g** in water as an environmentally benign solvent in the presence of a catalytic amount of ceric ammonium nitrate (CAN) *via* metal-catalyzed aerobic oxidation followed by *in situ* trapping with aromatic 1,2-diamines **3** (Chart 1).

Experimental

Apparatus Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. The elemental analyses were performed with an Elementar Analysensysteme GmbH VarioEL. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively.

All of the chemicals were purchased from Fluka, Merck and Aldrich and used without purification. All the products were identified by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

General Procedure for the Preparation of Quinoxalines (4a—g) α-Hydroxy ketone **1** or α-keto oxime **2** (1 mmol), 1,2-diamine **3** (1 mmol), CAN (0.05 mmol) and water (5 ml) were taken in 50 ml two-necked round bottomed flask equipped with a gas passing tube. Air was bubbled at a rate of 5 ml/min into the reaction mixture while stirring for appropriate time at room temperature. After completion of the reaction as indicated by TLC (ethyl acetate/*n*-hexane, 1 : 1), the reaction mixture was washed with water (3×10 ml) and the solid residue was crystallized from ethanol to give pure product **4**.

General Procedure for the Preparation of Pyrazine-2,3-dicarbonitriles (6a, b) α-Hydroxy ketone **1** (1 mmol), 2,3-diaminomaleonitrile **5** (1 mmol), CAN (0.05 mmol) and water (5 ml) were taken in 50 ml two-necked round bottomed flask equipped with a gas passing tube. Air was bub-

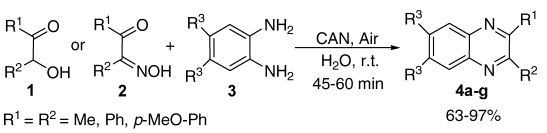

Chart 1. Synthesis of Quinoxaline Derivatives

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bled at a rate of 5 ml/min into the reaction mixture while stirring for appropriate time at room temperature. After completion of the reaction as indicated by TLC (ethyl acetate/*n*-hexane, 2 : 1), the reaction mixture was washed with water (2×10 ml) and the solid residue was crystallized from ethanol to give pure product **6**.

General Procedure for the Preparation of 2,3-Dihydro-1*H*-perimidins (8a, b) α-Hydroxy ketone **1** (1 mmol), naphthalene-1,8-diamine **7** (1 mmol), CAN (0.05 mmol) and water (5 ml) were taken in 50 ml two-necked round bottomed flask equipped with a gas passing tube. Air was bubbled at a rate of 5 ml/min into the reaction mixture while stirring for appropriate time at room temperature. After completion of the reaction as indicated by TLC (ethyl acetate/*n*-hexane, 3 : 1), the reaction mixture was washed with water (2×10 ml) and the solid residue was crystallized with ethanol to give pure product **8**.

Compounds Characterization Data 2,3-Diphenylquinoxaline (**4a**, $C_{20}H_{14}N_2$): White solid; mp 124—126 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.16—8.24 (2H, m), 7.74—7.80 (2H, m), 7.50—7.58 (4H, m), 7.30—7.38 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 153.5, 141.3, 139.1, 130, 129.9, 129.2, 128.8, 128.3. IR (KBr) cm^{-1}: 3055, 1550, 1488, 1436, 1342, 1071, 974, 768, 696. MS *m/z*: 282 (M^+), 205, 128, 77.

6,7-Dichloro-2,3-diphenylquinoxaline (**4b**, $C_{20}H_{12}Cl_2N_2$): Purple solid; mp 146—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.32 (2H, s), 7.50—7.54 (4H, m), 7.33—7.40 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 154.6, 140.5, 137.3, 132.8, 130.2, 129.9, 129.2, 128.9. IR (KBr) cm^{-1}: 3055, 1534, 1437, 1334, 1184, 1105, 1018, 960, 881, 765, 693. MS *m/z*: 350 (M^+), 204, 146, 77.

