JOURNAL OF HETEROCYCLIC CHEMISTRY

Overview

Aims and Scope

Overview. A heterocyclic compound is defined as any organic compound where their molecules are characterized by rings containing at least one atom other than carbon. These compounds are structurally similar to cyclic organic hydrocarbons, but their properties can vary widely from those of their hydrocarbon counterparts and are largely governed by the identity, location and number of heteroatoms present in the molecule. It is this rich diversity of physical and biological properties that has lead to intense study of heterocyclic compounds. It follows then that Heterocyclic Chemistry is the study of all aspects of heterocyclic compounds.

Heterocyclic chemistry has its origin in organic synthesis, natural products chemistry and medicinal chemistry. Indeed most any heterocyclic chemist will also consider themselves organic chemists and many will consider themselves to be natural products chemists and medicinal chemists as well. This relationship between disciplines arises because heterocyclic molecules are fundamental building blocks of biological systems. In addition to its importance to biology, heterocyclic chemistry has seen intense study in diverse areas such as dyes, photosensitizers, coordination compounds, polymeric materials and many other fields.

Policies. The *Journal of Heterocyclic Chemistry* is interested in publishing research on all aspects of Heterocyclic Chemistry. A perusal of any issue will show that the majority of manuscripts submitted are on the synthesis and properties of heterocyclic compounds. Many of those studies include a short history of the biological and commercial applications of related compounds, and often include biological screening data corresponding to newly reported compounds. This strong connection between the preparation of heterocyclic compounds and their potential benefit to humanity is both welcomed and encouraged. One will also find articles related to physical organic chemistry studies on heterocyclic compounds, mechanistic studies of reactions leading to heterocyclic compounds and studies of the photophysical properties of heterocyclic compounds, just to name a few.

Reviews, and **Communications**.

Articles must report the results of comprehensive research and will usually amount to more than four final printed journal pages. Shorter papers, usually classified as notes, are acceptable. Complete spectral characterization of all new compounds reported, is required for publication in the *Journal of Heterocyclic Chemistry*. All new compounds must be subjected to combustion analysis for at least two elements (typically C and H) and values within ± 0.4 must be obtained.

Notes are simply smaller articles that are concise reports of completed projects. The requirements for

Communications to the Editor may be of any length but should report new, important and timely research for which rapid publication is warranted. We require that communications include procedures, compound preparation data and related data in sufficient detail that an experienced chemist can duplicate the work. Elemental analysis and spectral data supporting all new compounds are a requirement for publication and must be included as part of the submitted manuscript.

Reviews may be exhaustive or may be short indicating only the highlights of a given area. It is wise to communicate with the editor in advance of preparation and/or submission to determine the timeliness of any given review.

Authors bear the *sole responsibility* for the contents of manuscripts and the accuracy of the data therein.

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An Efficient and Expeditious Microwave-assisted Synthesis of Quinoxaline Derivatives *via* Nucleophilic Heteroaromatic Substitution

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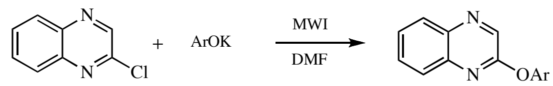

2a, Ar = 4-FC_6H_4; **2b**, 2,3-$F_2C_6H_3$; **2c**, Ar = 2,6-$F_2C_6H_3$; **2d**, Ar = 3-ClC_6H_4; **2e**, 2-BrC_6H_4**;** **2f**, Ar = 2-IC_6H_4; **2g**, Ar = 3-IC_6H_4; **2h**, Ar = 4-NCC_6H_4

A series of 2-substituted quinoxaline derivatives including five novel compounds have been successfully synthesized from 2-chloroquinoxaline using microwave methodology. The yields of the quinoxalines synthesized through this method, were an improvement over the thermal methods usually employed.

