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Darzens Reaction in the Synthesis of 3-(α-Chloroalkyl)quinoxalin-2(1*H*)-ones

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Abstract—A two-stage method was developed for the synthesis of 3-(α-chloroalkyl- and α-chlorophenylalkyl)-quinoxalin-2(1*H*)-ones proceeding from methyl chloroalkyl- and chlorophenylalkylpyruvates obtained by Darzens reaction from methyl dichloroacetate and appropriate aldehydes in the presence of *t*-BuOK.

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The undying interest to quinoxalines and their derivatives is primarily due to the appearance of their fragments in the structure of versatile biologically and pharmacologically important compounds, in particular, of agonists and antagonists of various receptors [1–4], of substances endowed with high antimicrobial action [5, 6] etc. [7–9].

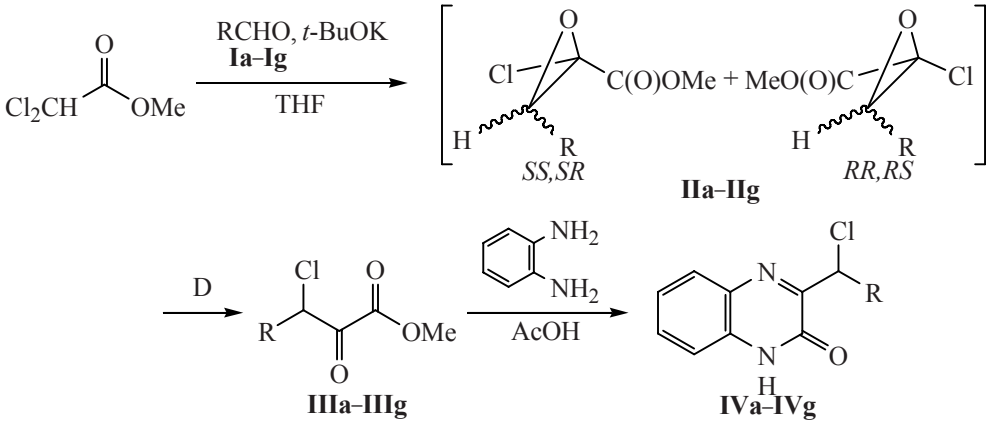
Among the numerous procedures for the synthesis of quinoxaline system the most commonly applied is the condensation of *ortho*-phenylenediamine with various substances supplying two-carbon fragments, like α-dicarbonyl compounds [10–25], α-halocarbonyl compounds [26, 27], and α-dihalides [28–30]. Besides the building up of the quinoxaline ring is often performed in reactions catalyzed by metal complexes thus extending the range of suitable two-carbon synthons. For instance, α-hydroxyketones undergo an oxidative cyclization with *o*-phenylendiamine in the presence of transition metals (Mn, Pd, Ru, Cu) giving quinoxalines [31–33], and ketones with a methylene group react with the *o*-phenylendiamine in the presence of PEG-400 [34]. Epoxides also are employed as two-carbon synthons in the reaction with *o*-phenylendiamine catalyzed by bismuth [35]. Still the dicarbonyl compounds are the most active: Reactions involving them are as a rule one-stage processes, give high yields, and do not require severe conditions and expensive catalysts.

In the published research the reactions with dicarbonyl compounds were limited to dimethyl oxalate [18, 19], methyl aryl or diaryl ketones [12–14], and aroyl or heteroylpyruvic acids [10, 11].

We developed efficient preparation procedures for 3-(α-chloroalkyl- and α-chlorophenylalkyl)quinoxalin-2(1*H*)-ones based on esters of chloroalkyl- and chlorophenylalkylpyruvic acids. The required α-oxoesters **III** can be obtained by Darzens reaction from methyl dichloroacetate and various aldehydes **I** (see the scheme). The variation of aldehydes **Ia–Ig** used in the reaction makes it possible to introduce into the position *3* of the quinoxalin-2(1*H*)-one substituents differing in the length, in the character and possessing a chlorine atom in the α-position.

