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3-(α-AZIDOALKYL)QUINOXALIN-2(1H)-ONES AND RELATED ALKYLQUINOXALINYL KETONES

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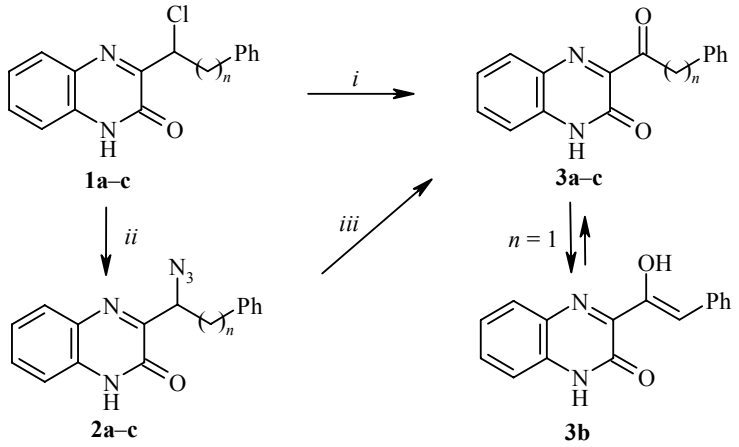
A convenient method has been developed for the synthesis of 3-alkanoyl- and 3-benzoyl-2-oxo-1,2-dihydroquinoxalines from the corresponding 3-(α-azidoalkyl)quinoxalines using acetic acid.

Keywords: 3-alkanoylquinoxalines, 3-(α-azidoalkyl)quinoxalines, Kornblum reaction.

The presence of a β-dicarbonyl and α-iminocarbonyl fragments in combination with other functional groups in 3-alkanoylquinoxalin-2(1H)-one molecules makes them promising key compounds in the synthesis of condensed heterocyclic systems *via* annelation of different heterocycles on the *a* and *b* sides of the quinoxaline [1-8]. The availability of alkanoylquinoxalin-2(1H)-ones containing in position 3 different alkyl fragments readily transformed to other functional groups opens up novel possibilities for the use of these hetaryl ketones in the synthesis of more complex and diverse pharmacologically interesting heterocycles.

The classical Kornblum reaction [9-11] is the oxidative dehydrohalogenation of primary and secondary alkyl halides to form the corresponding aldehydes or ketones in DMSO in the presence of bicarbonate, carbonate, or sodium acetate trihydrate. It is hindered when changing from iodides to chlorides and from primary derivatives to secondary [12] and is accompanied by side reactions [13] causing lowering of the yields of the target products. Hence to achieve good results nitrates [11] and tosylates [10, 13] were used instead of halides.



i Na_2CO_3, DMSO; *ii* NaN_3, DMSO; *iii* AcOH, **1**–**3** **a** *n* = 0, **b** *n* = 1, **c** *n* = 2

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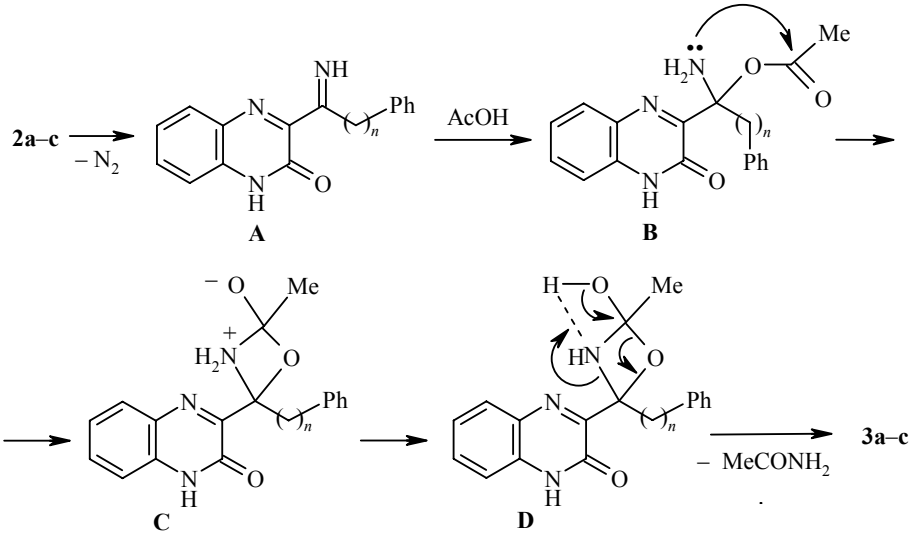
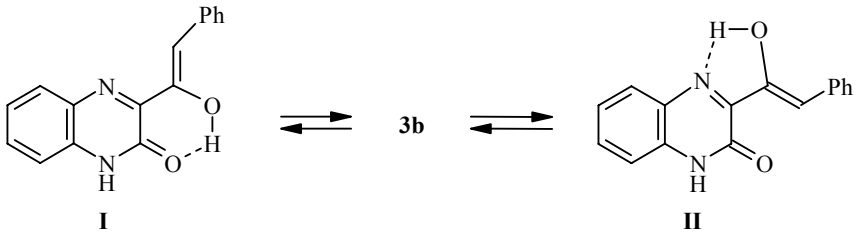
The use of this reaction in the synthesis of alkyl hetaryl ketones was not crowned with success (in contrast to the synthesis of aryl hetaryl ketones where high yields of the target products are achieved [14]). Independently of the 3-(α-chloroalkyl)quinoxaline used the reaction occurs to form many side and hard to separate products along with the target compound. Hence with the aim of preparing alkyl hetaryl ketones we have used not the 3-(α-haloalkyl)quinoxalines **1** but the 3-(α-azidoalkyl)quinoxalines **2** assuming that these compounds (similarly to 3-(α-azidobenzyl)quinoxaline **2a** [14]) are converted under the thermolysis conditions to the corresponding imines which subsequently hydrolyze with water present in AcOH to give ketones. We have found that refluxing 3-(α-azidoalkyl)quinoxalines **2** in glacial acetic acid or in a mixture of acetic anhydride and acetic acid (1 : 2) where traces of water are excluded gives high yields of the target ketones without any kind of admixture.

