A Facile Synthesis of Mono and Dialkoxyquinoxalines

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Abstract: 2,3-dichloroquinoxaline 3 on reaction with alcohols in the presence of K_2CO_3 as base and TEBAC as phase transfer catalyst at RT gave 1:1 products, i.e. 2-chloro-3-alkoxyquinoxalines 4. In the presence of the same reagent but under refluxing conditions, 3 gave 1:2 products i.e. 2,3-dialkoxyquinoxalines 5. 2,3-dichloro-6-nitroquinoxaline 7 on treatment with various alcohols in the presence of K_2CO_3 as base and TEBAC as phase transfer catalyst at −10° to -5°C gave the monoalkoxy derivatives of 7 i.e. 2-alkoxy-3-chloro-6-nitroquinoxalines 8 and at RT gave the dialkoxy derivative i.e. 2,3-dialkoxy-6-nitroquinoxaline 9. The structures of these compounds are supported by their spectral and analytical data and comparison with those known in literature.

Introduction

Quinoxaline derivatives and fused quinoxalines are reported[1] to possess interesting pharmacological properties. In continuation of our studies[2] on the synthesis of quinoxaline derivatives of potential biological activities, we have carried out studies on the reaction of 2,3-dichloroquinoxaline 3 with alcohols under different conditions leading to the formation of title mono and dialkoxyquinoxalines. These results are reported in this paper.

Results and Discussion

o-Phenylenediamine 1 was condensed with oxalic acid under Phillips' conditions[3] to obtain quinoxaline-2,3-dione 2. The latter on treatment with $POCl_3$ gave the previously reported[4] 2,3-dichloroquinoxaline 3. With a view to prepare the monoalkoxy derivative of 3, the reaction of the latter with methanol in the presence of K_2CO_3 as base and triethylbenzylammonium chloride (TEBAC) as phase transfer catalyst at RT was carried out. On processing, the reaction mixture yielded a product, which was found to be homogeneous on tlc and analyzed for a 1:1 composition. Its m.p. was found to be 74-76° C, different from starting material (i.e. 152-53° C). This compound was imagined to be 2-chloro-3-

methoxyquinoxaline (**4a**, i.e. 4, R = Me) and found to be so by comparison of the m.p. from literature[5] (74-75° C). Its structure was further confirmed from its spectral data. Thus, in its IR spectrum, compound showed peaks at 1570(vs), 1485(s), 1450(s), 1400(vs), 1370(s), 1335(vs), 1245(w), 1230(m) cm^{-1}etc. Its ^{1}H-NMR ($CDCl_3$) showed signals at δ 4.30 (s, 3H, $-OCH_3$), 7.5-8.2 (complex m, 4H, aryl protons).

The above reaction of 3 was extended to other alcohols and the products obtained have all been assigned structures 4 on the basis of spectral and analytical data (**Table**).

However, 3 on reaction with methanol under refluxing conditions using excess of K_2CO_3 as base and TEBAC as phase transfer catalyst yielded a product with a m.p. 92-94° C, different from starting material (i.e. 152-54° C). It was found to be homogeneous on tlc. This compound was imagined to be 2,3-dimethoxyquinoxaline (**5a**, i.e. 5, R = Me) and found to be so by comparison of the m.p. from literature[5] (92-93° C). Its structure was further confirmed from its spectral data. Thus, in its IR spectrum, compound showed peaks at 2950(vw), 1620(w), 1590(s), 1530(s), 1500(w), 1490(vs), 1455(s), 1430(s), 1380(vs), 1330(s), 1320(s), 1295(w), 1260(w), 1250(m), 1225(s) cm^{-1} etc. Its ^{1}H-NMR ($CDCl_3$) showed peaks at δ 4.18 (s, 6H, 2 × $-OCH_3$), 7.46-7.79 (A_2B_2, 4H, aryl protons).

The above reaction of 3 was extended to other alcohols and the products obtained have all been assigned structures 5 on the basis of spectral and analytical data (**Table**) and on comparison of m.ps. of compounds reported in literature.

2,3-Dihydroxy-6-nitroquinoxaline 6 was obtained by the nitration of 2,3-dihydroxyquinoxaline 2 with KNO_3 in conc. H_2SO_4 using a known procedure[6]. 6 on treatment with $POCl_3$ gave the previously reported[7] 2,3-dichloro-6-nitroquinoxaline 7.

Compound 7, on treatment with MeOH in the presence of K_2CO_3 as base and TEBAC as phase transfer catalyst at RT, gave a product with a m.p. 174-75° C, different from starting material (i.e. 152° C). It was found to be homogenous on tlc. In its IR spectrum in KBr phase the compound showed peaks at 1620 (vw), 1590 (vw), 1540 (w), 1515 (s), 1490 (s), 1420 (m), 1380 (m), 1340 (vs), 1300 (w), 1250 (w), 1220 (vw) cm^{-1} etc. Its ^{1}H-NMR in $CDCl_3$ / TMS showed signals at δ 4.2 (s, 6H, 2 × $-OCH_3$), 7.85 (d, 1H, $J_{7,8}$ = 10 Hz, H-8), 8.30 (dd, 1H, $J_{7,8}$ = 10Hz, $J_{7,5}$ = 2 Hz, H-7), 8.68 (d, 1H, $J_{5,7}$ = 2 Hz, H-5). Based on the above data, the compound was assigned 2,3-dimethoxy-6-nitroquinoxaline structure **9a** (i.e. 9, R = Me).