The reaction of methyl dichloroacetate with aldehydes **Ia–Ig** in the presence of *t*-BuOK in THF proceeded with the formation of oxiranes **II**, and the optimum temperature of the reaction with aldehydes **Ic–Ig** proved to be –10°C, and with aldehydes **Ia** and **Ib** , –40°C. The reaction occurred stereoselectively affording predominantly a single diastereomer [36], and the amount of the minor isomer by the ^{1}H NMR data did not exceed 2–3%. The thermal isomerization of oxiranes **IIa–IIg** diastereomers at 180°C provided the desired chloropyruvates **IIIa–IIIg** in nearly quantitative yields. The characteristic indication of the isomerization of oxiranes **IIa–IIg** into chloropyruvates **IIIa–IIIg** is the downfield shift of the signal of methine protons in the ^{1}H NMR spectra by ~1.5 ppm to the region characteristic of chloropyruvates

Scheme.



R = CH_2Ph (**a**), $(CH_2)_2Ph$ (**b**), Et (**c**), Pr (**d**), $(CH_2)_5CH_3$ (**e**), $(CH_2)_6CH_3$ (**f**), $(CH_2)_9CH_3$ (**g**).

with an aliphatic substituent (~5.0 ppm).

Chloropyruvates **IIIa–IIIg** were used without additional purification in the reaction with *o*-phenylenediamine. The synthesis of 3-(α-chloroalkyl)quinoxalin-2(1*H*)-ones **IVa–IVg** was carried out at room temperature in acetic acid.

IR spectra of all obtained chloroquinoxalines **IVa–IVg** are characterized by the presence of the absorption band of the C=O stretching vibrations at the frequency 1666 ± 5 cm^{-1} and of NH stretching vibrations in the region 2500–3200 cm^{-1}. ^1H NMR spectra alongside the signals of aromatic protons in the region 7.17–7.83, singlet signal of the carbamoyl NH group in the region 12.47–12.65, and multiplets of the aromatic protons in the range 0.89–3.64 contain a doublet of doublets signal of the methine proton at 5.39–5.72 ppm. In the spectrum of compound **IVa** the protons of the group $CHClCH_2$ appeared as signals of *ABX* system.

EXPERIMENTAL

Melting points were measured on a Boëtius heating block. IR spectra were recorded on a Fourier spectrophotometer Bruker Vector-22 from mulls in mineral oil. ^1H NMR spectra were registered on a spectrometer Bruker MSL-400 at operating frequency 400.13 MHz using the signal of residual protons of the deuterated solvents as reference.

Quinoxalines IVa–IVg. *General procedure.* To a mixture of aldehyde **Ia–Ig** and methyl dichloroacetate in anhydrous THF while stirring in an atmosphere of dry argon at cooling to –53...–55 (**Ia** or **Ib**) or to –10°C [37] (**Ic–Ig**) was slowly added an equimolar quantity of powdered *t*-BuOK, the reaction mixture was kept for 2 h at–40...–50°C (**Ia** or **Ib**) or at –5...–10°C (**Ic–Ig**), then it was warmed to room temperature and left standing for 10 h. Then the reaction mixture was washed with NaCl solution, extracted with toluene (3 × 50 ml). The extract was dried with $MgSO_4$ and evaporated in a vacuum of a water-jet pump. Then the residue was heated on an oil bath to 180°C for 2 h in a vacuum of a water-jet pump. The obtained reaction mixture was dissolved in acetic acid, the powder of *o*-phenylendiamine was added in an amount calculated from the data of ^1H NMR spectrum, the mixture was stirred for 5 h, the separated crystals were filtered off and washed with acetic acid.

