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Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on her jubilee

2-Alkoxypropenals as Synthetic Equivalents of Methylglyoxal in the Synthesis of Heterocycles

N. A. Keiko, N. V. Vchislo, and L. I. Larina

Favorskii Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia
e-mail: keiko@irioch.irk.ru

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Abstract—One-pot synthesis of 2-methylquinoxaline, 3-hydroxy-2-methylimidazo[1,2-*a*]pyridine, and 2-methyl-3,7-dihydroimidazo[1,2-*a*]pyrazin-3-one via cycloaddition of N,N-binucleophilic *o*-phenylenediamine, 2-aminopyridine, and 2-aminopyrazine, respectively, to methylglyoxal generated *in situ* by hydrolysis of 2-alkoxypropenals is reported for the first time. Thus 2-alkoxypropenals in weakly acidic medium (25–80°C, 1–4 h) are convenient synthetic equivalents of methylglyoxal in the synthesis of heterocyclic compounds.

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Unlike acrolein, 2-alkoxypropenals characteristically undergo facile hydration of the C=C bond in acid medium according to Markovnikov with formation of methylglyoxal (2-oxopropanal) [1]. The latter is a strong endogenous bielectrophile generated *in vivo* by mammalian cells [2–4], some microorganisms [5–7], and plants [8]. Methylglyoxal participates in numerous biochemical transformations and acts as low-molecular-weight cell growth regulator which inhibits cell division [7, 9] and favors cell death [5, 10]. Researchers' interest in the properties of methylglyoxal and its role in biological processes continuously increases [11].

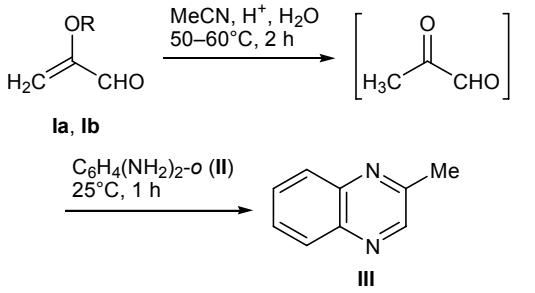
Methylglyoxal is used as starting compound in the synthesis of various heterocycles, in particular β-carbolines [12], dihydroimidazoles and their derivatives [13], functionalized pyrimidines [14], dihydropyrazines [3], quinoxalines [15], and imidazopyrazines [16]. Some of these were found to be formed in living cells [12, 17], as well as in foods [8, 12, 14] and drinks [18]. In biochemistry, the concentration of methylglyoxal in blood serum is determined by converting it into 2,3-diphenyl-2,3-dihydropyrazine [19] or dihydropyrazine [3]. However, detection of methylglyoxal and tracing of its transformation constitute a fairly difficult problem, for its concentration in biological liquids amounts to nanomoles per liter, e.g., 100 nM in blood plasma of healthy humans [16, 20]. Therefore, it is necessary to extend the series of methylglyoxal derivatives that could be used as new reference compounds in the monitoring of biological substrates.

Apart from fundamental research, heterocyclic compounds derived from methylglyoxal are used in fine organic synthesis [21]. Quinoxaline heteroring constitutes a structural fragment of a number of biologically active compounds and drugs exhibiting antibacterial, antitumor, and antiviral activity [22, 23]. Quinoxaline derivatives were recently reported as efficient electroluminescent materials [24] and fluorescent dyes [25]. Imidazopyrazinones were shown to act as potential antioxidants [26]. 3-Hydroxy-2-methylimidazo[1,2-*a*]pyridine turned out to be active toward some enzymes, in particular toward *Oplophorus* and *Cypridina luciferases*) [27].

Commercially available methylglyoxal in the form of a 40–50% aqueous solution contains a lot of impurities, and it cannot be used as reference compound without preliminary purification which is difficult because of its high reactivity and strong tendency to undergo polymerization [17]. Methylglyoxal in solution may exist as different species (mono- and dihydrates, dimers and trimers, and enol tautomers) [28] whose ratio depends on the solvent, temperature, concentration of water, and pH and strongly affects the reaction direction and yield.

In continuation of our studies on the properties of 2-alkoxypropenals as synthetic equivalents of methylglyoxal [1, 29], in the present work we examined the possibility of using these compounds in the synthesis of some fused heterocycles which were obtained previously from aqueous methylglyoxal. The hydrolysis of aldehydes **Ia** and **Ib** in the presence of HCl, followed by treatment with an equimolar amount of *o*-phenylenediamine (**II**), gave 2-methylquinoxaline (**III**) in 48–61% yield as a result of condensation at both carbonyl groups of methylglyoxal (Scheme 1). Thus, unlike the reaction of 2-alkoxypropenals with *o*-phenylenediamine under basic conditions, which afforded 2-(1-alkoxyvinyl)benzimidazoles [30], the proposed procedure ensures preparation of 2-methylquinoxaline from a different initial compound than methylglyoxal (cf. [31]).

Scheme 1.

