Reaction of 2-[(2-Oxo-2-arylethyl)anilino]-1-aryl-1-ethanones with *o*-Phenylenediamine: Formation of Quinoxalines

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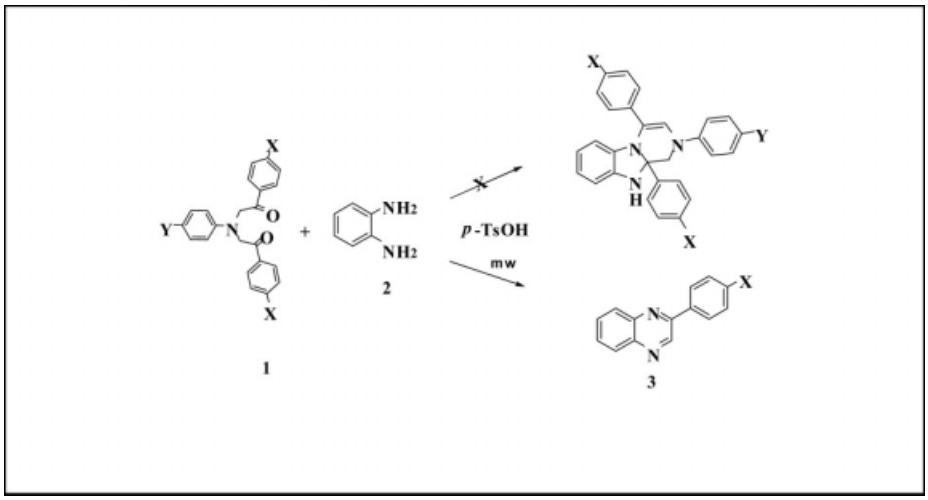
Received February 26, 2008
DOI 10.1002/jhet.73
Published online 13 April 2009 in Wiley InterScience (www.interscience.wiley.com).



Unexpected quinoxalines (**3**) have been obtained from a one-pot reaction of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanones (**1**) with *o*-phenylenediamine (**2**) in the presence of a catalytic amount of *p*-toluene sulfonic acid. The reaction presumably involves a tandem carbonyl addition—eliminative cyclization—air oxidation sequence.

J. Heterocyclic Chem., **46**, 332 (2009).

INTRODUCTION

Solvent-free approach using microwave irradiation opens numerous possibilities for conducting rapid heterocyclic synthesis *via* cyclocondensation reactions using a variety of supported reagents [1]. Generally, cyclocondensation reactions, where light polar molecules as water and alcohol are eliminated, constitute good candidates for microwaves. Furthermore, there are advantages of these solvent-free protocols with reduced reaction time and generally improved yields.

Nitrogen-containing heterocyclic compounds are indispensable structural units for both the chemist and the biochemist. In continuation of our work [2] on the chemistry of bis(aroylmethyl)anilines, which is relatively unexplored [3], herein, we report the condensation reaction of bis(aroylmethyl)anilines with 1,2-diaminobenzene. The reaction of diphenacyl aniline with 2-aminophenol and 2-aminothiophenol has led to diazine-fused benzheteroazole derivatives [4] (Fig. 1). In the same angle, the reaction of diphenacyl aniline with *o*-phenylenediamine is expected to give a related product. But unexpected quinoxaline is obtained as the major product in this reaction and the details are presented in this article.

RESULTS AND DISCUSSION

Hinsberg [5] reported that 2-bromoacetophenone gave directly 2-arylquinoxalines when reacted with *o*-phenylenediamine or *m*-tolylenediamine in boiling alcohol. He suggested that dihydroquinoxaline was an intermediate product which was readily oxidized by air to the corresponding quinoxaline. Buu-Hoi and Khoi [6] reported quantitative yields of 2-arylquinoxalines directly from the reaction of 2-bromo-3′-nitroacetophenone and 2-bromo-4′-nitroacetophenone with *o*-phenylenediamine in the presence of sodium acetate.