3-(α-Chlorophenylethyl)quinoxalin-2(1*H*)-one (IVa) was obtained from 5 g (0.022 mol) of ester **IIIa** and 2.38 g (0.022 mol) of *o*-phenylendiamine. Yield 5.12 g (82%), mp 199–200°C. IR spectrum, ν, cm^{-1}: 3157, 3065, 1661, 1609, 1599, 1577, 1498, 1482, 1432, 1031, 907, 761, 755, 709, 698, 589, 503. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.44 d.d (1H, CH_2Ph, J_{AB} 13.93, J_{AX} 7.96 Hz), 3.69 d.d (1H, CH_2Ph, J_{AB} 13.93, J_{BX} 6.97 Hz), 5.67 d.d (1H, CHCl, J_{AB} 13.93 Hz), 7.20 d.d.d (1H, H^6, *J* 7.29, 6.31, 1.99 Hz), 7.25–7.35 m (5H, C_6H_5), 7.37 d (1H, H^8, *J* 7.96 Hz), 7.57 d.d.d (1H, H^7, *J* 8.30, 7.30, 1.32 Hz), 7.83 d (1H, H^5, *J* 8.63 Hz), 12.48 br.s (1H, NH). Found, %: C 67.31; H 4.45; Cl 12.38; N 9.97. $C_{16}H_{13}ClN_2O$. Calculated, %: C 67.49; H 4.60; Cl 12.45; N 9.84.

3-(α-Chloro-γ-phenylpropyl)quinoxalin-2(1*H*)-one (IVb) was obtained from 5 g (0.021 mol) of ester **IIIb** and 2.25 g (0.021 mol) of *o*-phenylendiamine. Yield

5.32 g (85%), mp 201–203°C. IR spectrum, ν, cm^{-1}: 3067, 3021, 2720, 1671, 1608, 1560, 1429, 1289, 906, 764, 751, 738, 701, 586. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.75–2.83 m, 2.88–2.94 m (4H, CH_2CH_2), 5.40–5.45 m (1H, CHCl), 7.20–7.40 m (7H, Ph + H^6 and H^8), 7.60 d.d (1H, H^7, *J* 7.96, 7.32 Hz), 7.82 d (1H, H^5, *J* 7.96 Hz), 12.48 br.s (1H, NH). Found, %: C 68.13; H 4.93; Cl 11.75; N 9.55. $C_{17}H_{15}ClN_2O$. Calculated, %: C 68.34; H 5.06; Cl 11.87; N 9.38.

3-(α-Chloropropyl)quinoxalin-2(1*H*)-one (IVc) was obtained from 0.3 g (2 mmol) of ester **IIIc** and 0.20 g (2 mmol) of *o*-phenylendiamine. Yield 0.34 g (77%), mp 209–211°C. IR spectrum, ν, cm^{-1}: 3107, 2718, 1668, 1611, 1559, 1502, 1346, 910, 761, 590. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.07 t (3H, CH_3, *J* 7.3 Hz), 2.18–2.34 m (2H, CH_2), 5.40 d.d (1H, CHCl, *J* 8.24 Hz), 7.34–7.40 m (2H, H^6, H^8), 7.61 d.d.d (1H, H^7, *J* 8.08, 7.30, 1.24 Hz), 7.83 d.d (1H, H^5, *J* 7.76, 0.96 Hz). Found, %: C 59.10; H 4.76; Cl 15.77; N 12.67. $C_{11}H_{11}ClN_2O$. Calculated, %: C 59.33; H 4.98; Cl 15.92; N 12.58.

3-(α-Chlorobutyl)quinoxalin-2(1*H*)-one (IVd) was obtained from 1.46 g (8 mmol) of ester **IIId** and 0.88 g (8 mmol) of *O*-phenylendiamine. Yield 1.40 g (74%), mp 205–206°C. IR spectrum, ν, cm^{-1}: 2718, 1666, 1609, 1559, 1503, 907, 759, 711, 591. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.98 t (3H, CH_3, *J* 7.52 Hz), 1.40–1.63 m (2H, CH_2CH_3), 2.17–2.25 m (2H, CH_2CHCl), 5.47 d.d (1H, CHCl, *J* 7.68, 6.96 Hz), 7.34–7.40 m (2H, H^6, H^8), 7.61 d.d.d (1H, H^7, *J* 8.24, 7.16, 1.12 Hz), 7.83 d.d (1H, H^5, *J* 7.68, 0.72 Hz), 12.65 br.s (1H, NH). Found, %: C 60.70; H 5.42; Cl 14.87; N 11.95. $C_{12}H_{13}ClN_2O$. Calculated, %: C 60.89; H 5.54; Cl 14.98; N 11.83.

