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A novel three-component reaction for the synthesis of *N*-cyclohexyl-3-aryl-quinoxaline-2-amines

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ABSTRACT

Ferric perchlorate catalyzes the three-component condensation reaction of *o*-phenylenediamine, aromatic aldehydes, and cyclohexyl isocyanide to afford the corresponding *N*-cyclohexyl-3-aryl-quinoxaline-2-amines in good yields.

1. Introduction

Among the various classes of nitrogen-containing heterocyclic compounds, quinoxalines display a broad spectrum of biological activity.[1–4] This has contributed to their usefulness in combinatorial drug discovery libraries.[5–10] Quinoxalines play an important role as a basic skeleton for the design of a number of antibiotics such as echinomycin, actinomycin, and leromycin. It has been reported that these compounds inhibit the growth of gram-positive bacteria, and are active against various transplantable tumors.[11,12]

The quinoxaline ring is also a constituent of many pharmacologically and biologically active compounds such as insecticides, fungicides, herbicides, and anthelminitics.[13,14] Quinoxaline derivatives have found application in dyes,[15] electron luminescent materials,[16] organic semiconductors,[17] chemically controllable switches,[18] as building blocks for the synthesis of anion receptors,[19] cavitands,[20] dehydroannulenes,[21] DNA cleaving agents,[22] and also serve as useful rigid subunits in macrocyclic receptors or in molecular recognition.[23]

Despite remarkable efforts,[3,4] the development of an effective method for the synthesis of quinoxalines is still an important challenge. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[24–29] The most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2–12 h, and this typically gives yields of 34–70%.[30]

To the best of our knowledge, there is no report on the synthesis of these compounds with cyclohexyl isocyanide and aldehydes. The application of ferric perchlorate as a catalyst is becoming more widespread. It is used in organic chemistry for the protection of alcohols and deprotection of tetrahydropyranyl ethers,[31] acetylation of alcohols and phenols,[32] aromatization of Hantzsch 1,4-dihydropyridines,[33] synthesis of 1,5-benzodiazepine derivatives,[34] direct acetylation of THP ethers,[35] conversion of oximes to aryl and alkyl hydrazones,[36] and for the synthesis of α-aminonitriles using trimethylsilylcyanide.[37] In this Letter, and in continuation of our research, we report ferric perchlorate as an efficient catalyst for the synthesis of *N*-cyclohexyl-3-aryl-quinoxaline-2-amines in good yields from *o*-phenylenediamine, aromatic aldehydes, and cyclohexyl isocyanide (Scheme 1).

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because they increase the efficiency by combining several operational steps without isolation of intermediates or changing the reaction conditions.[38,39] MCRs have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds.[40–42] Isocyanide-based MCRs are especially important in this area.[43]

The MCR of cyclohexyl isocyanide, an aromatic aldehyde, and *o*-phenylenediamine in the presence of a catalytic amount of ferric perchlorate in acetonitrile was complete within 2 h to afford *N*-cyclohexyl-3-aryl-quinoxaline-2-amines in good yields (Table 1). The yields of the reactions increased as the reaction temperature was raised, and refluxing conditions were found to be optimum. Importantly, aromatic aldehydes carrying either

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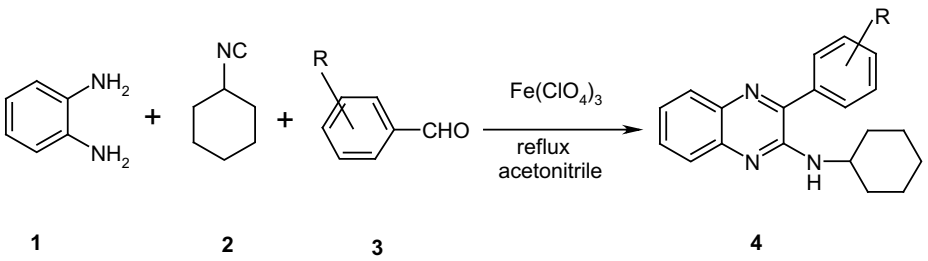


Scheme 1.

Table 1
Synthesis of *N*-cyclohexyl-3-aryl-quinoxaline-2-amines

Entry	Substrate	Product	Time (h)	Yield[a] (%)
1	Benzaldehyde	**4a**	2	92
2	3-Nitrobenzaldehyde	**4b**	2	92
3	4-Chlorobenzaldehyde	**4c**	2	91
4	4-Methoxybenzaldehyde	**4d**	2	93
5	4-Nitrobenzaldehyde	**4e**	2	92
6	4-Hydroxybenzaldehyde	**4f**	2	92
7	4-Methylbenzaldehyde	**4g**	2	92

[a] Yield of isolated product.

electron-donating or -withdrawing substituents afforded good yields of the expected products. The reaction proceeds cleanly and is free from side products. A possible reaction mechanism is suggested in Scheme 2.