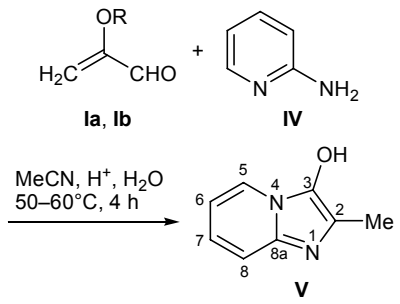


R = Et (**a**), Me (**b**).

The reaction of 2-alkoxypropenals **Ia** and **Ib** with equimolar amounts of 2-aminopyridine (**IV**) and water in the presence of HCl smoothly afforded 2-methylimidazo[1,2-*a*]pyridin-3-ol (**V**), which was isolated in 50% yield after recrystallization from methanol (Scheme 2). In this case, there was no need of preliminary hydrolysis of aldehydes **Ia** and **Ib**.

Compound **V** showed in the two-dimensional $^{1}H–^{15}N$ NMR spectrum a cross peak between N^{1} (δ_N –141.2 ppm) and protons in the methyl group, while the N^{4} nucleus (δ_N –180.2 ppm) displayed couplings with 5-H, 6-H, and 8-H. These findings, in combination with the ^{1}H and ^{13}C NMR data, unambiguously confirmed the assumed enol structure of **V**.

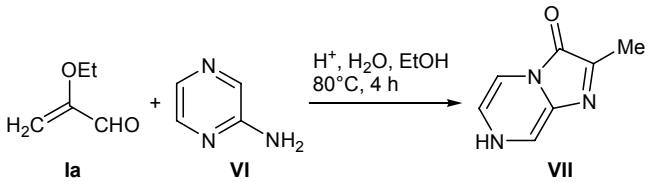
Scheme 2.



R = Et (**a**), Me (**b**).

According to published data, methylglyoxal reacts with 2-aminopyrazine [16] under argon in ethanol in the presence of 37% hydrochloric acid at room temperature (18 h) or at 80°C (4 h) [26] to produce 2-methyl-3,7-dihydroimidazo[1,2-*a*]pyrazin-3-one as hydrochloride. We found that the reaction of 2-ethoxypropenal (**Ia**) with 2-aminopyrazine (**VI**) in ethanol in the presence of 29% aqueous HCl at 80°C yields 70% of 2-methyl-3,7-dihydroimidazo[1,2-*a*]pyrazin-3-one (**VII**) in 4 h (Scheme 3).

Scheme 3.



To conclude, we have shown that fused heterocyclic compounds, which were previously available only with the use of methylglyoxal, can be synthesized by reaction of 2-alkoxypropenal with *o*-phenylenediamine, 2-aminopyridine, and 2-aminopyrazine in weakly acidic aqueous medium.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100.6 MHz, respectively, using hexamethyldisiloxane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Hewlett Packard 5971A mass-selective detector coupled with an HP 5890 gas chromatograph (Ultra-2 column, 5% of phenylmethylsilicone; injector temperature 250°C, oven temperature programming from 70 to 280°C at a rate of 20 deg/min). The melting points were measured on a Micro-Hot-Stage PolyTherm A instrument (Wagner and Munz). The elemental compositions were determined on a Thermo Fisher Scientific FlashEA 1112 automatic analyzer. Column chromatography was performed on silica gel 60 (70–200 mesh, Merck). Initial 2-alkoxypropenals were synthesized according to [32].

Reaction of 2-ethoxypropenal (Ia) with *o*-phenylenediamine in the presence of HCl. Concentrated hydrochloric acid, 0.5 ml, was mixed with 1 ml of

acetonitrile, 0.04 g of that mixture and 0.002 g of hydroquinone were dissolved in 0.18 g (10 mmol) of water, the solution was heated to 55°C, 0.3 g (3 mmol) of aldehyde **Ia** was added, and the mixture was heated for 50 min. The mixture was cooled to 25°C, $MgSO_4$ and a solution of 0.36 g (3 mmol) of *o*-phenylenediamine in 2 ml of acetonitrile were added, and the mixture was stirred for 1 h at room temperature and filtered from $MgSO_4$. According to the ^{1}H NMR data, the mixture contained 80% of **III**. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (9:1) as eluent to isolate 0.20 g (48%) of 2-methylquinoxaline (**III**) as a dark red liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.77 s (3H, CH_3), 7.71 m (2H, 6-H, 7-H), 8.01 d (1H, 5-H, J = 8.0 Hz), 8.06 d (1H, 8-H, J = 8.0 Hz), 8.73 s (1H, 3-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.3 (CH_3), 127.4, 127.5, 127.9, 128.7, 139.7 (C^2), 144.7 (C^3), 152.5 and 155.9 (C^4, C^{8a}). Mass spectrum, *m*/*z* (I_{rel}, %): 144 (100) $[M]^+$, 129 (1) $[M - CH_3]^+$, 117 (76) $[M - CCH_3]^+$, 104 (1), 90 (8), 76 (31), 50 (14). Found, %: C 74.91; H 5.31; N 18.98. $C_9H_8N_2$. Calculated, %: C 74.97; H 5.59; N 19.43. *M* 144.17.

