

DEVELOPMENT OF GREENER APPROACH: MICROWAVE ASSISTED SYNTHESIS OF QUINOXALINE DERIVATIVES IN WATER

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Abstract

A green protocol for the synthesis of quinoxaline derivatives by condensation reaction of isatin derivatives with *o*-phenylenediamine in water under microwave irradiation has been reported. The presented method is mild, environmentally friendly, inexpensive and highly effective to give the products in good to excellent yields. The structure of respective synthesized compounds were established by their spectral data.

Keywords: Isatin derivatives, Quinoxaline derivatives, *o*-Phenylenediamine, Microwave irradiation.

Introduction

The discovery of novel synthetic methodologies to facilitate the preparation of the compound libraries is a pivotal focal point of research activity in the field of modern medicinal and combinatorial chemistry.¹ Our approach to address this challenge involves the development of microwave assisted reaction for the quick synthesis of compounds. Microwave-induced organic reaction enhancements (MORE) chemistry can also be expressed e-chemistry due to its effective, economical nature, easy to handle and it is a step toward green synthesis.²

Water plays an essential role in life processes, however its use as a solvent has been limited in organic synthesis. Despite the fact that it is the cheapest, safest and most non toxic solvent in the world, its presence is generally avoided through the dehydrative drying of substrates and solvents. The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists.³

Quinoxaline is versatile nitrogen containing heterocyclic⁴ moiety and has been considered as a wonder nucleus that posses a variety of biological activities, specifically as AMPA/GlyN receptor⁵⁻⁶ antagonists, angiotensin II receptoantagonists,^{7,8} anti-cancer,⁹ anti-infection and immunomodulating activities.

Its core structure was found in several naturally occurring compounds such as flavor-enzymes, riboflavin, molybdopterines and antibiotics of streptomyces. The diversity in the biological response of quinoxaline derivatives has gained more attention of many scientists and researchers to explore this skeleton to its multiple potential against several diseases and pathological conditions.¹⁰

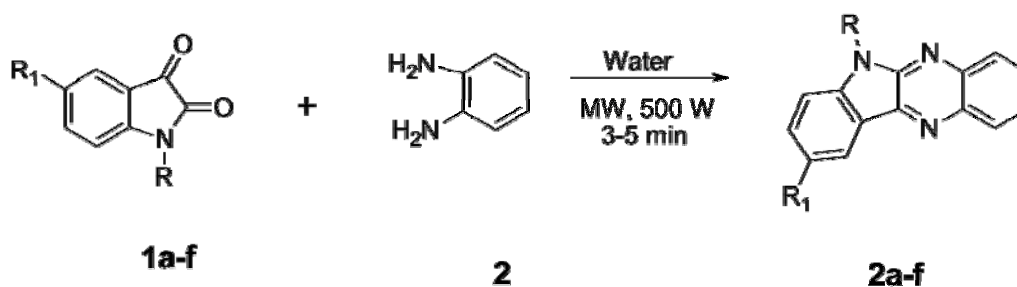
Keeping these points in view, we have developed a clean and green protocol for the synthesis of quinoxaline derivatives by the condensation reaction of *N*-substituted isatins with 1,2- diaminobenzene in water under microwave irradiation.

Results and discussion

In view of biological significance of isatin moieties and in our continued interest in growth of green chemistry,¹¹ it was planned to condense isatin moiety with *o*-phenylenediamine via two step process.

In first step, we have synthesized *N*- substitutedisatin derivatives **1a-f** by earlier reported procedures. These are then directly used for the synthesis of quinoxaline derivatives.

The quinoxaline derivatives (**2a-f**) were synthesized by the condensation reaction of isatin derivatives **1a-f** with 1, 2- diaminobenzene **2** in water under microwave irradiation(**Scheme 1**& **Table 1**).



Scheme 1

Table 1: Reaction of isatin derivatives with 1, 2- diaminobenzene^a

Entry	R ₁	R	%Yield	M.P.(^o C)
2a	Cl	COCH ₃	69	318
2b	H	CH ₂ CH ₂ CH ₃	80	218
2c	Cl	CH ₂ CH ₂ CH ₃	78	244
2d	H	CH ₂ Ph	77	176
2e	Cl	CH ₂ Ph	80	206
2f	H	COCH ₃	79	266

^aReaction condition: Isatin derivatives **1a-f**, *o*-phenylenediamine **2** (1:1) in 25 ml water were microwave irradiated at 5000 W to produce products.