Quinoxalines constitute the basis of many insecticides, fungicides, herbicides, and anthelmintics, as well as being important in human health and as receptor antagonists [7]. There are numerous methods of preparing quinoxalines, but the double condensation of a 1,2-dicarbonyl compound and a 1,2-diaminoaromatic is commonly used [8]. This article describes the first report

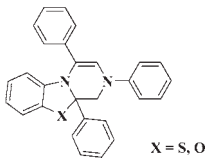
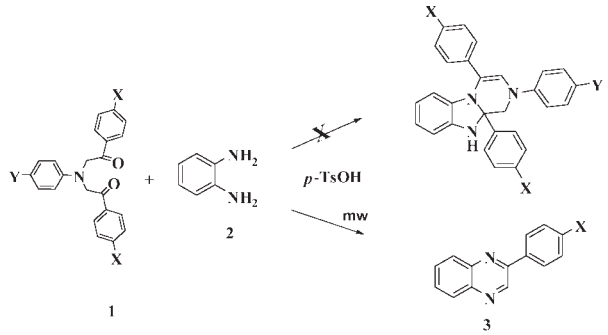


Figure 1. Benzheteroazoles.

of the formation of quinoxalines from 3-aza-1,5-diketones.

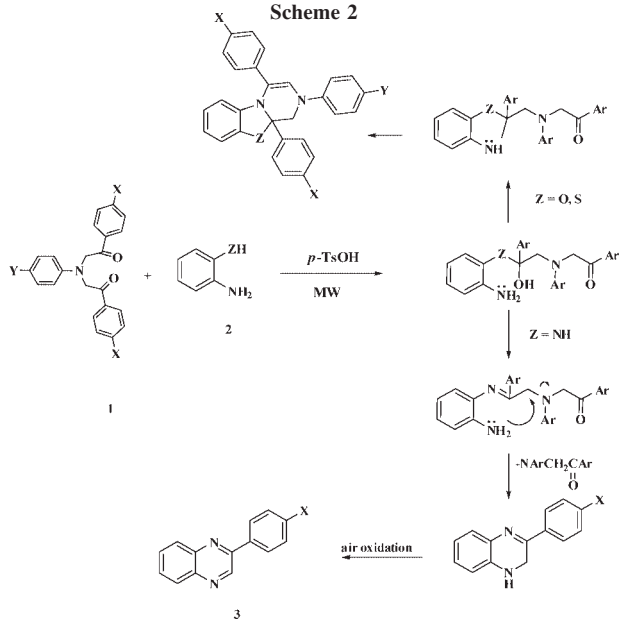
A mixture of *o*-phenylenediamine **2** with appropriately substituted diphenacyl aniline **1** was taken in a 1:1 molar ratio along with a catalytic amount of *p*-toluene sulfonic acid and ground well to ensure thorough mixing with no solvent. This mixture was placed in an open glass tube over a silica bath in a domestic microwave oven and irradiated for 10 min at 540 W. The major product **3** (Scheme 1) was isolated from the remaining mass of the reaction mixture by column chromatography and the product eluted first. Compound **3** was obtained in considerable yield and all the compounds were characterized by their NMR spectral data. The ^{1}H NMR spectrum of a representative compound, 2-(4-methylphenyl)quinoxaline (3, X = Me) showed the presence of one singlet at 2.38 ppm accounting for three hydrogen atoms. A two proton doublet is visible at 7.30 ppm (J = 8.4 Hz) and a six proton multiplet appears in the region 7.65–8.18 ppm. There is a singlet appearing downfield, 9.24 ppm. The ^{13}C NMR spectrum of this compound has signals at 20.4, 126.4, 128.0, 128.2, 128.5, 128.8, 129.2, 133.0, 139.5, 140.4, 141.3, 142.3, and 150.8 ppm. The data are very much consistence with 2-arylquinoxaline. Thus the major compound **3** formed in the reaction is unexpected 2-arylquinoxalines, which has been confirmed by comparing with an authentic sample of 2-phenylquinoxaline.

