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One-pot Three-Component Synthesis of Dihydroquinoxalin-2-amines Containing a Ferrocene unit with the Potential of Biological and Pharmacological Activities

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Abstract

A three-component reaction between 1,2-phenylenediamine, ferrocenecarbaldehyde, and isocyanides in the presence of a catalytic amount of *p*-toluenesulfonic acid for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives containing a ferrocene unit is reported. This approach is an effective procedure because the products have a broad spectrum of biological and pharmacological activities such as insecticide, fungicide, herbicide, anthelmintic, antibacterial, antimycobacterial, antiprotozoal, anticancer and antibiotic properties.

***Keywords*:** Multicomponent reaction, Ferrocene carbaldehyde, Quinoxaline, *p*-Toluenesulfonic acid.

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Introduction

Multicomponent reactions (MCRs), especially isocyanide-based MCRs (IMCRs), are used broadly in medicinal chemistry for the synthesis of organic and heterocyclic compounds[1-3].Heterocyclic chemistry is one of the most principal branches in organic chemistry [4].Heterocyclic compounds are the cyclic organic compounds which contain at least one heteroatom, the most common heteroatoms are the nitrogen, oxygen and sulfur. Heterocycles are the main group of organic compounds that are present in a great variety of drugs, many natural products, most vitamins, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, anti-HIV, antimicrobial, antibacterial, antiviral, antidiabetic, herbicidal, and insecticidal agents [5, 6].

Quinoxaline is one of the heterocyclic compounds containing nitrogen atom which shows a wide-ranging of biological and pharmacological activities such as fungicide and herbicide [7], antibacterial [8], antimycobacterial [9-11], antileishmanial [12], antimalarial [13, 14], antidepressant [15], antiprotozoal [16], anticancer [17], antitubercular [18], and antibiotic properties [19]. Several methods have been reported in the literature for the synthesis of quinoxaline derivatives. These methods are multistep in nature [20]. In recent years, Shaabani et al. reported novel routes for the synthesis of quinoxaline and benzodiazepine derivatives using isocyanide-based multicomponent reactions in the present amount of *p*-toluenesulfonic acid [21]. Taking into account the above-mentioned reports and in connection with our interest in the synthesis of heterocycles [22-27], in this research, we report the synthesis of some new quinoxaline derivatives containing a ferrocene unit.

Experimental

The starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. The melting points were measured with an Electrothermal 9100 apparatus and were uncorrected. The IR spectra were recorded on a Jasco FT-IR 6300 spectrometer. The ^{1}H-NMR and ^{13}C-NMR spectra were measured ($CDCl_3$ or DMSO solution) with a Bruker DRX-400 Avance spectrometer at 400.2 and 100.6 MHz, respectively. Mass spectra were recorded with an Agilent Technologies 5975C mass spectrometer. The elemental analyses were realized using a Heraeus CHN-O-rapid analyzer.

General procedure for the synthesis of dihydroquinoxalin-2-amines

To a solution of 1,2-phenylenediamine (**1**, 1 mmol), ferrocenecarbaldehyde (**2**, 1 mmol), and isocyanide (**3**, 1 mmol) in 3 mL of ethanol was added *p*-TsOH. H_2O (5 mol%). The resulting

mixture was stirred at room temperature for 3-5 hours. After completion of the reaction, as indicated by TLC, the product was precipitated by addition of 10 mL of water. The precipitate was filtered off and washed with 5% sodium hydroxide solution and then with water. The residue was purified by preparative layer chromatography (silica gel; petroleum ether–ethyl acetate (7:3)) to obtain products 4a–e. The characterization data of the products are given below:

N-cyclohexyl-3-ferrocenyl-3,4-dihydroquinoxalin-2-amine **(4a)**

Yellow solid; Yield: 95%; Anal. Calcd for $C_{24}H_{27}FeN_3$ (413.34): C, 69.74; H, 6.58; N, 10.17%. Found: C, 69.65; H, 6.64; N, 10.11; IR (KBr) (υ_{max}, cm^{-1}): 3420 (NH), 2928, 1566, 1418, 1274, 1108, 821; ^{1}H NMR ($CDCl_3$, 400.2 MHz): δ_H 1.32-1.93 (10 H, m, $5CH_2$ of cyclohexyl), 3.41- 3.79 (1H, m, CH of cyclohexyl), 4.30 (5H, s, C_5H_5), 4.56 - 4.99 (4H, m, C_5H_4), 5.38 (1H, br s, CH-Fc), 5.94 (1H, d, $^3J_{HH}$= 5.6 Hz, NH), 6.35 (1H, d, $^3J_{HH}$= 7.6 Hz, NH- Cyclohexyl), 7.32-7.85 (4H, m, arom CH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ_C 25.26 , 26.10 and 32.98 (CH_2 of cyclohexyl), 49.53 (CH of cyclohexyl), 50.34 (CH-Fc), 67.34, 68.12, 69.49, 70.55, 71.72 and 73.04 (Ferrocenyl carbons), 121.75, 122.95, 123.89, 125.84, 128.22 and 128.70 (aromatic carbons), 153.29 (C=N); MS (EI): *m/z* 413 (M^+, 0.35), 411 (1.43), 302 (100), 237 (31.16),181 (13), 154 (11), 121 (24.38), 83 (8.10).

N-tert-butyl-3-ferrocenyl-3,4-dihydroquinoxalin-2-amine **(4b)**

Yellow solid; Yield; 87%; Anal. Calcd for $C_{22}H_{25}FeN_3$ (387.30): C, 68.23; H, 6.51; N, 10.85%. Found: C, 68.31; H, 6.46; N, 10.78; IR (KBr) (υ_{max}, cm^{-1}): 3432 (NH), 2925, 1572, 1421, 1268, 1106, 820; ^{1}H NMR ($CDCl_3$, 400.2 MHz):δ_H 1.46 (9H, s, $C(CH_3)_3$), 4.19 (5H, s, C_5H_5), 4.49-5.12 (5H, m, C_5H_4 and CH-Fc), 5.94 (1H, d, , $^3J_{HH}$=5.6 Hz, NH), 7.41-7.70 (4H, m, arom CH), 8.06 (1H, s, NH);^{13}C NMR ($CDCl_3$, 100.6 MHz):δ_C 29.73 ($C(CH_3)_3$), 49.40 ($C(CH_3)_3$), 51.22 (CH-Fc), 66.04, 67.26, 68.54, 68.83, 68.80, and 70.23 (Ferrocenyl Carbons). 121.70, 122.84, 123.89, 125.66, 128.62 and 128.65 (aromatic carbons), 155.09 (C=N).

N-benzyl-3-ferrocenyl-3,4-dihydroquinoxalin-2-amine **(4c)**

Yellow solid; Yield; 89%; Anal. Calcd for $C_{25}H_{23}FeN_3$ (421.32): C, 71.27; H, 5.50; N, 9.97%. Found: C, 71.35; H, 5.45; N, 9.90;IR (KBr) (υ_{max}, cm^{-1}): 3434 (NH), 2924, 1567, 1419, 1275, 1107, 821;^{1}H NMR (DMSO, 400.2 MHz): δ_H 4.12 (5H, s, C_5H_5), 4.27-5.06 (7H, m, C_5H_4 and CH-Fc and CH_2 of benzyl), 7.16-7.35 (10H, m, arom CH and 1NH), 8.12 (1H br s, NH); ^{13}C NMR (DMSO, 100.6 MHz): δ_C51.49 (CH-Fc), 59.51 (CH_2 of benzyl), 67.78, 69.09, 69.17, 69.84, 70.19 and 74.80

(Ferrocenyl Carbons), 111.09, 118.48, 119,16, 120.02, 121.66, 121.84, 125.81, 126.95, 128.69, and 129.39 (aromatic carbons), 153.42 (C=N).

