A New Type of Reaction Between *o*-Phenylenediamines and Aromatic Aldehydes to Give 2,3-Diarylquinoxalines

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A new type of reaction between *o*-phenylenediamines and aryl aldehydes at high temperature is reported. The synthesis of 2,3-diarylquinoxalines by this procedure is described.

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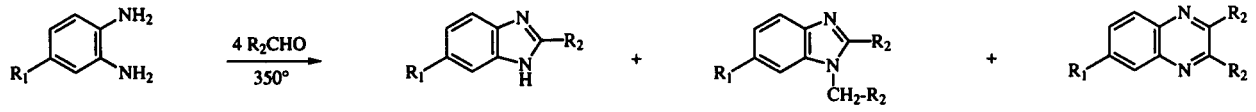
Reaction of *o*-phenylenediamines with aromatic aldehydes to yield 2- or 1,2-substituted benzimidazoles depending on the reaction conditions is known [1]. On the other hand, cyclocondensations of aromatic aldehydes with 3,4,5-triamino-1,2,6-thiadiazine 1,1-dioxide [2] or functional 5,6-diaminopyrimidine derivatives [3,4] to obtain [6]+[6] fused heterocycles, using anhydrous medium and mild oxidizing agents, have been reported. Extension of this type of cyclocondensation to *o*-phenylenediamine was achieved at high temperature.

Reaction of *o*-phenylenediamine with aromatic aldehydes in dry nitrobenzene heating up to 240°, under the same conditions in which 5,6-diaminopyrimidinedione gave 6,7-diarylpteridines [3,4], yielded 2-substituted benzimidazoles **1** (R_1 = H) or 1,2-disubstituted benzimidazoles **2** (R_1 = H) when an excess of aromatic aldehydes and diamine silyl derivatives were used. However, when the reaction was carried out at 350°, 2,3-diarylquinoxalines **3** (R_1 = H) were obtained together with benzimidazoles **1** (R_1 = H) and **2** (R_1 = H) (Scheme 1). The excess aldehyde could act as an oxidizing agent.

Scheme 1



1 **2** **3**

Cyclocondensation of *o*-phenylenediamines with aromatic aldehydes to give arylquinoxalines **3** involves the formation of a non-aromatic intermediate **5** which is readily aromatized by dehydrogenation, as is shown in the proposed mechanism in Scheme 2. The formation of this non-aromatic intermediate requires more energy than that arrangement in the double Schiff's base **4** to obtain benzimidazole **2** and so higher temperatures afford quinoxalines **3**.

In order to know the influence of substituents, cyclocondensations of a variety of aldehydes bearing electron-donating and electron-withdrawing substituents with either *o*-phenylenediamine or 4-nitro-1,2-phenylenediamine were performed. Reactions were carried out in two reaction media, without solvent or with sulfolane as the solvent. Results are summarized in Table I.

Quinoxalines **3a**, **3b**, **3c**, **3d**, **3g**, **3i**, and **3m** were previously synthesized by reaction between *o*-phenylenediamines and the appropriate α-dicarbonyl compounds. Quinoxalines **3e** and **3k** are described in this paper.

The reaction between *o*-phenylenediamines and aromatic aldehydes is a useful method to obtain 2,3-diarylquinoxalines **3** when the appropriate α-dicarbonyl derivative is not available to carry out the alternative synthesis. The ^{13}C-nmr data of the quinoxalines obtained by this reaction are shown in Table II. From the results in Table I the following conclusions are summarized. Total yields reached 50% in eight of the sixteen cases studied. The low yield obtained in the other cases must be due to the high reaction temperature used, which could bring about decomposition of either starting materials or final products. The highest total yield reached (84%) was obtained from 2-naphthaldehyde, which has a high thermal stability. Concerning percentages of **1**, **2**, **3** obtained, benzaldehyde, its *p*-halogen-derivatives and 2-thiophenecarboxaldehyde afforded better yields of quinoxalines **3** than benzimidazoles **1** and **2**. *p*-Fluorobenzaldehyde (97% of **3**) and *p*-bromobenzaldehyde (85% of **3**) gave the best results for the preparation of quinoxalines **3**. The lower yield of **3m** and **2m**, in comparison with **1m**, must be due to steric hindrance, produced by bulky 2-naphthaldehyde, in the formation of intermediate **4**. Aldehydes bearing nitro groups, **f** and **l** as well as those with electron-donating

Scheme 2

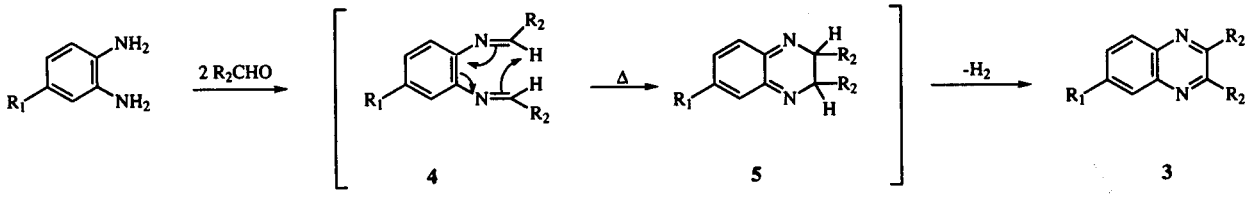


Table I

Results [a] of Cyclocondensations Between *o*-Phenylenediamines and Aryl Aldehydes