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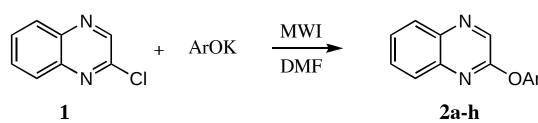
INTRODUCTION

Quinoxaline derivatives are important classes of nitrogen-containing heterocycles, as they constitute useful intermediates in organic synthesis [1-3]. In the context of our general interest on the effect of colloidal systems on nucleophilic heteroaromatic substitution reactions on quinoxaline derivatives [4,5] and as a continuation of our previous work [6,7] on the synthesis of some new quinoxaline derivatives, herein we wish to report an efficient and straightforward procedure for the synthesis of several 2-substituted quinoxaline derivatives **2a-h** applying microwave methodology. Recently, microwave irradiation (MWI) using domestic ovens has emerged as an important synthetic tool to accelerate organic reactions; the high heating efficiency gives remarkable rate enhancement and significant reduction in reaction time [8,9]. Quinoxalines derivatives are increasingly used in the pharmaceutical industry due to their wide spectrum of biological activities which comprise anticancer, antiviral, antimalarial and antibacterial properties [10]. The aim of this work is to demonstrate the advantage obtained by the use of microwave irradiation over thermal methods in the one-pot synthesis of quinoxaline derivatives **2a-h**.

RESULTS AND DISCUSSION

2-Chloroquinoxaline **1** reacts with the appropriate phenoxide ion to afford products **2a-h** under microwave or thermal treatment (Scheme 1). 2-Chloroquinoxaline **1** undergoes nucleophilic heteroaromatic substitution due to the aza activation of the heteroaromatic ring. Reaction conditions and yields are summarised in Table 1.

Scheme 1



2a, Ar = 4-FC_6H_4; **2b**, 2,3-$F_2C_6H_3$; **2c**, Ar = 2,6-$F_2C_6H_3$; **2d**, Ar = 3-ClC_6H_4; **2e**, 2-BrC_6H_4**;** **2f**, Ar = 2-IC_6H_4; **2g**, Ar = 3-IC_6H_4; **2h**, Ar = 4-NCC_6H_4

We took the advantage of microwave-assistance in nucleophilic heteroaromatic substitution reactions for the synthesis of compounds **2a-h**. Under thermal heating nucleophilic heteroaromatic substitution of 2-chloroquinoxaline **1** requires a catalyst (Ag^+) to assist low nucleophilicity of the electron-deficient phenoxide ions [6,7]. Results in Table 1 show very short reaction times and improved yields in microwave-assisted synthesis compared to traditional thermal heating. The methodology is a straightforward and economical procedure for the synthesis of quinoxalines derivatives **2a-h** in good yields (76-86 %) from common 2-chloroquinoxaline intermediate **1**. Our experimental results prove that MWI is extremely convenient for the preparation of such kind of heterocyclic compound. Preparation of compounds **2a-h** uses readily available starting material and simple experimental and work-up procedures. In the crude reaction mixtures no by-products were detected by chromatography. It has been previously reported [11] that when 2-chloroquinoxaline **1** is treated with a sodium aryloxide in an excess of phenol and its homologues, a mixture of the expected quinoxalinyl ether and the corresponding benzofuro[2,3-*b*]quinoxaline is obtained.

Table 1.

Thermal and Microwave Irradiation Conditions and Yield of Products.

Compounds	Ar	Time		Yield[a]	
		Δ, h	MWI, s	Δ, %	MWI, %
2a	4-FC_6H_4	4[b]	30	64	85
2b	2,3-$F_2C_6H_3$	2	30	63	78
2c	2,6-$F_2C_6H_3$	2	60	45	70
2d	3-ClC_6H_4	1.5	20	65	79
2e	2-BrC_6H_4	4[b]	30	68	76
2f	2-IC_6H_4	2	30	56	86
2g	3-IC_6H_4	2	30	57	84
2h	4-NCC_6H_4	5[b]	60	76	85

[a] Isolated yield. [b] Ref. 6.

However, no cyclised material was obtained in the synthesis procedure described here. New 2-substituted quinoxalines, **2b-d**, **2f**, **2g**, are stable compounds property which makes them useful substances in drug research. In all cases, any remaining starting material 2-chloroquinoxaline **1** could be easily removed by sublimation.