Reaction of 2-methoxypropenal (Ib) with *o*-phenylenediamine in the presence of HCl. Concentrated hydrochloric acid, 0.5 ml, was mixed with 1 ml of acetonitrile, 0.05 g of that mixture and 0.002 g of hydroquinone were dissolved in 0.144 g (8 mmol) of water, the solution was heated to 55°C, 0.7 g (8 mmol) of aldehyde **Ib** was added, and the mixture was heated for 50 min. After cooling to 25°C, $MgSO_4$ and a solution of 0.89 g (8 mmol) of *o*-phenylenediamine in 2 ml of acetonitrile were added, and the mixture was stirred for 1 h at room temperature and filtered from $MgSO_4$. According to the ^{1}H NMR data, the mixture contained 80% of compound **III**. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using hexane–ethyl acetate (9:1) as eluent to isolate 0.7 g (61%) of 2-methylquinoxaline (**III**) as a dark red liquid whose ^{1}H and ^{13}C NMR spectra fully coincided with those given above.

Reaction of 2-ethoxypropenal (Ia) with 2-aminopyridine (IV) in the presence of HCl. Aldehyde **Ia**, 0.75 g (7.5 mmol), was dissolved in 5 ml of acetonitrile, 0.135 g (7.5 mmol) of water, 0.07 g (0.55 mmol) of 28.6% aqueous HCl (0.73 mol %), and 0.7 g (7.5 mmol) of 2-aminopyridine were added, and the mixture (pH 6) was heated for 4 h at 50–60°C. The mixture was dried over $MgSO_4$, neutralized with K_2CO_3, and filtered, and the solvent was removed under reduced pressure to isolate compound **V** in 60% yield (^{1}H NMR). Recrystallization from methanol gave 0.52 g (47%) of 2-methylimidazo[1,2-*a*]pyridin-3-ol (**V**) as orange crystals with mp 149°C; published data [33]: mp 148–151°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.22 s (3H, CH_3), 6.81 t (1H, 7-H, J = 6.6 Hz), 7.18 t (1H, 6-H, J = 8.8 Hz), 7.48 d (1H, 8-H, J = 8.8 Hz), 7.82 d (1H, 5-H, J = 6.6 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.8 (CH_3), 111.1 (C^8), 116.2 (C^6), 118.5 (C^2), 123.0 (C^7), 123.4 (C^5), 136.5 (C^3), 141.2 (C^{8a}). ^{15}N NMR spectrum (DMSO-d_6), δ_C, ppm: –141.2 (N^1), –180.2 (N^4). Found, %: C 64.88; H 5.70; N 18.75. $C_8H_8N_2O$. Calculated, %: C 64.85; H 5.44; N 18.91.

Reaction of 2-methoxypropenal (Ib) with 2-aminopyridine (IV) in the presence of HCl. Aldehyde **Ib**, 0.25 g (2.9 mmol), was dissolved in 2 ml of acetonitrile, 0.05 g (2.8 mmol) of water, 0.015 g (0.1 mmol) of 28.6% aqueous HCl, and 0.27 g (2.9 mmol) of 2-aminopyridine were added, and the mixture (pH 6) was heated for 4 h at 50–60°C. The mixture was dried over $MgSO_4$, neutralized with K_2CO_3, and filtered, and the solvent was removed from the filtrate under reduced pressure. Yield of **V** 60% (^{1}H NMR). Recrystallization from methanol gave 0.215 g (50%) of **V**. Its ^{1}H and ^{13}C NMR spectra were identical to those given above.

Reaction of 2-ethoxypropenal (Ia) with 2-aminopyrazine (VI) in the presence of HCl. 2-Ethoxypropenal (**Ia**), 0.2 g (2 mmol), and 28.6% aqueous HCl, 0.175 g (1.37 mmol), were added to 0.13 g (1.3 mmol) of 2-aminopyrazine (**VI**) in 8 ml of ethanol, and the mixture was heated for 4 h at 80°C. The solvent was removed under reduced pressure, and the residue was recrystallized from methanol. Yield of 2-methyl-3,7-dihydroimidazo[1,2-*a*]pyrazin-3-one (**VII**) 0.13 g (68%), mp 251°C; published data [33]: mp 243°C. The spectral parameters of the product were consistent with those given in [26]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.07 s (3H, CH_3), 7.73 d (1H, 6-H, J = 5.3 Hz), 8.27 d (1H, 5-H, J = 5.3 Hz), 8.98 s (1H, 8-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.07 (CH_3), 114.5 (C^5), 119.5 (C^6), 129.0 (C^{8a}), 130.3 (C^8), 137.7 (C^2), 143.2 (C^3). Found, %: C 56.46; H 4.66; N 27.92. $C_7H_7N_3O$. Calculated, %: C 56.36; H 4.73; N 28.18.

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