2,3-Bis(4-methoxyphenyl)quinoxaline (**4c**, $C_{22}H_{18}N_2O_2$): Yellow solid; mp 150—151 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.10—8.17 (2H, m), 7.72—7.76 (2H, m), 7.52 (4H, d, J=8.7 Hz), 6.90 (4H, d, J=8.7 Hz), 3.85 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 160.2, 153.0, 141.1, 131.8, 131.3, 129.5, 129.0, 13.8, 55.3. IR (KBr) cm^{-1}: 3045, 2925, 1601, 1508, 1460, 1387, 1339, 1294, 1242, 1165, 1023, 971, 829, 764, 548. MS *m/z*: 342 (M^+), 313, 166, 76.

2,3-Dimethylquinoxaline (**4d**, $C_{10}H_{10}N_2$): Yellow solid; mp 105—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.93—7.99 (2H, m), 7.62—7.68 (2H, m), 2.71 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 153.4, 141.1, 128.8, 128.3, 23.2. IR (KBr) cm^{-1}: 3100, 2990, 1563, 1483, 1431, 1392, 1315, 1158, 984, 760, 669, 611. MS *m/z*: 158 (M^+), 117, 76, 50.

6,7-Dichloro-2,3-dimethylquinoxaline (**4e**, $C_{10}H_8Cl_2N_2$): Yellow solid; mp 198—200 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.08 (2H, s), 2.72 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 154.9, 139.8, 133.1, 129.1, 23.2. IR (KBr) cm^{-1}: 3135, 3000, 1591, 1455, 1391, 1317, 1170, 1098, 888, 847, 755. MS *m/z*: 226 (M^+), 185, 145, 118, 74.

2-Methyl-3-propylquinoxaline (**4f**, $C_{12}H_{14}N_2$): Yellow solid; mp 63—64 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.90—7.98 (2H, m), 7.61—7.67 (2H, m), 2.97 (2H, t, J=7.8 Hz), 2.76 (3H, s), 1.87—1.93 (2H, m), 1.09 (3H, t, J=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 156.3, 141.5, 130.2, 129.8, 128.6, 127.8, 126.6, 125.9, 35.6, 23.5, 19.3, 13.9. IR (KBr) cm^{-1}: 3100, 2995, 1556, 1481, 1457, 1320, 1148, 1126, 997, 768, 746, 609. MS *m/z*: 186 (M^+), 171, 158, 76, 45.

6,7-Dichloro-2-methyl-3-propylquinoxaline (**4g**, $C_{12}H_{12}Cl_2N_2$): Purple solid; mp 90—91 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.12 (1H, s), 8.09 (1H, s), 2.95 (2H, t, J=7.8 Hz), 2.75 (3H, s), 1.83—1.89 (2H, m), 1.08 (3H, t, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 158.0, 154.6, 139.9, 139.6, 132.9, 132.9, 129.3, 129.0, 37.7, 22.8, 20.9, 14.0. IR (KBr) cm^{-1}: 3040, 2950, 1589, 1369, 1310, 1169, 1131, 1100, 902, 874, 763, 656. MS *m/z*: 254 (M^+), 226, 144, 109, 74, 43.

5,6-Dimethylpyrazine-2,3-dicarbonitrile (**6a**, $C_8H_6N_4$): Yellow solid; mp 110—112 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 158.0, 130.3, 113.2, 22.7. IR (KBr) cm^{-1}: 3030, 2955, 2150, 1577, 1469, 1345. MS *m/z*: 158 (M^+), 117, 76, 41.

5,6-Bis(4-methoxyphenyl)pyrazine-2,3-dicarbonitrile (**6b**, $C_{20}H_{14}N_4O_2$): Pale yellow solid; mp 190—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.63 (4H, d, J=6.8 Hz), 6.95 (4H, d, J=6.8 Hz), 3.87 (6H, s). ^{13}C-NMR ($CDCl_3$) δ: 164.9, 155.2, 132.4, 129.2, 126.7, 117.4, 114.3, 55.7. IR (KBr) cm^{-1}: 3038, 2964, 2840, 2146, 1607, 1482, 1380, 1261, 1173. MS *m/z* (%): 342 (M^+), 234, 131, 117, 108, 76, 41.