Actually, microwave irradiation facilitates the polarization of the molecules under irradiation causing rapid reaction to occur. The impact of microwave irradiation and conventional heating for the synthesis of compound **2a-f** has been compared (**Table2**).

Table 2 : Comparison of microwave irradiation and conventional heating methods for the synthesis of compound **2a-f**

Entry	Conventional method		Microwave irradiation	
	Time (min)	%Yield	Time (min)	%Yield
2a	45	48	5	69
2b	45	62	3	80
2c	50	59	3	78
2d	50	64	3	77
2e	35	44	3	80
2f	40	50	5	79

The structures of isolated products were fully characterized by elemental analysis, IR and ¹H-NMR spectroscopy.

Conclusion

In conclusion we have discovered a novel synthetic route for the synthesis of quinoxaline derivatives. The proposed methodology strictly met with the requirements of green chemistry with several other advantages such as facile reaction conditions, the product can be isolated very easily without the use of column chromatography, high yield of products without use of any catalyst in short reaction time.

Experimental

General

All chemicals were procured from Aldrich, USA and E. Merck, Germany and used without further purification. TLC was carried out on SiO₂ gel (HF254, 200 mesh). The solvent system employed was ethyl acetate: n-hexane (11: 9) and the spots were identified by placing the plate in Iodine chamber. IR spectra were recorded on a PerkinElmer FT/IR version 10.03.05 spectrometer. NMR spectra were run on a JEOL AL300 FTNMR spectrometer; chemical shifts are given in δ ppm, relative to TMS as internal standard. Elemental microanalysis was performed on Exeter Analytical Inc Model CE-440 CHN Analyzer. Melting points were measured in open capillaries and are uncorrected. The microwave assisted reactions were carried out in a "MAS-II, Microwave Synthesis System" manufactured by Sineo microwave chemistry technology co. Ltd, having an output energy range of 0 to 1000 watts, based on temperature of reaction and individual sensor for temperature control with attachment

of reflux condenser with both magnetic and mechanical stirring device (thus avoiding the risk of high pressure development) and synthesis on preparative scales.

General procedure for synthesis of quinoxaline derivatives 2a-f

Equimolar quantity of *N*-substituted isatin **1a-f** (0.001 mol) and 1, 2-diaminobenzene **2** (0.001 mol) in H₂O (25 ml) was irradiated in microwave synthesizer at power (5000W) for 5-8 min and refrigerated for few hours and then filtered, dried and recrystallized in ethanol.

Characterization data for synthesized compounds 2a-f

1-(9-Chloro-6*H*-indolo[2,3-*b*]quinoxalin-6-yl)ethanone (2a)

Brownsolid, IR (KBr) ν : 3363, 3241, 3183, 3041, 2973, 2939, 2868, 1669, 1636, 1615, 1533, 1480, 1369, 1270, 1147, 1032, 954, 880, 752, 732, 666 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ : 1.91 (s, 3H), 7.29- 8.83 (m, 7H, aromatic protons) ppm. ¹³C NMR (75.45 MHz, DMSO) δ : 23.7, 115.1, 122.9, 123.1, 127.7, 128.5, 129.5, 130.2, 130.7, 131.9, 132.3, 136.8, 145.3, 154.4, 156.8, 167.9 ppm. Anal.Calcd for: C₁₆H₁₀ClN₃O: C, 64.98; H, 3.41; Cl, 11.99; N, 14.21; O, 5.41 Found: C, 65.00; H, 3.40; Cl, 11.00; N, 14.20; O, 5.42.

6-Propyl-6*H*-indolo[2,3-*b*]quinoxaline (2b)

Dark yellowsolid, IR (KBr) ν : 3173, 3120, 3059, 3037, 3009, 2885, 2972, 2873, 16100, 1600, 1569, 1473, 1356, 1264, 1156, 1019, 947, 863, 759, 746, 641, 1009 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ : 1.05-1.10 (t, *J*= 7.2, 3H), 1.70-1.81 (m, 2H), 3.18-3.23 (t, *J*=6.9, 2H), 6.68- 8.52 (m, 8H, aromatic protons), ppm. ¹³C NMR (75.45 MHz, DMSO) δ : 11.7, 22.3, 45.0, 111.2, 114.5, 115.0, 123.4, 127.5, 129.2, 131.1, 131.5, 131.6, 131.8, 148.7, 155.3, 155.8 ppm. Anal.Calcdfor : C₁₇H₁₅N₃: C, 78.13; H, 5.79; N, 16.08 Found: C, 78.11; H, 5.79; N, 16.10.