Scheme 1



Starting compound	X	Y	Percentage Yield of **3**
1a	H	H	68
1b	Cl	H	73
1c	Me	H	65
1d	Cl	Mc	70
1e	Mc	Mc	75
1f	Me	OMe	70

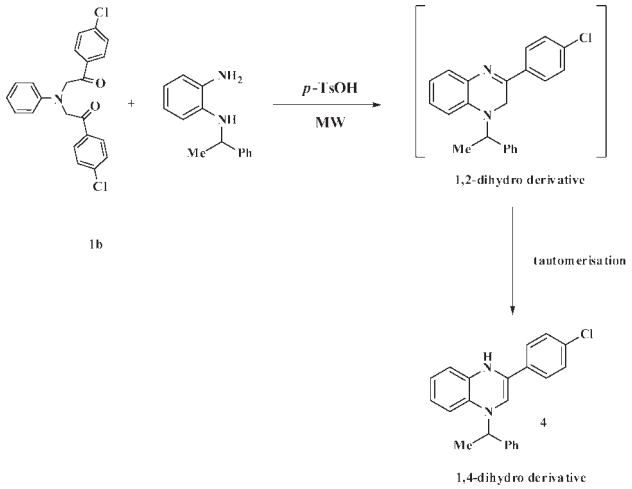
Scheme 2



The quinoxalines **3** presumably arise from a tandem sequence of reactions and the mechanism (Scheme 2) envisages an acid catalyzed imine formation followed by the attack of amino group on the methylene carbon—not on the imino carbon—displacing $NPhCH_2COPh$ group. This is contrary to the case of the reaction **1** with 2-aminophenol and 2-aminothiophenol. There the initial attack by the nucleophilic center SH or OH on the electrophilic carbonyl gives a tertiary alcohol and the nitrogen of the amino group attacks this carbon center, displacing hydroxyl group (probably *via* the initially formed carbocation with the help of *p*-toluene sulphonic acid). But in the present case, the initially formed tertiary alcohol undergoes 1,2-elimination forming an imine. Now the second nitrogen of the amino group does not attack this imino carbon rather attacks the methylene carbon displacing $NPhCH_2COPh$ group (again aided by *p*-toluene sulphonic acid through protonation of the leaving group, thus increasing its leaving group ability).

With the successful optimization results in hand, we investigated the scope of this process to another substituted diamine, *N*-(1-phenylethyl)-1,2-diaminobenzene.

Scheme 3



When the reaction is carried out with substituted 1,2-diaminobenzene, *N*-(1-phenylethyl)-1,2-diaminobenzene, prepared from 2-chloronitrobenzene and dl-phenylethylamine, the final oxidation step shown in Scheme 2 is not possible and the 1,2-dihydroquonoxaline can be expected. Hence, the proposed reaction of **1b** with *N*-(1-phenylethyl)-1,2-diaminobenzene was carried out under identical condition as depicted in Scheme 2. The reaction proceeds smoothly giving a product **4** (Scheme 3). The ^{1}H NMR spectrum has a three hydrogen doublet and one hydrogen multiplet at 1.85 ppm and 4.63 ppm, respectively. In the aromatic/olefinic region, there are 14 hydrogen resonances. In the ^{13}C NMR spectrum, there are signals at 22.2 and 43.9 ppm apart from 16 signals in the olefinic/aromatic region. There is no methylenic carbon or hydrogen. Thus the ^{1}H NMR and ^{13}C NMR spectra of the compound **4** clearly suggest the structure to be a 1,4-dihydroquinoxazine and not a 1,2-dihydroquinoxazine. It is surprising that the 1,2-dihydro system obtained has rearranged to a 1,4-dihydro system.

Even in the case of **3**, it is probable that if the air oxidation is prevented, then the 1,2-dihydro system would have not been isolated and the 1,4-dihydro system would have been obtained.