Five unknown quinoxaline derivatives **2b-d**, **2f** and **2g** were characterized on the basis of their elemental analysis, ms, ^{1}H nmr and ir spectral data. The synthesis of **2a**, **2e** and **2h** was earlier reported by us [6] under thermal conditions and are now prepared under MWI. All compounds were obtained in high purity as indicated by TLC and spectral analysis.

EXPERIMENTAL

2-Choroquinoxaline **1** was prepared according to the literature method by Castle and Onda [12]. Ir spectra were obtained on a Bruker, Tensor 27 instrument. ^{1}H rmn spectra were recorded at room temperature on a Jeol Eclipse + 400 NMR spectrometer. Mass spectra were determined on a Jeol JMS-AX505WA spectrometer. Melting points (mp) in °C are uncorrected.

General Procedure for the Synthesis of Quinoxaline Derivatives (2a-h) Under Thermal Conditions. A typical procedure is a follows: 2-chloroquinoxaline **1** (2-4 mmol) and a catalytic amount of $AgNO_3$ were added to a solution of equivalent amounts of KOH (2-4 mmol) and the corresponding phenol derivative in 8 mL of *N,N*-dimethylformamide (DMF). The resulting mixture was stirred under reflux condition for the appropriate time according to Table 1. The progress of the reaction was monitored by TLC, hexane-ethyl acetate (7:3). The reaction mixture was cooled to room temperature, filtered, and the solution poured onto cold water. The resulting solid was collected by filtration, washed with water, dried in vacuum and recrystallized from chloroform to yield the desired product.

General Procedure for the Synthesis of Quinoxaline Derivatives (2a-h) Under Microwave Irradiation. 2-Chloroquinoxaline **1** (2-3 mmol) was added to a mixture of equimolar amounts of KOH (2-3 mmol) and the corresponding phenol previously dissolved in DMF (2 mL). The mixture was placed into a pyrex-glass open vessel and irradiated intermittently at 20 s intervals at 700 W in a domestic microwave oven (2450 MHz) for the appropriate time according to Table 1. The reaction mixture was allowed to reach room temperature and poured onto crushed ice. The precipitate was collected by filtration, washed with water, dried under vacuum and recrystallized from chloroform to afford the desired products.

2-(2,3-Difluorophenoxy)quinoxaline (**2b**). This compound was obtained as a white solid, mp = 139-140 °C; ir (potassium bromide): 3047, 1576, 1306, 1265, 1211 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.15 (m, 3H, 2'-H, 3'-H, 4'-H), 7.69 (m, 2H, 6-H, 7-H), 7.73 (dd, 1H, 5-H, J= 1.8, 8.1 Hz), 8.08 (dd, 1H, 8-H, J = 1.8, 7.7 Hz), 8.77 (s, 1H, 3-H); ^{13}C nmr ($CDCl_3$) δ: 114.5, 119.0, 123.6, 127.0, 127.9, 129.1, 130.7, 138.3, 139.8, 140.0, 141.5, 143.5, 151.0, 155.9; ms: m/z = 258 (M^+), 239 (M^+-F), 230 (M^+-CH_2N), 129 (M^+- OC_6H_3 F_2), 102 (129-HCN). *Anal.* Calcd. for $C_{14}H_8N_2OF_2$: C, 67.70; H, 3.12; N, 10.85; F, 14.71. Found: C, 67.69 ; H, 3.16; N, 10.80; F, 14.68.

2-(2,6-Difluorophenoxy)quinoxaline (**2c**). This compound was obtained as a light brown solid, mp = 140-141 °C; ir (potassium bromide): 3060, 1577, 1501, 1213, 1014 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.04 (m, 2H, 3'-H, 5'-H), 7.21 (m, 1H, 4'-H), 7.62 (m, 2H, 6-H, 7-H), 7.70 (m, 1 H, 5-H), 8.07 (m, 1H, 8-H), 8.83 (s, 1H, 3-H); ^{13}C nmr ($CDCl_3$) δ: 112.2, 112.6, 126.2, 127.8, 129.1, 130.6, 138.1, 139.8, 140.1, 154.7, 155.4, 157.2; ms: m/z = 258 (M^+), 239 (M^+-F), 129 (M^+-$OC_6H_3F_2$), 102 (129-HCN), 76 (102-CN). Anal. Calcd. for $C_{14}H_8N_2OF_2$: C, 67.70; H, 3.12; N, 10.85; F, 14.71. Found: C, 67.73; H, 3.10; N, 10.81; F, 14.70.