The formation of the alkylhetaryl ketones *via* refluxing the 3-(α-azidoalkyl)quinoxalin-2(1H)-ones **2a-c** in glacial acetic acid can be represented in the following way:



The reaction of AcOH with the intermediately formed imine **A** leads to the unstable quinoxaline derivative **C** containing 1,3-oxaazetidine ring. The intermediate **C** gives compound **D**, which eliminates a molecule of acetamide to form the target compounds **3a-c**.

Compound **3b** exists as a mixture of two tautomeric forms. As evident from the intensities of the methylene signals (ketone form) and olefin (enol form) protons in the ^{1}H NMR spectrum, the olefin predominates in this mixture (ratio of enol to keto forms 4 : 1). This is possibly due to stabilization of the given structure in DMSO-d_6 solution by intramolecular hydrogen bonding involving the carbamoyl oxygen atom to form a chelated structure with a six-membered ring **I** or of the imine nitrogen atom to form a chelated structure with a five-membered ring **II**.



The oxidative cleavage of 3-(α-azidobenzyl)quinoxalin-2(1H)-one **2a** in glacial acetic acid or its mixture with acetic anhydride occurs similarly but in this case the reaction product 3-benzoylquinoxalin-2(1H)-one (**3a**) precipitates from the reaction mixture cooled to room temperature as shining needle-like crystals with a yellowish coloration.

EXPERIMENTAL

The IR spectra of all of the compounds were recorded on a Bruker Vector-22 spectrometer using vaseline oil. ^{1}H NMR spectra were taken on a Bruker MSL-400 (400 MHz) spectrometer or Bruker AVANCE-600 (600 MHz) spectrometer. Chemical shifts are presented in ppm relative to TMS using it or residual signals from the corresponding solvent as internal standard. Melting points for the reaction products were taken on a Boetius block.

3-(α-Azidophenethyl)quinoxalin-2(1H)-one (2b). Sodium azide (0.26 g, 4.0 mmol) was added to a solution of 3-(α-chlorophenethyl)quinoxalin-2(1H)-one (1 g, 3.5 mmol) in DMSO (20 ml) and stirred at 35-40ºC for 4 h. The mixture was held at room temperature for about 15 h and then treated with distilled water. The precipitated crystals were filtered off. Yield 0.97 g (95%); mp 157-159ºC. IR spectrum (vaseline oil), ν, cm^{-1}: 487, 593, 889, 1143, 1438, 1496, 1560, 1663, 2118, 2715, 3061, 3100, 3154. ^{1}H NMR spectrum ($CDCl_3$ + DMSO-d_6), δ, ppm (*J*, Hz): 3.16 (1H, J_{ab} = 14.0, J_{ax} = 9.2, C$\underline{H_2}$C$_6$H$_5$); 3.38 (1H, J_{ab} = 14.0, J_{bx} = 5.3, C$\underline{H_2}$C$_6$H$_5$); 5.12 (1H, J_{ax} = 9.2, J_{bx} = 5.3, CHN_3); 7.24-7.39 (7H, m, C_6H_5 + H-6,8); 7.59 (1H, dd, *J* = 8.3, *J* = 7.0, H-7); 7.83 (1H, d, *J* = 8.3, H-5); 12.54 (1H, br. s, NH). Found, %: C 65.65; H 4.31; N 24.15. $C_{16}H_{13}N_5O$. Calculated, %: C 65.97; H 4.50; N 24.04.