The first step may involve reaction of the aromatic aldehyde with *o*-phenylenediamine followed by attack of cyclohexyl isocyanide on the resulting intermediate. Following rearrangement and catalytic oxidation by ferric perchlorate,[33] the product is obtained.

In conclusion, we have demonstrated a very simple, efficient, clean, and practical method for the synthesis of *N*-cyclohexyl-3-aryl-quinoxaline-2-amines in good yields (91–93%) in the presence of ferric perchlorate as an efficient catalyst.

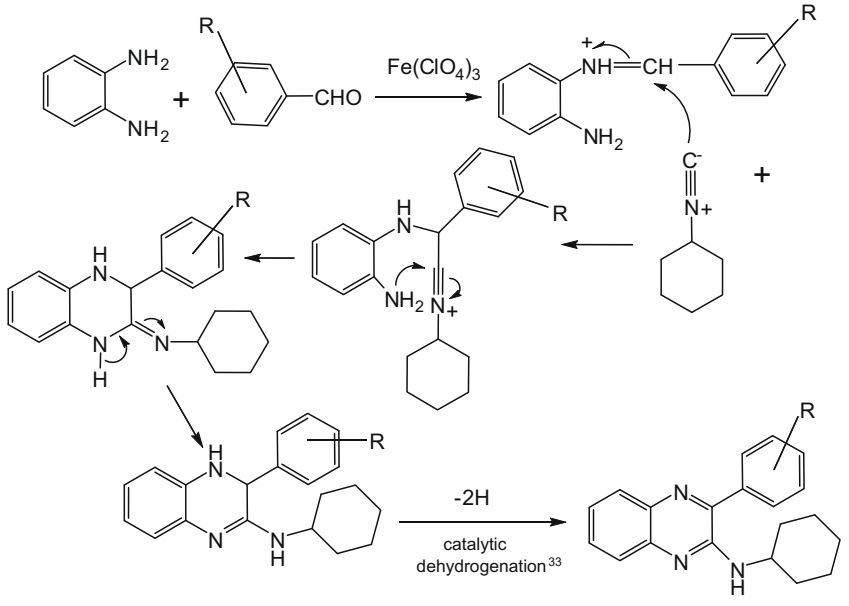
Although Fe(III) reagents are known to be strong oxidants,[44] ferric perchlorate in this reaction behaves solely as a powerful and highly selective Lewis acid. The oxidation potential of ferric perchlorate in methanol is 0.70 eV.[45]

2. Preparation of *N*-cyclohexyl-3-aryl-quinoxaline-2-amines: general procedure

To a mixture of *o*-phenylenediamine (1 mmol), benzaldehyde (1 mmol), and cyclohexyl isocyanide (1 mmol) in acetonitrile (5 mL), a catalytic amount of ferric perchlorate (0.2 mmol) was added and the mixture was refluxed for 2 h. The progress of the reaction was monitored by TLC (ethyl acetate–hexane 1:3). After completion of the reaction, acetonitrile was removed and the reaction mixture was diluted with water (10 mL), and CH_2Cl_2 (10 mL) was added. The organic layer was separated and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the product was obtained without any further purification.

3. *N*-Cyclohexyl-3-phenyl-quinoxaline-2-amine (4a)

Mp 187 °C; IR (KBr) (ν_{max}, cm^{-1}): 3200, 1632, 1620; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 1.11–2.12 (m, 10H), 3.24 (m, 1H), 4.75 (s, 1H, NH), 7.51–8.02 (m, 9H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 24.81, 26.53 ($2CH_2$), 33.30 ($2CH_2$), 51.24, 126.26 (2CH), 128.21, 128.62, 129.13, 131.55 (2CH), 131.5, 132.2, 134.7, 136.5 (C=N), 141.1, 142.1, 145.4 (NH–C=N). GC/MS: 303 (M^+). Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 79.11; H, 6.92; N, 13.81.



Scheme 2.

4. *N*-Cyclohexyl-3-(3-nitrophenyl)-quinoxaline-2-amine (4b)

Mp 195 °C; IR (KBr) (ν_{max}, cm^{-1}): 3165, 1635, 1628; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 1.24–2.29 (m, 10H), 3.40 (m, 1H), 4.51 (s, 1H, NH), 7.51–8.43 (m, 8H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 25.22, 26.15 ($2CH_2$), 33.53 ($2CH_2$), 52.10, 127.56, 128.42, 129.91, 129.12, 129.96, 130.11, 131.16, 132.20, 132.94, 134.12, 138.55 (C=N), 141.51, 142.23 (NH–C=N), 150.95 (C–NO_2). GC/MS: 348 (M^+). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.88; H, 5.81; N, 16.11.

