

Full Length Research Paper

# One-pot synthesis of some (1H)-quinoxalin-2-ones

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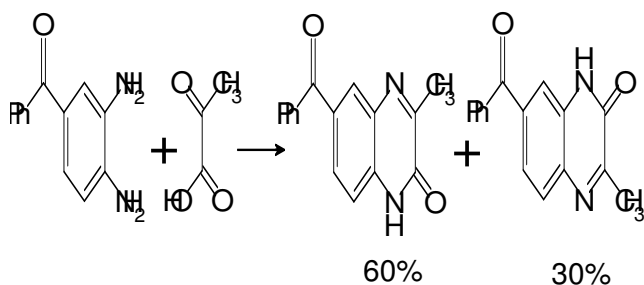
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***o*-Phenylenediamine and 4-benzoyl-1,2-diaminobenzene react with ethyl bromoacetate in basic medium under mild reaction conditions to give directly 1H-quinoxalin-2-one (2) and 7-benzoyl-1H-quinoxalin-2-one (4), respectively. Alkylation at the nitrogen atoms of 7-benzoyl-3,4-dihydro-1H-quinoxalin-2-one (3) and compound 4 has been also carried out.**

**Key words:** *o*-Phenylenediamines, 3,4-dihydro-1H-quinoxalin-2-ones, 1H-quinoxalin-2-ones, ethyl bromoacetate.

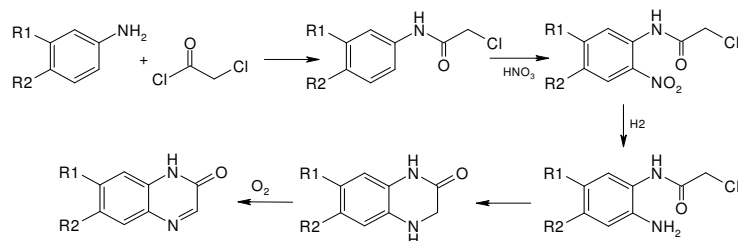
## INTRODUCTION

The presence of two functionally active amino groups in *o*-phenylenediamines increases the possibility of various interactions that in many cases lead to a number of products some of them are unexpected. When a symmetrically substituted *o*-phenylenediamine is subjected to react with an active halogen, a ketoester or a diketone, in a mild reaction condition, a mixture of different products is usually formed (Rosa et al., 2006; Hasan et al., 1998). In unsymmetrical molecule, a regioisomeric mixture is often obtained; its structures are dependent upon the type of the substituent(s) already present in the molecule (Ali et al., 2000, Roman et al., 2006).

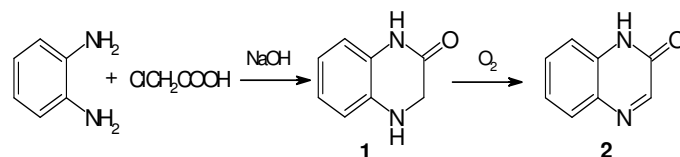


Xun et al. (2004) has used an indirect synthetic method to prepare regioisomeric isomers of quinoxalinones having different substituents.

The following scheme illustrates the synthesis of dihydroquinoxalinones and its oxidation into the corresponding quinoxalinones.



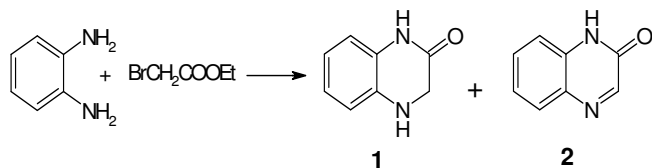
Generally, most of the reported methods to prepare 1H-quinoxalin-2-ones was by oxidation of the corresponding 3,4-dihydro-1H-quinoxalin-2-ones by using hydrogen peroxide in an acid medium (Perkin 1923, Xun, 2004).