Compound	R	R_1	(%) of **1**	(%) of **2**	(%) of **3**	Medium [b]	Yield (%)
a	Ph	H	45	4	51	A	25
a	Ph	H	46	6	48	B	30
b	Ph	NO_2	58	38	4	B	30
c	*p*-FPh	H	3	0	97	A	56
d	*p*-ClPh	H	36	14	50	A	49
d	*p*-ClPh	H	69	1	30	B	55
e	*p*-BrPh	H	15	0	85	A	61
f	*p*-NO_2Ph	H	58	38	4	B	30
g	*p*-MeOPh	H	57	13	30	A	31
g	*p*-MeOPh	H	65	34	1	B	48
h	*o*-ClPh	H	0	0	0	A	0
i	2-thienyl	H	30	20	50	A	54
j	3-thienyl	H	0	0	0	A	0
k	5-Me-2-thienyl	H	80	0	20	A	35
l	5-NO_2-2-thienyl	H	100	0	0	A	50
m	2-naphthyl	H	83	6	11	A	84

[a] The ratios of **1**, **2** and **3** ratio were obtained by hplc from the reaction mixture; [b] Without solvent (A), with sulfolane (B).

Table II

^{13}C-NMR Data [a] of 2,3-Diarylquinoxalines **3**

Compound	C-2 / C-3	C-4a / C-8a	C-5 / C-8	C-6 / C-7	R_2
3a	153.0	140.4	130.4	128.8	138.7,129.7 128.1
3c	152.2	141.2	130.2	129.1	163.2 [b], 134.9 [c] 131.8 [d], 115.5 [e]
3d	151.8	140.5	130.7	128.8	137.4,133.9 131.6,128.3
3e	151.9	141.2	130.4	129.2	137.7,131.7 131.4,123.7
3g	158.5	129.3	126.0	125.7	129.6,127.6 127.0,113.9 (54.7, OMe)
3i	146.1	140.8	129.8	129.4	139.8,128.4 127.8,130.6
3k	144.0	138.5	129.6	129.4	129.7,129.2 129.0,128.7
3m	134.6	133.2	128.9	128.0	132.5,127.6 127.3,126.2 126.1,123.5

[a] Chemical shifts, δ in ppm, deuteriochloroform as solvent; [b] $^1J_{C,F} = 250$; [c] $^4J_{C,F} = 1.1$; [d] $^3J_{C,F} = 8.6$; [e] $^2J_{C,F} = 21.0$ Hz.

substituents, **g** and **k**, decrease the percentage of **3** and increase that of monosusbstituted benzimidazole **1**. Reaction of 4-nitro-1,2-phenylenediamine with benzaldehyde afforded mainly monosubstituted benzimidazole **1b**, and in lower yield disubstituted benzimidazole **2b**, formation of quinoxaline **3b** being clearly unfavorable. In all cases, on using sulfolane as solvent (method B), the yield of **3** decreases in comparison with method A. This is probably due to a lower temperature reached in the reaction mixture (boiling point of sulfolane).

Condensations with 2-thiophenecarboxaldehyde, 3-thiophenecarboxaldehyde and *p*-chlorobenzaldehyde were attempted by the microwave-assisted method by using maximum power and reaction times between 3 to 10 minutes. No quinoxalines **3** were obtained but mono- and disubstituted benzimidazoles **1i**, **2i**, **1j**, **2j**, **1d** and **2d**, compound **2j** being now described. These results are probably due to the fact that the reaction temperature reached was not high enough, only 250° and thus the importance of the thermal factor in the preparation of **3** was demonstrated. The synthesis of benzimidazoles **1j** and **2j** by this procedure confirms that decomposition of 3-thiophenecarboxaldehyde at 350° is the cause of the lack of obtaining of **1j**, **2j**, or **3j** at this temperature (Table 1).

EXPERIMENTAL

Melting points were taken using a Reichert-Jung Thermovar and are uncorrected. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded in a Varian Gemini-200 spectrometer at 200 and 50 MHz, respectively. Merck silica gel 60GF_{254} was used for analytical and preparative tlc. Column chromatography was performed on Merck silica gel 60 (70-230 mesh).

General Method of Preparation of 2,3-Diarylquinoxalines.

o-Phenylenediamine (540 mg, 5 mmoles) and the appropriate arylaldehyde (20 mmoles) were placed into a round bottom flask. A sand bath was previously heated at 350° and then the flask was introduced into the bath. The reaction mixture was vigorously stirred and heated at 350° for three to ten minutes. The reaction mixture then was cooled, dissolved in methanol and analyzed by hplc to evaluate the ratios of **1**, **2**, and **3**. Compounds were purified by column chromatography using dichloromethane as the eluent.