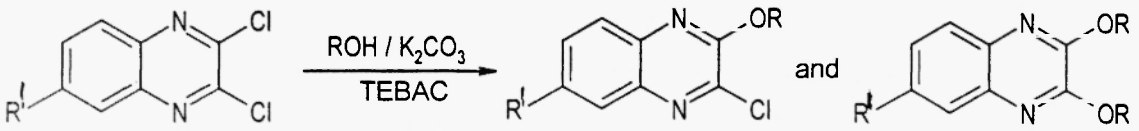
The above reaction of 7 was extended to other alcohols and the products obtained have all been assigned structures 9 on the basis of spectral and analytical data (**Table**).

To obtain the monoalkoxy derivatives of 7, the latter was treated with MeOH in the presence of K_2CO_3 and TEBAC at 0-5° C. On processing, the reaction yielded a mixture of two compounds, which were separated by column chromatography. One of these was identified as 2,3-dimethoxy-6-nitroquinoxaline **9a** (i.e. 9, R = Me) by comparison of tlc, m.p. and m.m.p. with the sample obtained above. The other compound showed a m.p. 140-42° C different from starting material (i.e. 153° C). In its IR spectrum in KBr phase it showed peaks at 1620 (m), 1580 (w), 1570 (vs), 1535 (s), 1530 (vs), 1500 (m), 1470 (s), 1440 (m), 1400 (vs), 1350 (vs), 1330 (vs), 1240 (m), 1230 (s) cm^{-1} etc. Its ^{1}H-NMR in $CDCl_3$ / TMS showed signals at δ 4.25 (s, 3H, $-OCH_3$), 8.0 (d, 1H, $J_{8,7}$ = 10 Hz, H-8), 8.5 (dd, 1H, $J_{7,8}$ = 10 Hz, $J_{7,5}$ = 2 Hz, H-7), 8.85 (d, 1H, $J_{5,7}$ – 2 Hz , H-5). Based on this data and on the basis of the consideration that the chlorine most affected by electron-withdrawing effect of the nitro group is likely to undergo facile nucleophilic displacement, the compound was assigned 2-methoxy-3-chloro-6-nitroquinoxaline structure **8a** (i.e. 8, R = Me).

The above reaction was repeated using the same reagents but under conditions of -10 to –5° C temperature. Processing the reaction mixture yielded a product homogeneous on tlc. The structure of the compound was imagined to be 2-methoxy-3-chloro-6-nitroquinoxaline (**8a**, i.e. 8, R = Me) and found to be so by comparison of tlc, m.p., m.m.p., and superimposable IR with the 1:1 sample obtained above.

The above reaction of 7 with MeOH at –10 to –5° C was extended to other alcohols and the products obtained have all been assigned structures 8 on the basis of spectral and analytical data (**Table**).

It thus appears that the reactions of 3 and 7 with alcohols in the presence of K_2CO_3 as base and TEBAC as phase transfer catalyst can be suitably controlled to obtain the desired products. Under mild conditions, i.e., at RT and –10 to –5° C respectively, 1:1 products are formed and under little stronger conditions, i.e., at reflux and RT respectively, 1:2 products are formed.



3, 7 (R^1 = H, NO_2) 4, 8 5, 9

Experimental Section

General. Melting points are uncorrected and were determined in open capillaries in a sulfuric acid bath. TLC analyses were carried out on glass plates coated with silica gel – G and spotting was done using iodine or UV lamp. ^{1}H-NMR spectra were recorded on a 100 MHz Varian or 200 MHz Tecmag instrument using TMS as internal standard.

Preparation of 4 from 3 (General Procedure). A mixture of **3** (1.99 gms, 10 mM), K_2CO_3 (1.38 gms, 10 mM) and TEBAC (0.15 gms) in appropriate alcohol (20 mL) was stirred at RT for 4-6 hrs. At the end of this period, the reaction mixture was diluted with water (100 mL), neutralized with acetic acid and the resultant solid was filtered, washed with water and dried to obtain pure **4** (**Table**).

Preparation of 5 from 3 (General Procedure). A mixture of **3** (1.99 gms, 10 mM), K_2CO_3 (2.76 gms, 20 mM) and TEBAC (0.3 gms) in appropriate alcohol (20 mL) was refluxed for 4 hrs. At the end of this period, alcohol was distilled off and the residue stirred with water (50 mL). The resultant solid was filtered, washed with water and dried to obtain pure **5** (**Table**).