3-ferrocenyl-N-[(4-methylbenzene-1-sulfonyl)methyl]-3,4-dihydroquinoxalin-2-amine **(4d)**

Yellow solid; Yield; 90%; Anal. Calcd for $C_{26}H_{25}FeN_3$ (499.41): C, 62.53; H, 5.05; N, 8.41%. Found: C, 62.47; H, 5.08; N, 8.36; IR (KBr) (υ_{max}, cm^{-1}): 3426 (NH), 2925, 1567, 1418, 1275, 1107, 821;^{1}H NMR (DMSO, 400.2 MHz): δ_H 2.42 (3H, s, CH_3), 4.11 (5H, s, C_5H_5), 4.45-4.53 (2H, m, C_5H_4), 4.74 (2H, d, $^3J_{HH}$= 6.8 Hz, CH_2), 4.79 (1H, d, $^3J_{HH}$= 6.8 Hz CH-Fc), 5.04-5.09 (2H, m, C_5H_4), 7.14-7.82 (8H, m, arom CH), 8.00 (1H, s, NH), 9.08 (1H, br t, N*H*-CH_2); ^{13}C NMR (DMSO, 100.6 MHz): δ_C21.60 (CH_3), 51.04 (CH-Fc), 58.98 (CH_2), 63.11, 67.78, 69.17, 69.84, 70.19, and 74.78 (Ferrocenyl Carbons), 121.78, 125.98, 129.00, 129.16, 130.29, 130.48, 134.18, 134.88, 145.18 and 145.30 (aromatic carbons), 153.42 (C=N).

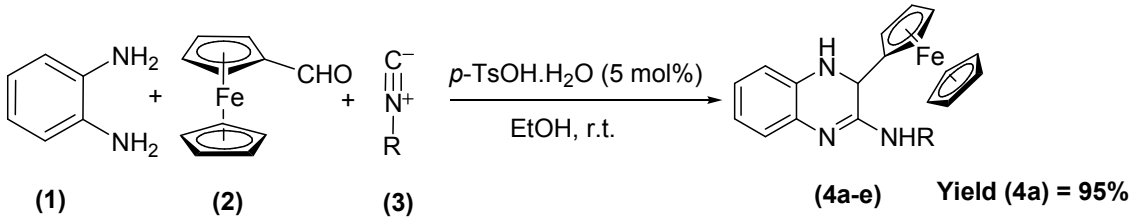
3-ferrocenyl-N-(2,4,4-trimethyl pentan-2-yl)-3,4-dihydroquinoxalin-2-amine **(4e)**

Brown solid; Yield; 92%; Anal. Calcd for $C_{26}H_{33}FeN_3$ (443.41): C, 70.43; H, 7.50; N, 9.48%. Found: C, 70.47; H, 7.44; N, 9.53; IR (KBr) (υ_{max}, cm^{-1}): 3407 (NH), 2926, 1567, 1418, 1261, 1106, 819; ^{1}H NMR (DMSO, 400.2 MHz):δ_H 1.10 (9H, s, $C(CH_3)_3$), 1.46 (6H, s, $C(CH_3)_2$), 1.54 (2H, s, CH_2), 4.17 (5H, s, C_5H_5), 4.22- 4.44 (4H, m, C_5H_4), 5.03 (1H, s, CH-Fc), 6.46 (1H, s, NH), 7.02-7.57 (5H, m, arom CH and 1NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz):δ_C 29.73 (2 CH_3), 30.98 ($C(CH_3)_3$), 31.25 ($C(CH_3)_3$, 49.80 (CH-Fc), 51.98 (CH_2), 67.80, 69.17, 69.37, 69.85, 70.18, and 74.82 (Ferrocenyl Carbons), 118.41, 121.75, 125.98, 128.55, 132.68 and 133.83 (aromatic carbons), 153.45 (C=N).

Results and discussion

The three-component reaction between 1,2-phenylenediamine **(1)**, ferrocenecarbaldehyde **(2)**, and isocyanides **(3)** proceeds very smoothly and cleanly in the presence of a catalytic amount of *p*-toluenesulfonic acid in ethanol at room temperature, and affords the corresponding 3,4-dihydroquinoxalin-2-amine derivatives (**4a-e**) in high yields (Scheme 1 and Table 1), and no undesirable side reactions were observed. A mechanistic rationalization for this reaction is provided in Scheme 2. The structures of the products were deduced from their IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra, and elemental analysis. For example the ^{1}H-NMR spectrum of **4a** exhibited distinct signals arising from five CH_2 and one CH of cyclohexyl group (1.32-1.93 ppm and 3.41- 3.79 ppm, 2m), five CH of C_5H_5 (4.30 ppm, s), four CH of C_5H_4 (4.56 - 4.99 ppm, m), aliphatic CH (5.38 ppm, br s), NH (5.94 ppm, d, $^3J_{HH}$= 5.6 Hz), NH- Cyclohexyl (6.35 ppm, d, $^3J_{HH}$= 7.6 Hz), and