3-(α-Azido-γ-phenylpropyl)quinoxalin-2(1H)-one (2c). Sodium azide (0.22 g, 3.3 mmol) was added to a solution of 3-(α-chloro-γ-phenylpropyl)quinoxalin-2(1H)-one (1 g, 3.3 mmol) in DMSO (20 ml) with gentle heating and stirring over 4 h. The mixture was held for about 15 h at room temperature and treated with distilled water in the ratio 1 : 5. The precipitated crystals were filtered off. Yield 0.95 g (93%); mp 211-213ºC. IR spectrum (vaseline oil), ν, cm^{-1}: 472, 593, 692, 713, 739, 760, 865, 907, 915, 1022, 1219, 1266, 1316, 1334, 1350, 1498, 1559, 1609, 1664, 2114, 2717, 3028, 3064, 3086. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.12-2.33 (m); 2.69-2.95 (4H, m, CH_2CH_2); 4.80-4.85 (1H, m, CHN_3); 7.10-7.35 (7H, m, C_6H_5 + H-6,8); 7.55 (1H, dd, *J* = 7.1, *J* = 6.8, H-7); 7.78 (1H, d, *J* = 7.1, H-5); 12.50 (1H, br. s, NH). Found, %: C 66.45; H 4.52; N 23.27. $C_{17}H_{15}N_5O$. Calculated, %: C 66.87; H 4.95; N 22.94.

Tautomeric Mixture of 3-(β-Hydroxystyryl)- and 3-Phenylacetylquinoxalin-2(1H)-ones (3b). A solution of the azido ketone **2b** (0.4 g, 1.4 mmol) in acetic acid (35 ml) was refluxed for 3 h. The precipitated crystals were filtered off. Yield 0.29 g (81%). The ratio of the ketone to enol form was calculated from the ^{1}H NMR spectrum using the integrated intensities of the methylene group protons (0.35) and the enol form vinyl proton (0.70). Mp 214-216ºC. M = 264. IR spectrum (vaseline oil), ν, cm^{-1}: 593, 689, 754, 1186, 1337, 1395, 1527, 1636, 1662, 3088, 3266. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 4.36 (2H, s, CH_2); 7.57 (1H, dd, *J* = 7.8, *J* = 7.3, H-7); 7.60 (1H, dd, *J* = 7.6, *J* = 7.6, H-7 ketone form); 7.65 (1H, s, C(OH)=CH); 7.23-7.40 (m), 7.83-7.90 (16H, m, 2C_6H_5, 2H-5, 2H-6, 2 H-8); 9.72 (1H, s, C(OH)=CH); 12.77 (1H, br. s, NH enol form); 12.78 (1H, br. s, NH ketone form). Found, %: C 72.52; H 4.31; 10.19. $C_{16}H_{12}N_2O_2$. Calculated, %: C 72.72; H 4.58; N 10.60.

3-Phenylpropanoylquinoxalin-4(5H)-one (3c). A solution of the azido ketone **2c** (1 g, 3.3 mmol) in acetic acid (35 ml) was refluxed for 3 h. The precipitated crystals were filtered off. Yield 0.58 g (64%). IR spectrum (vaseline oil), ν, cm^{-1}: 573, 587, 699, 753, 770, 920, 962, 945, 1147, 1293, 1402, 1495, 1609, 1656, 1717. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.00 (2H, t, *J* = 7.5, $CH_2C_6H_5$); 3.39 (2H, t, *J* = 7.5, CH_2CO); 7.20-7.40 (7H, m, C_6H_5 and H-6,8); 7.66 (1H, dd, *J* = 8.6, 7, H-7); 7.86 (1H, d, *J* = 8, H-5); 11.9 (1H, br. s, NH). Found, %: C 73.04; H 5.00; N 9.91. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.37; H 5.07; N 10.07.

3-Benzoylquinoxalin-2(1H)-one (3a). A solution of 3-(α-azidobenzyl)quinoxalin-2(1H)-one (0.5 g, 1.8 mmol) in acetic acid (35 ml) or a mixture of acetic acid (15 ml) and acetic anhydride (15 ml) was refluxed for 3 h and left overnight. The precipitated crystals were filtered off and dried in air to give compound **3a** (0.42 g, 93%). All of the characteristics were identical to literature data [14, 15].

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