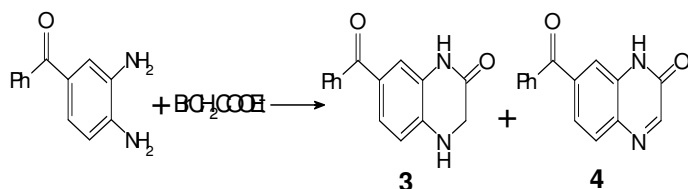
In this work, we report an interesting observation during our trial to prepare some derivatives from 3,4-dihydroquinoxalinone (1), with the aim to study some of their pharmacological activities. We followed the old method shown above (Perkin 1923) to prepare compound 1 (from *o*-phenylenediamine and chloroacetic acid). However, upon using ethyl bromoacetate instead of chloroacetic

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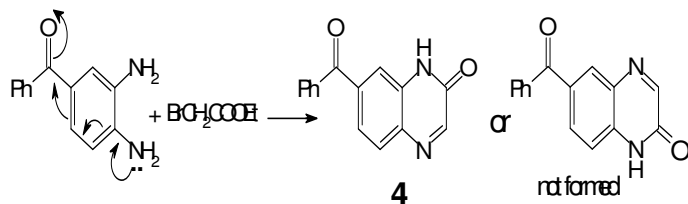
acid in acetonitrile as solvent and triethylamine as catalyst, we obtained directly 1*H*-quinoxalin-2-one (2) in addition to 3,4-dihydro-1*H*-quinoxalin-2-one (1).



In a similar way, reaction of ethyl bromoacetate with 4-benzoyl-1,2-diaminobenzene, under the same reaction condition, gave 7-benzoyl-1*H*-quinoxalin-2-one (4) in addition to 7-benzoyl-3,4-dihydro-1*H*-quinoxalin-2-one (3). It is worth mentioning that chloroacetic acid did not behave like ethyl bromoacetate.



The formation of the compounds 3 and 4, and not any other isomers, can be explained in terms of the electron withdrawing property of the carbonyl group and its influence on any of the two amino groups. In the present example, the amine protons located at the para-position to the benzoyl group are easier to be eliminated by the rather more electronegative bromine atom, thus forming the 7-benzoyl derivatives 3 and 4.



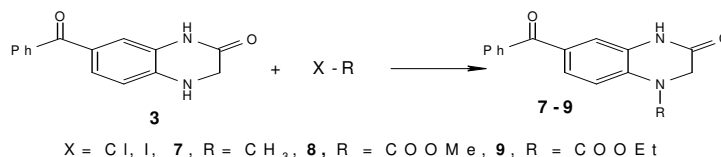
Furthermore, upon reaction of 7-benzoyl-3,4-dihydro-1*H*-quinoxalin-2-one (3) with ethyl bromoacetate, the oxidation product 4 was formed. In the same way, compound 1 reacted to give the oxidation product 2. This transformation from compound 3 into 4 (also from 1 into 2) has driven our belief that, during the alkylation reaction product 3 is formed first, which further reacts with another molecule of ethyl bromoacetate to give 4-ethylacetate derivative 5 as an unstable intermediate, which under the reaction condition undergoes elimination of ethyl acetate (simple base catalyzed elimination reaction) to give overall the oxidation product 4 (Scheme 1). This mechanism is tentative since there was no intermediate could be isolated in this reaction that helps or supports this explanation. This also can explain the

low yields obtained in these reactions since some of the reagent goes in the elimination reaction.

These results have led us to repeat the reaction by using two mole equivalents, or a little excess, of ethyl bromoacetate. Under this condition, the products obtained from each of the studied compounds 1 and 3 were solely the oxidation products 2 and 4. Moreover, reaction of compound 3 or 4 with ethyl bromoacetate in acetonitrile in the presence of sodium carbonate gave (7-benzoyl-2-oxo-2*H*-quinoxalin-1-yl) acetic acid ethyl ester 6. Compound 6 could be also obtained by the reaction of the starting 4-benzoyl-1,2-diaminobenzene with excess (three to four mole equivalents) of ethyl bromoacetate, (Scheme 2).

It is of interest to mention that, this elimination reaction was not observed with other alkylating agents used in this study.

Reaction of compound 3 with methyl iodide, methyl- or ethyl chloroformate, gave the corresponding 4-methyl-, 4-methoxycarbonyl, or 4-ethoxycarbonyl derivatives (7-9), respectively. There was no oxidation products formed in these alkylation reactions. Elucidation of the structures 7-9 was achieved by comparing the location of the N-H signals in the <sup>1</sup>H-NMR spectra of compounds 3 with that of the alkylated products (7-9). The N<sup>4</sup>-H signal of compound 3 appears at 6.30 ppm, while that for the N<sup>1</sup>-H amide appears at lower field strength (10.65 ppm).