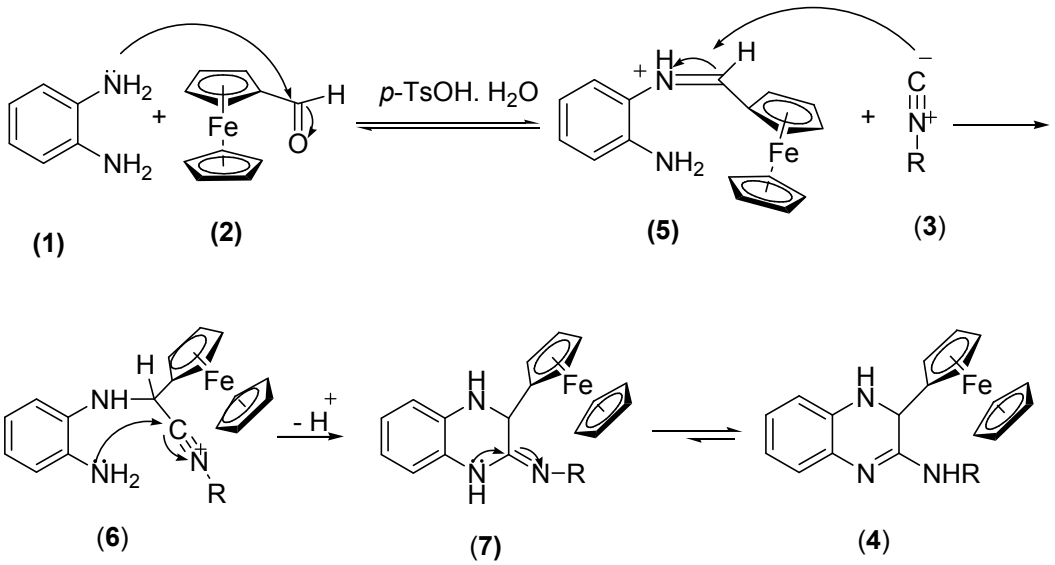
aromatic CH (7.32-7.85 ppm, m). The ^{13}C NMR spectrum of 5a shows 18 distinct resonances arising from CH_2 of cyclohexyl group (25.26 , 26.10 and 32.98 ppm), CH of cyclohexyl group (49.53 ppm), aliphatic CH (50.34 ppm), carbons of ferrocene moiety (67.34, 68.12, 69.49, 70.55, 71.72 and 73.04 ppm), aromatic carbons (121.75, 122.95, 123.89, 125.84, 128.22 and 128.70 ppm) and C=N carbon (153.29). The mass spectrum of 4a displays a molecular ion peak at m/z 413.



Scheme 1. Three-component reaction of 1,2-phenylenediamine, ferrocenecarbaldehyde, and isocyanides (See Table).

Table 1. Synthesis of 3,4-dihydroquinoxalin-2-amine derivatives **(4a-e).**

Entry	Compounds	Yield%	R
1	4a1	95	cyclohexyl
24b2		87	*t*-Bu
3	4c	89	benzyl
4	4d	90	tosylmethyl
5	4e	92	1,1,3,3-tetramethylbutyl



Scheme 2. A proposed mechanism for the formulation of 3,4-dihydroquinoxalin-2-amine derivatives.

Conclusion

In the present work, the three-component reaction between 1,2-phenylenediamine, ferrocenecarbaldehyde, and isocyanides in the presence of a catalytic amount of *p*-toluenesulfonic acid to produce 3,4-dihydroquinoxalin-2-amine derivatives containing a ferrocene unit was reported. The reported method offers a mild and efficient procedure for the preparation of these compounds.

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