Preparation of 9 from 7 (General Procedure). A mixture of **7** (2.44 gms, 10 mM), K_2CO_3 (1.38 gms, 10 mM) and TEBAC (0.3 gms) in appropriate alcohol (20ml) was stirred at RT for 4-5 hrs. At the end of this period, the reaction mixture was diluted with water to obtain an insoluble product, which was filtered, washed with water and dried to obtain pure **9** (**Table**).

Preparation of 8a and 9a from 7. A mixture of **7** (2.44 gms, 10 mM), K_2CO_3 (1.38 gms, 10 mM) and TEBAC (0.15 gms) in MeOH (20ml) was stirred at 0-5° C for 4-6 hrs. At the end of this period, the reaction mixture was diluted with water, to obtain a solid, which was filtered, washed with water to obtain crude **8a** and **9a**. Compounds **8a** and **9a** were separated by column chromatography using silicagel and hexane-ethyl acetate (9.9:0.1) as elutent (**Table**).

Table: Reaction of 3 or 7 with various alcohols to obtain corresponding product.

Sl. No.	Starting Material Used	Alcohol Used	Reaction Condition	Product Obtained *	Yield (%)	M.P. (°C)	^{1}H-NMR (DMSO-d_6 or $CDCl_3$ / TMS), δ ppm
1.	3	MeOH	RT	**4a** (R = Me)	99.8	74-76[5]	(Given in results and discussion)
2.	3	EtOH	RT	**4b** (R = Et)	95	72-73[5]	δ 1.52 (t, 3H, J = 10 Hz, -CH_3), 4.6 (q, 2H, J =10 Hz, -CH_2), 7.50-8.0 (Complex m, 4H, aryl protons).
3.	3	Isopropyl alcohol	RT	**4c** [R =CH $(CH_3)_2$]	89	56-57[5]	----
4.	3	Ethoxy ethanol	RT	**4d** (R = CH_2-CH_2-O-CH_2-CH_3)	94	<40	δ 1.25 (t, 3H, J = 10 Hz, -CH_3), 3.65 (q, 4H, J = 10 Hz, -CH_2), 3.91 (t, 2H, J = 5 Hz, Hr-O-CH_2-CH_2-O-CH_2), 4.7 (t, 2H, J = 5 Hz, Hr-O-CH_2), 7.50-8.0 (Complex m, 4H, aryl protons).
5.	3	MeOH	Refluxing	**5a** (R = Me)	97	92-93[5]	(Given in results and discussion)
6.	3	EtOH	Refluxing	**5b** (R = Et)	95	76-78[5, 8]	δ 1.55 (t, 6H, J = 10 Hz, 2 x -CH_3), 4.6 (q, 4H, J = 10 Hz, 2 x -CH_2), 7.40-8.0 (AA', BB', 4H, aryl protons).
7.	3	Isopropyl alcohol	Refluxing	**5c** [R = CH $(CH_3)_2$]	92	93-94[5]	----
8.	3	Ethoxy ethanol	Refluxing	**5d** (R = CH_2-CH_2-O-CH_2-CH_3)	96	<40	δ 1.25 (t, 6H, J = 10 Hz, 2 x -CH_3), 3.6 (q, 4H, J = 10 Hz, 2 x O-CH_2-CH_3), 3.9 (t, 4H, J = 5 Hz, 2 x Hr-O-CH_2-CH_2-O-), 4.7 (t, 4H, J = 5 Hz, Hr-O-CH_2), 7.40-7.8 (A_2B_2, 4H, aryl protons).
9.	7	MeOH	RT	**9a** (R = Me)	95	175-76[9]	(Given in results and discussion)
10.	7	EtOH	RT	**9b** (R = Et)	95.3	106-08	δ 1.45-1.70 (two triplets, 6H, 2 x -CH_3), 4.65 (two quartets, 4H, 2 x -CH_2), 7.8 (d, 1H, $J_{8,7}$ = 10 Hz, H-8), 8.25 (dd, 1H, $J_{7,8}$ = 10 Hz, $J_{7,5}$ = 2 Hz, H-7), 8.62 (d, 1H, $J_{5,7}$ = 2 Hz, H-5).
11.	7	MeOH	0-5° C	**8a, 9a** (R = Me)	92, 8	----	----
12.	7	EtOH	0-5° C	**8b, 9b** (R = Et)	90, 10	----	----
13.	7	MeOH	-10 to -5°C	**8a** (R = Me)	98.9	140-42	(Given in results and discussion)
14.	7	EtOH	-10 to -5° C	**8b** (R = Et)	99.2	93-95	δ 1.56 (t, 3H, J = 6 Hz, -CH_3), 4.69 (q, 2H, J = 6 Hz, -CH_2), 8.4-8.9 (m, 3H, aryl protons).

*Satisfactory elemental analysis for Nitrogen was obtained for all compounds.

Preparation of 8 from 7 (General Procedure). A mixture of 7 (2.44 gms, 10 mM), K_2CO_3 (1.38 gms, 10 mM) and TEBAC (0.3 gms) in appropriate alcohol (20ml) was stirred at -10 to -5° C for 4-6 hrs. At the end of this period, the reaction mixture was diluted with water and the separated solid was filtered, washed with water and dried to obtain pure 8 (**Table**).

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