1-(2,3-Dihydro-2-methyl-1*H*-perimidin-2-yl)ethanone (**8a**, $C_{14}H_{14}N_2O$): Brown solid; mp 184—187 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 7.12 (2H, t, J=7.64 Hz), 6.91 (2H, d, J=8.1 Hz), 6.46 (2H, d, J=7.2 Hz), 3.32 (2H, br s), 2.07 (3H, s), 1.45 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 212.0, 141.7, 134.6, 127.5, 115.6, 112.0, 104.5, 71.9, 24.8, 23.8. IR (KBr) cm^{-1}: 3280, 3242, 3050, 2950, 1710, 1589, 1469. MS *m/z*: 226 (M^+), 157, 126, 72, 43. *Anal*. Calcd: C, 74.31; H, 6.24; N, 12.38; Found: C, 74.35; H, 6.22; N, 12.43.

(2,3-Dihydro-2-phenyl-1*H*-perimidin-2-yl)(phenyl)methanone (**8b**, $C_{24}H_{18}N_2O$): Dark brown solid; mp 195—197 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 7.66—7.83 (2H, m), 7.36—7.53 (3H, m), 6.86—7.23 (9H, m), 6.42 (2H, d, J=7.9 Hz), 3.75 (2H, br s). ^{13}C-NMR ($CDCl_3$) δ: 203.1, 143.1, 141.2, 138.0, 135.9, 134.2, 134.11, 133.6, 132.6, 131.9, 130.3, 128.3, 128.2, 126.7, 126.2, 124.2, 123.1, 122.7, 121.5, 119.2, 117.2, 114.1, 109.4, 98.8. IR (KBr) cm^{-1}: 3325, 3263, 3056, 2954, 1707, 1582, 1473. MS *m/z*: 350 (M^+), 246, 170, 157, 126, 77. *Anal*. Calcd: C, 82.26; H, 5.18; N, 7.99; Found: C, 82.20; H, 5.22; N, 7.96.

Results and Discussion

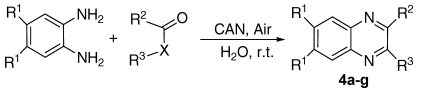
Although CAN is far superior to many other one-electron oxidants, the vast majority of CAN-mediated oxidations require more than two equivalents of the oxidant for completion of the reaction. This precludes its use in large-scale transformations. Development of reactions requiring only catalytic amounts of CAN is therefore very important.[30—32]

To illustrate the need of catalyst, the reaction between *o*-phenylenediamine and benzoin has been studied in various molar ratios of CAN under air blowing in water. In the absence of CAN, the reaction yield was trace. The best results have been obtained with 5 mol% of CAN after 45 min at room temperature. The yield of reaction with increasing the quantity of CAN is not considerably increased.

It is important to note, this reaction didn't proceed efficiently without air blowing and the reaction yield was only about 30% after stirring 5 h at room temperature.

The results of *in situ* aerobic oxidation and CAN catalyzed condensation reaction of α-hydroxy ketone **1** or α-keto

Table 1. Synthesis of Quinoxalines in the Presence of CAN *via* Aerobic Oxidation in Water at Room Temperature



4a-g

Entry	R^1	R^2	R^3	X	Product	Yield[a] (%) (Time, min)
1	H	Ph	Ph	CHOH	**4a**	97 (45)
2	Cl	Ph	Ph	CHOH	**4b**	92 (50)
3	H	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	CHOH	**4c**	93 (45)
4	H	Me	Me	CHOH	**4d**	86 (55)
5	Cl	Me	Me	CHOH	**4e**	80 (50)
6	H	Me	*n*-Pr	C=NOH	**4f**	65 (60)
7	Cl	Me	*n*-Pr	C=NOH	**4g**	67 (60)
8	H	Ph	Ph	C=NOH	**4a**	72 (55)
9	Cl	Ph	Ph	C=NOH	**4b**	63 (45)
10	H	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	C=NOH	**4c**	70 (50)

a) Isolated yields.

