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Synthesis of 3-Alkylquinoxalin-2(1*H*)-ones via Grignard Reaction

A. A. Kalinin and V. A. Mamedov

Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia
e-mail: mamedov@iopc.knc.ru

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Abstract—A two-step procedure has been developed for the synthesis of 3-alkylquinoxalin-2(1*H*)-ones from *o*-phenylenediamine and ethyl 2-oxoalkanoates prepared by the Grignard reaction of diethyl oxalate with alkyl bromides. Analogous reaction with α,ω-dibromoalkanes instead of alkyl bromides leads to the formation of 3,3′-(alkane-α,ω-diyl)di[quinoxalin-2(1*H*)-ones].

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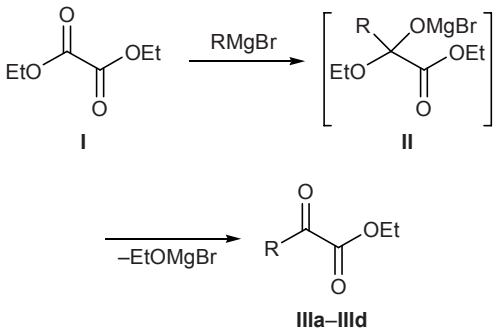
Quinoxaline derivatives are used as starting compounds in the synthesis of various more complex heterocyclic systems. On the other hand, quinoxaline core constitutes a structural fragment of many important pharmaceuticals and biologically active substances so that compounds containing a quinoxaline fragment attract strong interest of synthetic chemists and biochemists. Quinoxaline derivatives were found to exhibit antimicrobial [1–3], antitumor [4], and antituberculous activity [5].

Conventional methods for the synthesis of quinoxaline derivatives are based on reactions of *o*-phenylenediamines with two-carbon synthons such as α-dicarbonyl [6] and α-halocarbonyl compounds [7, 8]. Some *o*-nitroanilines [9] and benzofuroxans [5] can also be used instead of *o*-phenylenediamines. Among known methods for the preparation of 2-hydroxyquinoxalines or quinoxalin-2(1*H*)-ones, the following four general procedures may be noted: (1) condensation of *o*-phenylenediamine with α-halocarboxylic acids [10, 11] and subsequent oxidation of dihydroquinoxalines thus formed, (2) reaction of *o*-phenylenediamine with 2-ethoxalylpropionates followed by alkaline hydrolysis [12], (3) reaction of 3-methylquinoxalin-2(1*H*)-one with alkyl halides in the presence of butyllithium [13], and (4) reaction of α-hydroxyiminocarboxylic acid esters with *o*-phenylenediamine [14]. The first three procedures include three steps. The first procedure ensures only 8–34% yield of the target products [10], the scope of the second procedure is restricted due to inaccessibility of initial ethoxalylalkanoates [12], and the third procedure involves experimental difficulties [13]. On the other hand, the procedure based on the condensation of *o*-phenylenediamine with α-dicarbonyl compounds [6], despite mild reaction conditions and high yields, has not found wide application in the synthesis of 3-alkylquinoxalin-2(1*H*)-ones [15] because of difficult accessibility of α-keto acids and their esters (except for pyruvic acid derivatives). The fourth general procedure is four-step [14].

Taking the above stated into account, the present study was aimed at developing a simple general procedure for the synthesis of 3-alkylquinoxalin-2(1*H*)-ones, as well as of α,ω-bis(2-oxo-1,2-dihydroquinoxalin-3-yl)alkanes, from accessible starting compounds. Bisquinoxaline derivatives attracted specific interest, for such compounds were shown to possess stronger biological activity as compared to those containing only one quinoxaline fragment [16].

We synthesized 3-alkylquinoxalin-2(1*H*)-ones by condensation of *o*-phenylenediamine with α-oxo esters which were prepared by the Grignard reaction from

Scheme 1.

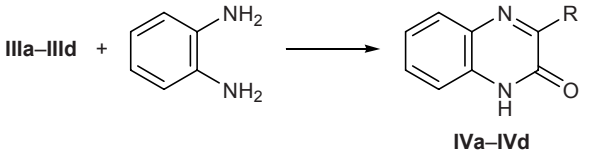


R = Et (**a**), Bu (**b**), C_8H_{16} (**c**), C_9H_{18} (**d**).

diethyl oxalate (**I**) and alkyl bromides. Taking into account that carboxylic acid esters react with Grignard compounds to give tertiary alcohols, the main problem was to find conditions (temperature, reactant ratio, reaction time) ensuring formation of adduct **II** (hemiacetal salt) [17] which is unstable (it readily undergoes decomposition to give highly reactive oxo ester **III** and the corresponding alkoxide; Scheme 1).