EXPERIMENTAL

All chemicals were of reagent grade quality and used without further purification. All melting points were recorded in open capillaries and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer at 300 and 75 MHz respectively in $CDCl_3$ using TMS as internal standard. The related 2D NMR spectra also recorded on the same instrument. Chemical shifts are given in parts per million (δ-scale) and coupling constants are given in hertz.

General procedure for the preparation of 2-arylquinoxaline (3). A mixture of 2-[(2-oxo-2-arylethyl)anilino]-1-aryl-1-ethanone **1** (0.0015 mol), 1,2-benzenediamine (0.2 g, 0.0015 mol) and catalytic amount of *p*-toluenesulfonic acid was irradiated in an open glass tube over a silica bath in a domestic microwave oven and irradiated for 10 min at power level 5 (540 W). The reaction mixture was treated with water and then extracted with dichloromethane. The organic layer was washed with water repeatedly and dried over anhydrous calcium chloride and evaporated to give the crude product. Purification of the product was performed by column chromatography on silica gel using petroleum ether-ethyl acetate [97:3 (*v*/*v*)] mixture as eluent. The signal due to NH hydrogen is so broad that it is not visible in these compounds. However, when exchanged with D_2O, the HOD peak appears confirming the presence of NH signal.

2-Phenylquinoxaline (3, X = H). This compound was obtained as colorless solid, mp, 79°C (Lit. m.p. 76–77°C [9]); ^{1}H NMR (300 MHz, $CDCl_3$): 7.51–7.56 (m, 3H), 7.73–7.82 (m, 2H), 8.11–8.22 (m, 4H), 9.3 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 127.5 (d), 129.0 (d), 129.1 (d), 129.5 (d), 129.6 (d), 130.1 (d), 130.3 (d), 136.7 (s), 141.5 (s), 142.2 (s), 143.3 (d), 151.8 (s).

2-(4-Chlorophenyl)quinoxaline (3, X = Cl). This compound was obtained as colorless solid, mp, 128°C (Lit. m.p. 137°C [10]); ^{1}H NMR (300 MHz, $CDCl_3$): 7.53–7.56 (m, 2H), 7.78–7.83 (m, 2H), 8.15–8.18 (m, 4H), 9.3 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 129.2 (d), 129.5 (d), 129.8 (d), 129.9 (d), 130.2 (d), 130.8 (d), 135.5 (s), 137.0 (s), 142.0 (s), 142.6 (s), 143.3 (d), 151.0 (s).

2-(4-Methylphenyl)quinoxaline (3, X = Me). This compound was obtained as colorless solid, mp, 92°C (Lit. m.p. 94°C [10]); ^{1}H NMR (300 MHz, $CDCl_3$): 2.38 (s, 3H); 7.30(d, 2H, J = 8.4 Hz); 7.65–7.73 (m, 2H); 8.02–8.08 (m, 4H); 9.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 20.4 (q), 126.4 (d), 128.0 (d), 128.2 (d), 128.5 (d), 128.8 (d), 129.2 (d), 133.0 (s), 139.5 (s), 140.4 (s), 141.3 (s), 142.3 (d), 150.8 (d).

3-(4-Chlorophenyl)-1-(1-phenylethyl)-1,4-dihydroquinoxaline (4). This compound was obtained as yellow solid, yield 68%, mp, 146°C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.85 (d, J = 6.9 Hz, 3H); 4.63 (q, J = 6.9 Hz, 1H); 7.14–8.31 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): 22.2 (q), 43.9 (d), 126.4 (d), 127.8 (d), 128.4 (d), 128.5 (d), 129.0 (d), 129.1 (d), 129.6 (d), 129.8 (d), 130.3 (d), 135.0 (d), 137.4 (s), 140.4 (s), 141.5 (s), 144.2 (s), 154.2 (s), 157.3 (s); *Anal*. Calcd. for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08%. Found: C, 76.25, H, 5. 54; N, 8.03%.

Acknowledgments. The authors thank DST, New Delhi for assistance under the IRHPA program for the NMR facility.

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