5. *N*-Cyclohexyl-3-(4-chlorophenyl)-quinoxaline-2-amine (4c)

Mp 192 °C; IR (KBr) (ν_{max}, cm^{-1}): 3155, 1629, 1620; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 1.12–2.20 (m, 10H), 3.49 (m, 1H), 4.45 (s, 1H, NH), 7.42–8.46 (m, 8H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 23.34, 26.15 ($2CH_2$), 33.71 ($2CH_2$), 52.18, 127.32, 128.82, 128.55, 129.73, 130.15, 131.19, 132.67, 133.39, 134.51, 138.57 (C=N), 141.22, 142.67 (NH–C=N), 148.87, 150.99 (C–NO_2). GC/MS: 337 (M^+). Anal. Calcd for $C_{20}H_{20}N_3Cl$: C, 71.10; H, 5.97; N, 14.44. Found: C, 71.01; H, 5.81; N, 14.33.

6. *N*-Cyclohexyl-3-(4-methoxyphenyl)-quinoxaline-2-amine (4d)

Mp 179 °C; IR (KBr) (ν_{max}, cm^{-1}): 3168, 1642, 1638; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 1.20–2.29 (m, 10H), 2.68 (s, 3H), 3.44 (m, 1H), 4.51 (s, 1H, NH), 7.27–8.29 (m, 8H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 25.49, 26.31 ($2CH_2$), 32.97 ($2CH_2$), 33.67, 51.97, 123.37 (2CH), 127.64, 128.43 (2CH), 121.41, 130.07, 131.27, 134.46, 138.59 (C=N), 141.77, 142.21 (NH–C=N), 148.87, 150.97 (C–NO_2). GC/MS: 333 (M^+). Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.57; H, 7.02; N, 12.56.

7. *N*-Cyclohexyl-3-(4-nitrophenyl)-quinoxaline-2-amine (4e)

Mp 209 °C; IR (KBr) (ν_{max}, cm^{-1}): 3150, 1622, 1610; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 1.20–2.29 (m, 10H), 3.44 (m, 1H), 4.38 (s, 1H, NH), 7.49–8.33 (m, 8H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 25.43, 26.48 ($2CH_2$), 33.21 ($2CH_2$), 52.68, 127.71 (2CH), 128.78, 129.36 (2CH), 121.27, 130.08, 131.33, 134.42, 138.57 (C=N), 141.91, 142.28 (NH–C=N), 148.92, 150.86 (C–NO_2). GC/MS: 348 (M^+). Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.86; H, 5.77; N, 16.02.

8. *N*-Cyclohexyl-3-(4-hydroxyphenyl)-quinoxaline-2-amine (4f)

Mp 176 °C; IR (KBr) (ν_{max}, cm^{-1}): 3143, 1642, 1638; ^1H NMR $CDCl_3$, 300 MHz) δ_H (ppm): 1.18–2.19 (m, 10H), 3.24 (m, 1H), 4.32 (s, 1H, NH), 4.86 (s, 1H, OH), 7.41–8.62 (m, 8H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 24.44, 25.97 ($2CH_2$), 33.07 ($2CH_2$), 52.43, 126.94 (2CH), 128.31, 129.17 (2CH), 121.27, 130.91, 131.32, 133.31, 137.79 (C=N), 139.91, 143.01 (NH–C=N), 148.8, 150.9 (C–NO_2). GC/MS: 319 (M^+). Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.09; H, 6.55; N, 13.24.

9. *N*-Cyclohexyl-3-(4-methylphenyl)-quinoxaline-2-amine (4g)

Mp 201 °C; IR (KBr) (ν_{max}, cm^{-1}): 3163, 1638, 1622; ^1H NMR ($CDCl_3$, 300 MHz) δ_H (ppm): 1.17–2.39 (m, 10H), 2.59 (s, 3H), 3.34 (m, 1H), 4.37 (s, 1H, NH), 7.22–8.27 (m, 8H, arom). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C (ppm): 24.13, 25.57 ($2CH_2$), 30.17 ($2CH_2$), 39.84, 52.51, 126.67 (2CH), 128.51, 128.47 (2CH), 129.97, 130.74, 131.27, 134.17, 138.56 (C=N), 141.97, 141.09 (NH–C=N), 142.97, 150.93 (C–NO_2). GC/MS: 317 (M^+). Anal. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.14; H, 7.25; N, 13.08.

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