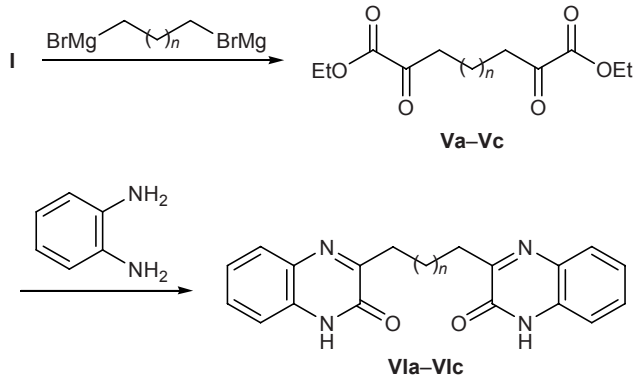
In the ^{1}H NMR spectra of Grignard reaction products **IIIa**–**IIId** we observed signals from the ester ethoxy group (a triplet at δ 1.1 ppm and a quartet at δ 4.1 ppm), while signal from protons in the CH_2CO group appeared separately from the other signals as a quartet (**IIIa**) or triplet (**IIIb**–**IIId**). Therefore, we were able to determine the yield of α-oxo esters **IIIa**–**IIId**, which ranged from 70 to 80% (20–30% of unreacted diethyl oxalate was present). Taking into account different reactivities of diethyl oxalate (**I**) and α-oxo esters **III**, the latter were brought into reaction with *o*-phenylenediamine without isolation from the reaction mixtures. We thus succeeded in simplifying the experimental technique and raising the yield of 3-alkylquinoxalin-2(1*H*)-ones. Reactions of ethyl 2-oxoalkanoates **IIIa**–**IIId** with *o*-phenylenediamine in ethanol at room temperature gave the corresponding 3-alkylquinoxalin-2(1*H*)-ones **IVa**–**IVd** in almost quantitative yield (Scheme 2). Using α,ω-dibromoalkanes instead of alkyl bromides we obtained diesters **Va**–**Vc** which reacted with 2 equiv of *o*-phenylenediamine to give 3,3′-(alkane-α,ω-diyl)bis[quinoxalin-2(1*H*)-ones] **VIa**–**VIc** (Scheme 3).

Scheme 2.



R = Et (**a**), Bu (**b**), C_8H_{16} (**c**), C_9H_{18} (**d**).

Scheme 3.



n = 2 (**a**), 3 (**b**), 4 (**c**).

EXPERIMENTAL

The melting points were determined on a Boetius melting point apparatus. The IR spectra were recorded on a Bruker Vector-22 spectrometer with Fourier transform from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker Avance-600 instrument at 600 MHz using the residual proton signal of the solvent as reference.

3-Ethylquinoxalin-2(1*H*)-one (IVa). A solution of 40.0 g (0.37 mol) of ethyl bromide in 100 ml of freshly distilled tetrahydrofuran was added dropwise over a period of 1 h under stirring to 8.8 g (0.37 mol) of magnesium turnings and 300 ml of THF. During the addition, the mixture became turbid and warmed up to the boiling point, so that the rate of addition of ethyl bromide was controlled to maintain the mixture slightly boiling. When the addition was complete, the mixture was stirred for 30 min at 60°C, cooled, and added dropwise under stirring to a solution of 53.0 g (0.36 mol) of diethyl oxalate (**I**) in 100 ml of THF, preliminarily cooled to –60°C. The mixture spontaneously warmed up, and its temperature was maintained below –15°C. The mixture was stirred for 2 h at –15°C, cooled to –30°C, and neutralized by quickly adding a solution of 65 ml of 6 N hydrochloric acid in 200 ml of water. The organic phase was separated, washed with water (2 × 100 ml), and dried over Na_2SO_4 or $MgSO_4$, and the aqueous phase was extracted with methylene chloride (3 × 50 ml). The extract was washed with water, combined with the THF solution, filtered, and evaporated. The residue was 47 g of a mixture of ethyl 2-oxobutanoate (**IIIa**) and diethyl oxalate (**I**), containing 80% of the former (according to the ^{1}H NMR data). It was dissolved in 400 ml of ethanol, 31 g (0.29 mol) of *o*-phenylenediamine was added to the solution, and the mixture was stirred for 6 h and left overnight (a solid separated in 5 min). The crystals were filtered off and washed with ethanol, the filtrate was poured into water and left overnight, and the precipitate was filtered off. Yield 93%, mp 192–194°C (from acetone); published data: mp 192°C [14], 198°C [12]). IR spectrum, ν, cm^{-1}: 2380–3220, 1660, 1605, 1570, 1500, 1490, 1430, 1160, 900, 720. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 t (3H, $CH_2C\mathbf{H}_3$, *J* = 7.4 Hz), 2.91 q (2H, $C\mathbf{H}_2CH_3$, *J* = 7.4 Hz), 7.30–7.58 m (3H, 6-H, 7-H, 8-H), 7.80 d (1H, 5-H, *J* =

7.9 Hz), 11.21 br.s (1H, NH). Found, %: C 68.75; H 5.97; N 16.25. $C_{10}H_{10}N_2$. Calculated, %: C 68.95; H 5.79; N 16.08.