3-(α-Chloroheptyl)quinoxalin-2(1*H*)-one (IVe) was obtained from 0.3 g (1 mmol) of ester **IIIe** and 0.15 g (1 mmol) of *o*-phenylendiamine. Yield 0.25 g (70%), mp 188–190°C. IR spectrum, ν, cm^{-1}: 2717, 1666, 1609, 1560, 1502, 1430, 903, 756, 592. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.90 t (3H, CH_3, *J* 6.42 Hz), 1.29–1.57 m [8H, $(CH_2)_4$], 2.15–2.27 m (2H, CH_2CHCl), 5.45 d.d (1H, CHCl, *J* 6.6, 6.6 Hz), 7.33–7.40 m (2H, H^6, H^8), 7.61 d.d (1H, H^7, *J* 8.08, 7.32 Hz), 7.82 d (1H, H^5, *J* 8.04 Hz), 12.64 br.s (1H, NH). Found, %: C 64.48; H 8.72; Cl 12.57; N 10.15. $C_{15}H_{19}ClN_2O$. Calculated, %: C 64.63; H 6.87; Cl 12.72; N 10.05.

3-(α-Chlorooctyl)quinoxalin-2(1*H*)-one (IVf) was obtained from 0.9 g (4 mmol) of ester **IIIf** and 0.41 g (4 mmol) of *o*-phenylendiamine. Yield 0.88 g (75%), mp 173–175°C. IR spectrum, ν, cm^{-1}: 2720, 1666, 1610, 1557, 1503, 1349, 903, 757, 591. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.89 t (3H, CH_3, *J* 6.96 Hz), 1.28–1.54 m [10H, $(CH_2)_5$], 2.13–2.29 m (2H, CH_2CHCl), 5.45 d.d (1H, CHCl, *J* 6.24, 6.2 Hz), 7.34–7.38 m (2H, H^6, H^8), 7.60 d.d.d (1H, H^7, *J* 7.88, 7.68, 1.48 Hz), 7.82 d.d (1H, H^5, *J* 7.68, 0.72 Hz), 12.64 br.s (1H, NH). Found, %: C 65.48; H 7.12; Cl 12.01; N 9.75. $C_{16}H_{21}ClN_2O$. Calculated, %: C 65.63; H 7.23; Cl 12.11; N 9.57.

3-(α-Chloroundecyl)quinoxalin-2(1*H*)-one (IVg) was obtained from 1.4 g (5 mmol) of ester **IIIg** and 0.55 g (5 mmol) of *o*-phenylendiamine. Yield 1.27 g (76%), mp 168–170°C. IR spectrum, ν, cm^{-1}: 3104, 2717, 1666, 1609, 1558, 1502, 1239, 908, 758, 592. ^{1}H NMR spectrum (DMSO-d_6 + $CDCl_3$), δ, ppm: 0.86 t (3H, CH_3, *J* 6.97 Hz), 1.23–1.54 m [16H, $(CH_2)_8$], 2.13–2.27 m (2H, CH_2CHCl), 5.39 d.d (1H, CHCl, *J* 6.24, 6.24 Hz), 7.27 d.d.d (1H, H^6, *J* 7.52, 7.52, 1.1 Hz), 7.34 d.d (1H, H^8, *J* 8.07, 0.73 Hz), 7.49 d.d.d (1H, H^7, *J* 7.88, 7.52, 1.1 Hz), 7.76 d.d (1H, H^5, *J* 8.07, 0.74 Hz), 12.52 br.s (1H, NH). Found, %: C 67.98; H 8.02; Cl 10.41; N 8.50. $C_{19}H_{27}ClN_2O$. Calculated, %: C 68.14; H 8.13; Cl 10.59; N 8.36.

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