2,3-Bis(*p*-bromophenyl)quinoxaline (**3e**).

Following the general method from *p*-bromobenzaldehyde (3.68 g, 20 mmoles) 1.12 g, 51% yield of **3e** was obtained as white needles, mp 201-202° (aqueous ethanol); ^{1}H-nmr (deuteriochloroform): δ 8.17 (dd 2H, ^{3}J = 6.4, ^{4}J = 3.4 Hz, H-5, H-8), 7.81 (dd, 2H, ^{3}J = 6.4, ^{4}J = 3.4 Hz, H-6, H-7), 7.52 (d, 4H, ^{3}J = 8.5 Hz, H-*m*), 7.41 (d, 4H, ^{3}J = 8.5 Hz, H-*o*).

Anal. Calcd. for $C_{20}H_{12}Br_2N_2$: C, 54.79; H, 2.74; Br, 36.07; N, 6.39. Found: C, 54.55; H, 2.80; Br, 35.83; N, 6.25.

2,3-Bis(5'-methyl-2'-thienyl)quinoxaline (**3k**).

Following the general method from 5-methyl-2-thiophenecarboxaldehyde (2.52 g, 20 mmoles) 112.7 mg (7% yield) of **3k** was obtained as yellow needles, mp 166-167° (aqueous methanol); ^{1}H-nmr (acetone-d_6): δ 8.01 (dd, 2H, ^{3}J = 6.2, ^{4}J = 3.4 Hz, H-5, H-8), 7.77 (dd, 2H, ^{3}J = 6.2, ^{4}J = 3.4 Hz, H-6, H-7), 7.17 (d, 2H, ^{3}J = 3.6 Hz, H-3'), 6.78 (dq, 2H, ^{3}J = 3.6, (^{J}H-4', CH_3) = 1.1 Hz, H-4'), 2.25 (d, 6H, ^{4}J = 1.1 Hz, CH_3).

Anal. Calcd. for $C_{18}H_{14}N_2S_2$: C, 67.08; H, 4.35; N, 8.70; S, 19.87. Found: C, 66.76; H, 4.50; N, 8.43; S, 19.55.

2-(3'-Thienyl)-1-(3'-thenyl)benzimidazole (**2j**).

o-Phenylenediamine (540 mg, 5 mmoles) and 3-thiophencarboxaldehyde (2.24 g, 20 mmoles) were carefully mixed and placed into a pyrex-glass open vessel and irradiated in a microwave domestic oven for three minutes and at output power of 750 watts. When the irradiation was stopped the final temperature attained in the reaction was measured (250°) by introducing a glass thermometer into the reaction mixture and homogenizing it, in order to obtain a temperature value representative of the whole mass. Benzimidazoles **1j** and **2j** obtained were chromatogaphed using dichloromethane as the eluent; 666 mg (45%) of compound **2j** were isolated as white needles, mp 177-178° (acetone); ^{1}H-nmr (DMSO-d_6): δ 8.04 (m, 1H, H-2'), 7.73 (m, 2H, H-5', H-5"), 7.66 (m, 2H, H-4, H-7), 7.53 (dd, 1H, ^{4}J = 2.9, ^{4}J = 1.2 Hz, H-2"), 7.24 (m, 2H, H-5, H-6), 7.17 (d, 1H, ^{3}J = 5.3 Hz, H-4'), 6.80 (d, 1H, ^{3}J = 5.0 Hz, H-4"), 6.64 (s, 2H, CH_2); ^{13}C-nmr (DMSO-d_6): δ 148.6 (C-2), 142.4 (C-7a), 137.8 (C-3a), 135.7 (C-3"), 130.8 (C-3'), 128.3 (C-4"), 127.5 (C-4'), 127.3 (C-2"), 126.8 (C-2'), 126.3 (C-5"), 122.6 (C-5'), 122.3 (C-6), 122.2 (C-5), 119.0 (C-7), 110.8 (C-4), 43.5 (CH_2).

Anal. Calcd. for $C_{16}H_{12}N_2S_2$: C, 64.86; H, 4.05; N, 9.46; S, 21.62. Found: C, 64.53; H, 4.20; N, 9.24; S, 21.32.

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REFERENCES AND NOTES

[1] G. P. Ellis, in The Chemistry of Heterocyclic Compounds, Synthesis of Fused Heterocycles, Vol **47**, E. C. Taylor, ed, John Wiley and Sons, New York, 1987, p 404.

[2] A. Herrero and C. Ochoa, *J. Heterocyclic Chem.*, **25**, 891 (1988).

[3] W. Plfeiderer and H. U. Blank, *Angew. Chem., Int. Engl.*, **7**, 535 (1968).

[4] C. Ochoa, J. Rodríguez, M. L. López García, A. R. Martínez and M. M. Martínez, *Arzneim. Forsch. Drug Res.*, **46**, 643 (1996).