3-Butylquinoxalin-2(1*H*)-one (IVb) was synthesized in a similar way. From 9.00 g (0.37 mol) of magnesium turnings, 50.7 g (0.37 mol) of 1-bromobutane, and 54.7 g (0.37 mol) of diethyl oxalate we obtained 49.0 g of a mixture of diethyl oxalate and compound **IIIb** (74% of the latter, according to the ^{1}H NMR data). Yield of **IVb** 88%, mp 158–160°C (from *i*-PrOH); published data: mp 156°C [14], 154–155°C [10, 15], 153–154°C [11]. IR spectrum, ν, cm^{-1}: 2500–3300, 1666, 1608, 1565, 1287, 1150, 624, 943, 893, 751, 706, 590, 469. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.93 t (3H, CH_3, J = 7.3 Hz), 1.33–1.45 m (2H, C**H**$_2$CH$_3$), 1.63–1.77 m (2H, C**H**$_2$-CH$_2$CH$_3$), 2.80 t (2H, 3-CH$_2$, J = 7.8 Hz), 7.33 d (1H, 8-H, J = 7.8 Hz), 7.36 d.d (1H, 6-H, J = 8.3, 7.3 Hz), 7.50 d.d (1H, 7-H, J = 7.8, 7.3 Hz), 7.91 d (1H, 5-H, J = 8.3 Hz), 12.08 br.s (1H, NH). Found, %: C 71.34; H 7.09; N 14.04. $C_{12}H_{14}N_2O$. Calculated, %: C 71.26; H 6.98; N 13.85.

3-Octylquinoxalin-2(1*H*)-one (IVc) was synthesized in a similar way. From 1.1 g (0.04 mol) of magnesium turnings, 8.2 g (0.04 mol) of 1-bromooctane, and 6.2 g (0.04 mol) of diethyl oxalate (**I**) we obtained 5.5 g of a mixture of initial diethyl oxalate and ethyl 2-oxodecanoate (**IIIc**), containing 70% of the latter (according to the ^{1}H NMR data). Yield of **IVc** 91%, mp 126–128°C (from EtOH); published data [14]: mp 126°C. IR spectrum, ν, cm^{-1}: 2715–3165, 1667, 1608, 1564, 1433, 1377, 1151, 941, 892, 750, 708, 590, 469. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.85 t (3H, CH_3, J = 6.9 Hz), 1.26–1.37 m (10H, CH_2), 1.64–1.75 m (2H, 3-CH$_2$C**H**$_2$), 2.77 t (2H, 3-CH$_2$, J = 7.55 Hz), 7.26 d.d.d (1H, 6-H, J = 7.6, 7.6, 1.3 Hz), 7.27 d (1H, 8-H, J = 7.3 Hz), 7.47 d.d.d (1H, 7-H, J = 7.6, 7.3, 0.8 Hz), 7.71 d (1H, 5-H, J = 7.8 Hz), 12.28 br.s (1H, NH). Found, %: C 74.18; H 8.18; N 10.84. $C_{16}H_{22}N_2O$. Calculated, %: C 74.05; H 8.13; N 10.98.

3-Nonylquinoxalin-2(1*H*)-one (IVd) was synthesized in a similar way. From 1.0 g (0.04 mol) of magnesium turnings, 8.3 g (0.04 mol) of 1-bromononane, and 5.9 g (0.04 mol) of diethyl oxalate (**I**) we obtained 5.1 g of a mixture of initial diethyl oxalate and ethyl 2-oxoundecanoate (**IIId**), containing 74% of the latter (according to the ^{1}H NMR data). Yield of **IVd** 96%, mp 132–133°C (from EtOH); published data [14]: mp 127°C. IR spectrum, ν, cm^{-1}: 2718–3310, 1667, 1609, 1600, 1561, 1470, 1432, 1152, 894, 757, 750, 710, 702, 589, 469. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.86 t (3H, CH_3, J = 6.80 Hz), 1.26–1.37 m (12H, CH_2), 1.65–1.76 m (2H, 3-CH$_2$-C**H**$_2$), 2.79 t (2H, 3-CH$_2$, J = 7.6 Hz), 7.28 d.d.d (1H, 6-H, J = 7.8, 7.7, 1.0 Hz), 7.29 d (1H, 8-H, J = 7.8 Hz), 7.48 d.d.d (1H, 7-H, J = 7.8, 7.7, 1.1 Hz), 7.71 d (1H, 5-H, J = 7.8 Hz). Found, %: C 74.46; H 8.88; N 10.28. $C_{17}H_{24}N_2O$. Calculated, %: C 74.33; H 8.81; N 10.33.