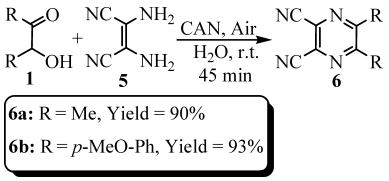


Chart 2. Synthesis of Pyrazine-2,3-dicarbonitriles

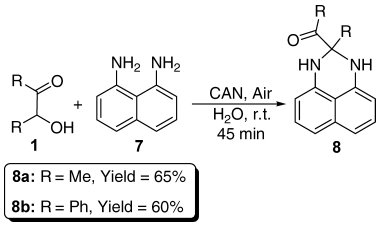


Chart 3. Synthesis of 2,3-Dihydro-1*H*-perimidines

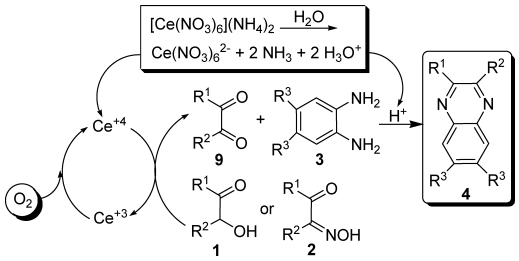


Chart 4. Proposed Mechanism for the Synthesis of Quinoxalines

oxime **2** with 1,2-diamine **3** are given in Table 1. The procedure gives the products in excellent yields.

In order to explore the scope and limitations of this reaction, we extended the procedure to various 1,2-dialkyl and 1,2-diaryl α-hydroxy ketones and α-keto oximes. We found that the reaction proceeds very efficiently in all cases and the reaction time decreased for 1,2-diaryl ones.

We also extended this approach to the reaction of α-hydroxy ketones **1** with 2,3-diaminomaleonitrile (DAMN) **5** and naphthalene-1,8-diamine **7**. In the case of DAMN, the reaction gave the pyrazine-2,3-dicarbonitriles **6a**, **b** in excellent yields within very short reaction times (Chart 2) and with naphthalene-1,8-diamine **7** the 2,3-dihydro-1*H*-perimidines **8a**, **b** were obtained (Chart 3).

Although the mechanism of the reaction between the α-hydroxy ketones **1** or α-keto oximes **2** and 1,2-diamines **3** in the presence of CAN has not yet been established experimentally, a possible explanation is proposed in Chart 4. CAN plays dual roles in this reaction: (i) Ce^{+4} Moiety of CAN catalyzed oxidation of α-hydroxy ketone **1** or α-keto oxime **2** to the corresponding 1,2-diketone **9**. (ii) NH_4^+ Moiety of CAN acts as an protic acid catalyst, which promotes the condensation of 1,2-diketone **9** with 1,2-diamine **3** during the activation process and reaction times decreased.

Conclusions

In summary, a new, green and efficient approach for the synthesis of quinoxaline derivatives by the *in situ* oxidation and condensation of aliphatic and aromatic α-hydroxy ketones or α-keto oximes with various 1,2-diamines using CAN as a promoter was developed in aqueous medium in high yields at room temperature. To the best of our knowledge this is the first report of the synthesis of quinoxalines using CAN in conjunction with aerobic oxidation in water and this new reaction conditions open an important alternative to the use of toxic solvents. Also this protocol gives excellent results for the synthesis of pyrazine and perimidine annulated heterocyclic systems from the reaction of α-hydroxy ketones with 2,3-diaminomaleonitrile and naphthalene-1,8-diamine, respectively.

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