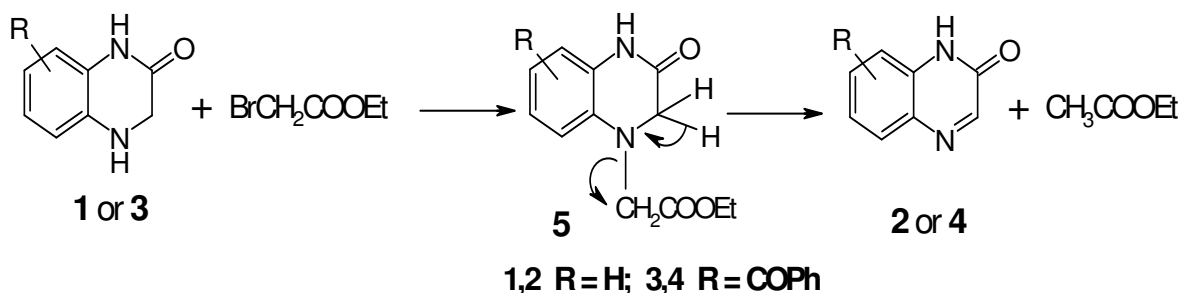
The <sup>1</sup>H-NMR spectra of compounds 7 - 9 showed signals for N-H protons appeared in the range 9.49 - 8.86 ppm, which correspond to N<sup>1</sup>-H (CONH) protons.

## MATERIALS AND METHODS

Melting points were taken on a capillary melting point apparatus and are uncorrected. The IR spectra were recorded with a Philips Infracord Spectrophotometer Model PU9712 in KBr discs. NMR spectra were measured in CDCl<sub>3</sub> and DMSO-d<sub>6</sub> on JEOL-270 spectrometer with Me<sub>4</sub>Si as an internal standard. Mass spectra were obtained with a Shimadzu GCS-QP 1000 EX spectrometer at 70eV. Elemental analyses were performed at the Microanalytical Laboratory of the National Research Centre.

### General method for preparation of 3,4-dihydro-1*H*-quinoxalin-2-ones and 1*H*-quinoxalin-2-ones (1 - 4).

A mixture consisted of *o*-phenylenediamine (1.08 g) or 4-benzoyl-1,2-diaminobenzene (2.12 g) (10 mmole), ethyl bromoacetate (2.75 g, 11 mmole) and triethylamine (3 ml) in acetonitrile (30 ml), were stirred at room temperature. After few minutes a precipitate was formed; stirring was continued until completion of the reaction. TLC



**Scheme 1.** Simple base catalyzed elimination reaction (to give overall the oxidation product 4).

analysis showed the presence of two products. Solvent was then removed under vacuum and the product was taken with water, filtered and dried. The products from 1 - 4 were separated by fractional crystallization from methanol.

**Compound 1:** Yield 0.52 g, m.p. 136-138°C (reported 138°C) (Perkin 1923).

**Compound 2:** Yield 0.64 g, m.p. 271-273°C (reported 265°C) (Perkin 1923).

**Compound 3:** Yield 1.10 g, m.p. 252°C, MS (m/z, %): 252.03 ( $M^+$ , 100); 250.03 ( $M^+$ , -2H, 65); 173.03 ( $M^+$ -2H-C<sub>6</sub>H<sub>5</sub>, 85.1); 105.01 (C<sub>6</sub>H<sub>5</sub>CO, 15.16); and 77.01 (C<sub>6</sub>H<sub>5</sub>, 5.43); <sup>1</sup>HNMR, (CDCl<sub>3</sub>, □, ppm), 10.65 (s, 1H, NH-CO); 7.65 (t, *J* = 3.5, 3H, C<sub>3',4',5'</sub>H); 7.55 (d, *J* = 3.5, 2H, C<sub>2',6'</sub>H); 7.13 (s, 1H, C<sub>8</sub>H); 7.02 (d, *J* = 3.6, 1H, C<sub>6</sub>H); 6.85 (d, *J* = 3.6, 1H, C<sub>5</sub>H); 6.30 (br s, 1H, NH); 3.81 (s, 2H, CH<sub>2</sub>).