3,3′-(Butane-1,4-diyl)bis[quinoxalin-2(1*H*)-one] (VIa) was synthesized in a similar way. From 4.4 g (0.18 mol) of magnesium turnings, 20 g (0.09 mol) of 1,4-dibromobutane, and 27 g (0.18 mol) of diethyl oxalate (**I**) we obtained 16 g of a mixture containing initial diethyl oxalate and diethyl 2,7-dioxooctanedioate (**Va**) (12% of the latter, according to the ^{1}H NMR data). Yield of **VIa** 74%, mp >300°C (decomp., from DMSO). IR spectrum, ν, cm^{-1}: 2500–3200, 1662, 1610, 1562, 1486, 1502, 1433, 1345, 1139, 1107, 896, 705, 589. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.80–1.85 m (4H, 3-CH$_2$C**H**$_2$), 2.87 t (4H, 3-CH$_2$, J = 6.66 Hz), 7.22–7.32 m (2H, 6-H, 8-H), 7.48 d.d.d (2H, 7-H, J = 8.4, 7.2, 1.4 Hz), 7.70 d.d (2H, 5-H, J = 8.2, 1.4 Hz), 12.28 s (2H, NH). Found, %: C 70.26; H 5.38; N 16.03. $C_{20}H_{18}N_4O_2$. Calculated, %: C 69.35; H 5.24; N 16.17.

3,3′-(Pentane-1,5-diyl)bis[quinoxalin-2(1*H*)-one] (VIb) was synthesized in a similar way. From 3.0 g (0.12 mol) of magnesium turnings, 14.1 g (0.06 mol) of 1,5-dibromopentane, and 18.2 g (0.12 mol) of diethyl oxalate (**I**) we obtained 16.8 g of a mixture of initial diethyl oxalate and diethyl 2,8-dioxononanedioate (**Vb**) (54% of the latter, according to the ^{1}H NMR data). Yield of **VIb** 85%, mp 268–270°C (decomp., from DMSO). IR spectrum, ν, cm^{-1}: 2500–3500, 1663, 1612, 1563, 1500, 1431, 1348, 1290, 1152, 1114, 911, 868, 751, 707, 591. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.76–1.88 m (6H, CH_2), 2.82 t (4H, 3-CH$_2$, J = 7.6 Hz), 7.25–7.32 m (4H, 6-H, 8-H), 7.48 d.d.d (2H, 7-H, J = 8.4, 7.1, 1.4 Hz), 7.70 d (2H, 5-H, J = 7.9 Hz), 12.28 s (2H, NH). Found, %: C 69.76; H 5.68; N 15.71. $C_{22}H_{22}N_4O_2$. Calculated, %: C 69.98; H 5.59; N 15.55.

3,3′-(Hexane-1,6-diyl)bis[quinoxalin-2(1*H*)-one] (VIc) was synthesized in a similar way. From 3.0 g (0.12 mol) of magnesium turnings, 15.3 g (0.06 mol) of 1,6-dibromohexane, and 18.2 g (0.12 mol) of diethyl oxalate we obtained 16 g of a mixture containing initial diethyl oxalate (**I**) and diethyl 2,9-dioxodecanedioate (**Vc**) (60% of the latter, according to the ^{1}H NMR data). Yield of **VIc** 92%, mp 249–251°C (from DMSO). IR spectrum, ν, cm^{-1}: 2500–3500, 1658, 1557, 1498,

1429, 1347, 1286, 1148, 1109, 946, 878, 756, 704, 589. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35–1.50 m (4H, 3′-H, 4′-H), 1.70–1.80 m (4H, 2′-H, 5′-H), 2.80 t (4H, 1′-H, 6′-H, J = 7.6 Hz), 7.27 d.d (2H, 6-H, J = 8.0, 7.6 Hz), 7.29 d (2H, 8-H, J = 8.3 Hz), 7.48 d.d (2H, 7-H, J = 7.6, 7.6 Hz), 7.72 d (2H, 5-H, J = 7.8 Hz), 12.28 s (2H, NH). Found, %: C 70.76; H 5.88; N 14.83. $C_{22}H_{22}N_4O_2$. Calculated, %: C 70.57; H 5.92; N 14.96.

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