Synthesis and Functionalization of 3-Ethylquinoxalin-2(1H)-one


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.kcn.ru

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Abstract—A new and effective procedure was developed for the synthesis of 3-ethylquinoxalin-2(1H)-one from o-phenylenediamine and ethyl 2-oxobutanoate. The latter was prepared by the Grignard reaction of diethyl oxalate with ethylmagnesium bromide or iodide. The ethyl group in 3-ethylquinoxalin-2(1H)-one can readily be converted into various functional groups: α-bromoethyl, α-thiocyanato, α-azidoethyl, α-phenylaminoethyl, acetyl, and bromoacetyl. The reaction of 3-(bromoacetyl)quinoxalin-2(1H)-one with thiourea and hydrazine-1,2-dicarbothioamide gives the corresponding 3-(2-amino-4-thiazolyl) derivatives.

We previously showed that 3-(α-chlorobenzyl)quinoxalin-2(1H)-one (I), which is readily available via reaction of 3-chloro-3-phenyl-2-oxopropionates with o-phenylenediamine, is a convenient polyfunctional reagent for the synthesis of various fused quinoxaline derivatives, such as thiazolo[3,4-a]-, imidazo[1,5-a]-, pyrrolo[1,2-a]-, pyrazolo[3,4-b]-, pyrano[5,6-b]-, and indolizino[2,3-b]quinoxalines [1–5]. The key factor in the formation of all these compounds is favorable arrangement of the α-chlorobenzyl group with respect to the endocyclic imino and carbamoyl moieties. Replacement of the chlorine atom by appropriate groups gives rise to structural fragments necessary for the subsequent ring closure at the a or b side of the pyrazine ring in the initial quinoxaline.

Replacement of the phenyl group in molecule I by methyl could considerably extend the synthetic potential due to ready transformation of the α-chloroethyl fragment into various functional groups. Therefore, the goal of the present work was to develop procedures for the preparation of 3-ethylquinoxalin-2(1H)-one (IIa) as a convenient intermediate product for the synthesis of various quinoxaline derivatives which are promising building blocks in the design of macroheterocyclic systems.

The only reported method for the synthesis of 3-ethylquinaxalin-2(1H)-one (IIa) includes three steps: (1) reaction of ethyl α-(ethoxalyl)propionate [6] with o-phenylenediamine, (2) alkaline hydrolysis of intermediate ethyl α-(2-hydroxyquinoxalin-3yl)propionate, and (3) decarboxylation of the acid thus formed [7]. The procedure based on oxidation of 3-alkyltetrahydroquinoxalin-2-ones formed by condensation of o-phenylenediamine with α-halo carboxylic acids also seems to be unreasonable: the yield of the target 3-alkylquinoxalin-2(1H)-ones ranges from 8 to 34% [8]. By analogy with the synthesis of 3-(α-chlorobenzyl)quinoxalin-2(1H)-one (I), one of the simplest procedures for the preparation of 3-(α-bromoethyl)-quinaxalin-2(1H)-one (III) may be that based on reaction of methyl 3-chloro-2-oxobutanoate with o-phenylenediamine [9]. However, unlike 3-chloro-3-phenyl-2-oxopropionates which are readily formed in high yields by the Darzens reaction of dichloroacetates with benzaldehyde [10], 3-chloro-2-oxobutanoates are very difficult to obtain in such a way because of numerous competing processes with participation of acetaldehyde used as electrophilic reagent.

Retrosynthetic analysis [11] shows that molecule IIa is built up from synthons A and B whose synthetic equivalents are, respectively, o-phenylenediamine and 2-oxobutanoic acid derivatives IV (Scheme 1). Among various methods for the preparation of 2-oxobutanoic acid derivatives IV, we selected the Grignard reaction...
of diethyl oxalate with ethylmagnesium bromide or iodide [12]. Taking into account that this reaction usually leads to formation of tertiary alcohols, it was necessary to find out temperature conditions, reactant ratio, and reaction time to force the process to be terminated at the stage of formation of adduct C [13] (Scheme 2). The subsequent decomposition of unstable adduct C should give highly reactive keto ester IV and halomagnesium alkoxide.

Scheme 2.

The resulting mixture containing diethyl oxalate and keto ester IV (without additional purification or separation) was brought into reaction with o-phenylenediamine to obtain quinoxaline IIa; here, the required amount of o-phenylenediamine was calculated from the $^1$H NMR spectrum of crude product IV. Insofar as the reactivity of ethyl 2-oxobutanoate is higher than that of diethyl oxalate, 3-ethylquinoxalin-2(1H)-one (IIa) was smoothly obtained at room temperature, and it contained no quinoxaline-2,3-dione impurity.

The structure of compound IIa was confirmed by elemental analysis and spectral methods, as well as by comparing with published data [6, 7]. 3-Ethylquinoxalin-2(1H)-one (IIa) can readily be alkylated at the nitrogen atom with ethyl bromide under standard conditions [14] (in boiling dioxane in the presence of potassium hydroxide) to afford 1,3-diethylquinoxalin-2(1H)-one (IIb) (no O-alkyl derivative V is formed; Scheme 3). The structure of N-ethylquinoxalinone IIb is confirmed by the presence in its IR spectrum of absorption bands due to stretching vibrations of C=N and C=O bonds at 1602 and 1655 cm$^{-1}$, respectively; these bands are displaced to higher frequencies by 5 and 15 cm$^{-1}$, respectively, relative to the corresponding bands in the spectrum of initial quinoxalinone IIa. The $^1$H NMR spectrum of IIb contained signals from protons in the benzo fragment at $\delta$ 7.25–7.82 ppm and protons of two nonequivalent methylene groups at $\delta$ 2.95 (CCH$_2$) and 4.29 ppm (NCH$_2$).

Functionalization of quinoxalinone IIa was performed via substitution of the bromine atom in $\alpha$-bromoethyl derivative III by the action of various nucleophiles. Compound III is readily obtained by bromination of IIa in acetic acid; however, this reaction is accompanied by side bromination at the aromatic ring. In order to avoid this process, we carried out bromination of IIa under mild conditions, by treatment of a suspension of IIa in dioxane with bromine at 12–15°C; in this case, the brominating agent is a complex of bromine with dioxane. As a result, quinoxalinone III thus obtained contained no impurity of dibromo derivative. The bromine atom in III is readily replaced by such nucleophiles as KSCN, NaN$_3$, and PhNH$_2$ in DMSO to give the corresponding 3-($\alpha$-X-ethyl)quinoxalines VI–VIII (Scheme 4).

Compounds VI–VIII displayed in the IR spectra absorption bands typical of the quinoxalin-2-one system and those corresponding to vibrations of the thiocyanato group (2160 cm$^{-1}$, VI), azido group (2135 cm$^{-1}$, VII), and amino group (3300 cm$^{-1}$, VIII). The $^1$H NMR spectra of $\alpha$-substituted 3-ethylquinoxalin-2-one derivatives VI–VIII contained signals from the CH and CH$_3$ protons of the substituent in position 3, which appeared as a quartet and doublet,