**Compound 4:** Yield, 0.82 g, m.p. 180 - 182°C; MS (m/z, %): 250.03 ( $M^+$ , 100); 173.01 ( $M^+$ -C<sub>6</sub>H<sub>5</sub>, 85.1); 105.01 (C<sub>6</sub>H<sub>5</sub>CO, 15.16); 77.01 (5.43), <sup>1</sup>HNMR, (CDCl<sub>3</sub>, □, ppm), 8.36 (s, 1H, NH-CO); 8.30 (s, 1H, C<sub>8</sub>H); 8.10 (s, 1H, C<sub>3</sub>H); 7.82 (d, *J* = 3.5, 2H, C<sub>2',6'</sub>H); 7.63 (d, *J* = 3.5, 1H, C<sub>6</sub>H); 7.6-7.53 (m, 3H, C<sub>3',4',5'</sub>H); 7.40 (d, *J* = 3.5 Hz, 1H, C<sub>5</sub>H).

#### General method for preparation of 1H-quinoxalin-2-ones (2 and 4)

A mixture consisted of *o*-phenylenediamine (1.08 g) or 4-benzoyl-1,2-diaminobenzene (2.12 g) (10 mmole), ethyl bromoacetate (3.66 g, 22 mmole) and triethylamine (4 ml) in acetonitrile (30 ml) were stirred at room temperature for 1 hour, then heated under reflux for 3 hours (monitored by TLC). After completion of the reaction, solvent was removed under vacuum and the product was taken with water and filtered. The solid obtained was washed, dried and crystallized from ethanol.

#### Synthesis of (7-benzoyl-2-oxo-2H-quinoxalin-1-yl) acetic acid ethyl ester (6)

a) From 4-benzoyl-1,2-diaminobenzene: A mixture of 4-benzoyl-1,2-diaminobenzene (2.12 g, 10 mmole), ethyl bromoacetate (7 g, 40 mmole) and sodium carbonate (4 g) in dioxan (50 ml) was heated under reflux for 6 - 8 h (monitored by TLC). After completion of the reaction solvent was partially removed under vacuum and the product was taken with water, filtered and dried to give 2.60 g (78%) of the product which was crystallized from methanol. M.p.

221 - 223°C; MS (m/z, %): 337.1 ( $M^+$ +1, 100), 290.07 (25), 259.13 (56.50), 250.14 (3.35), 235.13 (86.29), 105.06 (36.12), 77.09 (26.71); <sup>1</sup>HNMR, (CDCl<sub>3</sub>, □, ppm), 8.37 (d, *J* = 12.5 Hz, 2H, C<sub>2',6'</sub>H); 8.11 (s, 1H, C<sub>3</sub>H), 7.80 (d, *J* = 3.5, 1H, C<sub>5</sub>H); 7.61-7.53 (m, 3H, C<sub>3',4',5'</sub>H); 7.40 (d, *J* = 3.5 Hz, 1H, C<sub>6</sub>H); 5.03 (s, 2H, CH<sub>2</sub>-CO); 4.36 (q, 2H, -CH<sub>2</sub>CH<sub>3</sub>); 1.29 (t, 3H, CH<sub>3</sub>); Analysis, for C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (336.35), calcd., C, 67.85; H, 4.79; N, 8.33%; found: C, 67.65; H, 4.85; N, 8.30%.

#### General method for preparation of 6-benzoyl-4-substituted-3,4-dihydro-1H-quinoxalin-2-one (7 - 9)

To a mixture of compound 3 (2.52 g, 10 mmole), anhydrous sodium carbonate (3 g) and acetone (50 ml) was added to any of methyl iodide, methyl- or ethyl chloroformate (12 mmole), the mixture was then heated under reflux for 6-8 h (monitored by TLC). After completion of the reaction solvent was removed and the product was taken with water and filtered, washed thoroughly with water, dried and crystallized from ethanol.