2-(3-Chlorophenoxy)quinoxaline (**2d**). This compound was obtained as light yellow solid, mp = 74-75 °C.; ir (potassium bromide): 3070, 1588, 1498, 1135, 1072, 784; ^{1}H nmr ($CDCl_3$) δ: 7.19 (m, 1H, 5'-H), 7.26 (m, 1H, 4'-H), 7.35 (m, 2H, 2'-H, 6'-H), 7.64 (m, 2H, 6-H, 7-H), 7.77 (dd, 1H, 5-H, J = 0.7, 7.7), 8.06 (dd, 1H, 8-H, J = 1.4, 8.4 Hz), 8.69 (s, 1H, 3-H); ^{13}C nmr ($CDCl_3$) δ: 119.8, 122.1, 125.8, 127.8, 129.1, 130.4, 130.6, 134.9, 139.1, 139.9, 153.3, 156.5; ms: m/z = 256 (M^+); 228 (M^+-HCN); 129 (M^+-OC_6H_4Cl); 102 (129-HCN); 76 (102-CN). *Anal.* Calcd. for $C_{14}H_9N_2OCl$: C,65.51; H, 3.53; N, 10.91. Found: C, 65.52; H, 3.48; N, 10.94.

2-(2-Iodophenoxy)quinoxaline (**2f**). This compound was obtained as a brown solid, mp = 83-84 ºC; ir (potassium bromide): 3058, 1569, 1500, 1224, 1136, 594 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 7.05 (m, 1H, 6'-H), 7.28 (m, 1H, 4'-H), 7.45 (m, 1H, 5'-H), 7.64 (m, 2H, 6-H, 7-H), 7.73 (m, 1H, 3'-H), 7.91 (dd, 1H, 5-H, J = 1.5, 8.0 Hz), 8.07 (m, 1H, 8-H), 8.76 (s, 1H, 3-H); ^{13}C nmr ($CDCl_3$) δ: 90.7, 123.4, 127.4, 127.7, 127.9, 129.0, 129.6, 130.5, 139.2, 139.9, 140.0, 153.0, 156.3; ms: m/z = 348 [M^+], 221(M^+-I), 129 (M^+-OC_6H_4I), 102 (129-HCN), 76 (102-CN), 50 (76-C_2H_2). *Anal.* Calcd. for $C_{14}H_9N_2OI$: C, 48.30; H, 2.61; N, 8.05; I, 36.45. Found: C, 48.01; H, 2.68; N, 8.28; I, 36.02.

2-(3-Iodophenoxy)quinoxaline (**2g**). This compound was obtained as a yellow crystalline solid, mp = 74-75. ir (potassium bromide): 3050, 1569, 1498, 1212, 661 cm^{-1}; ^1H nmr ($CDCl_3$) δ:7.18 (t, 1H, 6-H, J = 8.0 Hz), 7.27 (m, 1H, 7-H), 7.64 (m, 4H, 2'-H, 4'-H, 5'-H, 6'-H), 7.78 (dd, 1H, 5-H, J = 1.4, 8.2 Hz), 8.06 (dd, 1H, 8-H, J= 1.4, 8.0), 8.69 (s, 1H, 3-H); ^{13}C nmr ($CDCl_3$) δ: 93.9, 121.1, 127.8, 129.1, 129.4, 130.7, 131.0, 134.6, 139.0, 139.9, 153.1, 156.5; ms: m/z = 348 (M^+), 320 (33, M^+-CH_2N), 221 (M^+-I), 129 (M^+-OC_6H_4I), 102 (129–HCN), 76 (M^+-C_2HN_2Cl), 50 (76-C_2H_2). *Anal*. Calcd. for $C_{14}H_9N_2OI$: C, 48.30; H, 2.61; N, 8.05; I, 36.45. Found: C, 48.01; H, 2.65; N, 8.26; I, 36.02.

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