9-Chloro-6-propyl-6*H*-indolo[2,3-*b*]quinoxaline (2c)

Reddish yellowsolid, IR (KBr) ν : 3184, 3120, 3059, 3037, 2882, 2980, 2873, 16100, 1600, 1567, 1469, 1352, 1284, 1144, 1002, 947, 860, 759, 746, 651, 522 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ : 1.05-1.10 (t, *J*= 6.9, 3H), 1.70-1.81 (m, 2H), 3.19-3.23 (t, *J*=6.9, 2H), 6.75- 8.60 (m, 7H, aromatic protons), ppm. ¹³C NMR (75.45 MHz, DMSO) δ : 11.5, 21.9, 45.1, 112.4, 114.9, 117.0, 123.2, 127.3, 129.4, 131.0, 131.2, 134.6, 148.6, 153.8, 155.1 ppm. Anal.Calcd for C₁₇H₁₄ClN₃: C, 69.03; H, 4.77; Cl, 11.99; N, 14.21 Found: C, 69.00; H, 4.78; Cl, 11.98; N, 14.24

6-Benzyl-6*H*-indolo[2,3-*b*]quinoxaline (2d)

Yellowsolid, IR (KBr) ν : 3286, 3171, 3090, 2996, 2886, 2839, 1648, 1612, 1567, 1482, 1357, 1268, 1175, 1026, 942, 802, 753, 743, 647, 581 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ : 5.71 (s, 2H), 7.24- 8.100 (m, 13H, aromatic protons) ppm. ¹³C NMR (75.45 MHz, DMSO) δ : 44.9, 110.1, 119.6, 121.1, 122.7, 126.1, 127.1, 127.6, 127.8, 128.7,

129.3, 130.9, 136.4, 139.5, 140.0, 140.6, 144.2, 145.8 ppm. Anal. Calcd for: C₂₁H₁₅N₃: C, 81.53; H, 4.89; N, 13.58 Found: C, 81.55; H, 4.86; N, 13.59.

6-Benzyl-9-chloro-6H-indolo[2,3-b]quinoxaline (2e)

Light yellow solid, IR (KBr) ν : 3300, 3184, 3100, 2976, 2890, 2839, 16100, 1614, 1567, 1478, 1363, 1281, 1167, 1016, 9100, 823, 753, 745, 643, 581 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ : 5.67 (s, 2H), 7.22- 8.42 (m, 12H, aromatic protons) ppm. ¹³C NMR (75.45 MHz, DMSO) δ : 45.0, 111.1, 120.7, 122.3, 122.4, 126.4, 126.8, 127.1, 127.8, 127.9, 128.8, 129.2, 130.7, 136.0, 138.8, 139.6, 140.8, 142.2, 145.8 ppm. Anal. Calcd for: C₂₁H₁₄ClN₃: C, 73.36; H, 4.10; Cl, 10.31; N, 12.22 Found: C, 73.36; H, 4.11; Cl, 10.30; N, 12.22.

1-(6H-indolo[2,3-b]quinoxalin-6-yl)ethanone (2f)

Light yellow solid, IR (KBr) ν : 3240, 3112, 3030, 2994, 2985, 2952, 2830, 1670, 1645, 1614, 1543, 1452, 1370, 1272, 1153, 1009, 899, 828, 748, 6100 cm⁻¹. ¹H NMR (300 MHz, DMSO) δ : 1.90 (s, 3H), 7.28- 8.82 (m, 8H, aromatic protons) ppm. ¹³C NMR (75.45 MHz, DMSO) δ : 23.7, 115.1, 122.9, 123.1, 127.7, 128.5, 129.5, 130.2, 130.7, 132.0, 132.3, 136.8, 146.1, 154.4, 156.8, 167.9 ppm. Anal. Calcd for: C₁₆H₁₁N₃O: C, 73.55; H, 4.24; N, 16.08; O, 6.12 Found: C, 73.52; H, 4.24; N, 16.08; O, 6.15.

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