#### 6-Benzoyl-4-methyl-3,4-dihydro-1H-quinoxalin-2-one (7)

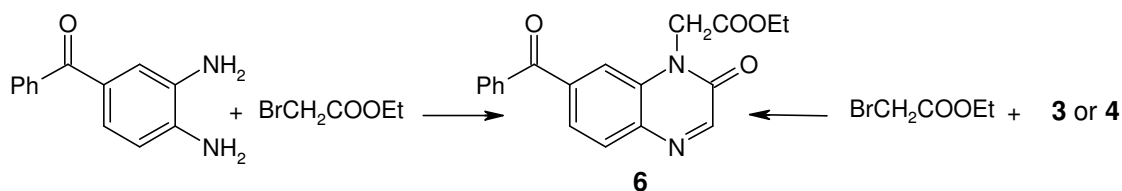
m.p. 153 - 155°C, MS (m/z, %): 266.1 (100), 250.14 (20.35), 105.06 (76.12), 77.09 (28.70); <sup>1</sup>HNMR (CDCl<sub>3</sub>, ppm): 8.86 (s, 1H, NH-CO); 7.75 (d, *J* = 3.6 Hz, 2H, C<sub>2',6'</sub>H); 7.65 (t, *J*=3.5 Hz, 3H, C<sub>3',4',5'</sub>H); 7.47 (s, 1H, C<sub>8</sub>H); 7.18 (d, *J* = 3.6 Hz, C<sub>6</sub>H); 6.79 (d, *J*=3.6 Hz, 1H, C<sub>5</sub>H); 3.86 (s, 2H, CH<sub>2</sub>); 2.91 (s, 3H, CH<sub>3</sub>); Analysis, for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> (266.30), calcd., C, 72.17; H, 5.30; N, 10.52%; found: C, 72.10; H, 5.36; N, 10.48%.

#### 6-Benzoyl-4-methoxycarbonyl-3,4-dihydro-1H-quinoxalin-2-one (8)

m.p. 178-180°C, MS (m/z, %): 310.03 (100), <sup>1</sup>HNMR (CDCl<sub>3</sub>, □ ppm): 9.49 (s, 1H, NH-CO); 8.10 (s, 1H, C<sub>8</sub>H); 7.79 (d, *J* = 3.6 Hz, 2H, C<sub>2',6'</sub>H); 7.61 (t, *J* = 3.5 Hz, 3H, C<sub>3',4',5'</sub>H); 7.48 (d, *J* = 3.6 Hz, 1H, C<sub>6</sub>H); 7.01 (d, *J* = 3.6 Hz, C<sub>5</sub>H); 4.50 (s, 2H, CH<sub>2</sub>); 3.81 (s, 3H, CH<sub>3</sub>); Analysis, for C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub> (310.31), calcd., C, 65.80; H, 4.55; N, 9.03%; found: C, 65.75; H, 4.60; N, 9.00%.

#### 6-Benzoyl-4-ethoxycarbonyl-3,4-dihydro-1H-quinoxalin-2-one (9)

m.p. 158 - 170°C, MS (m/z, %): 324.03 (100), <sup>1</sup>HNMR (CDCl<sub>3</sub>, ppm): 9.28 (s, 1H, NH-CO); 8.03 (s, 1H, C<sub>8</sub>H); 7.56 (d, *J* = 3.6 Hz,



**Scheme 2.** 4-benzoyl-1,2-diaminobenzene with excess (three to four mole equivalents) of ethyl bromoacetate to give compound 6.

2H,  $C_{2,6}H$ ); 7.45 (t,  $J = 3.5$  Hz, 3H,  $C_{3,4,5}H$ ); 7.37 (d, 1H,  $C_6H$ ); 7.01 (d,  $J = 3.6$  Hz,  $C_5H$ ); 4.50 (s, 2H,  $CH_2$ ); 4.36 (q, 2H,  $-CH_2CH_3$ ); 1.29 (t, 3H,  $CH_3$ ); Analysis, for  $C_{18}H_{16}N_2O_4$ , (324.34), calcd.: C, 66.66; H, 4.97; N, 8.64%, found: calcd.: C, 66.60; H, 5.00; N, 8.56%.

## Conclusion

The work done in this investigation represents an easy method for preparation of some quinoxalinone derivatives from dihydroquinoxalines via an unexpected elimination reaction affected by a usual alkylating agent, in particular, ethyl bromoacetate. The use of hydrogen peroxide for conversion of dihydroquinoxalines into quinoxalines, may lead to undesirable byproducts, mostly, the N-oxide derivatives (Elina, 1968).

Because of the importance of quinoxalinones as precursors for the synthesis of many pharmaceuticals and pesticides (Sarges et al 1986, Buchtík et al 2004, 2006; Forloni et al 2003; Obafemi 2005, Sakata et al 1985), further study is required to investigate new compounds in one hand, on the other hand, to generalize and clarify the scope of the present work.

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