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Mendeleev Commun., 2016, **26**, 431–433
Mendeleev Communications

Hydrolysis of (*Z*)-2-alkoxy-3-arylpropenals as a short-cut to benzylglyoxals

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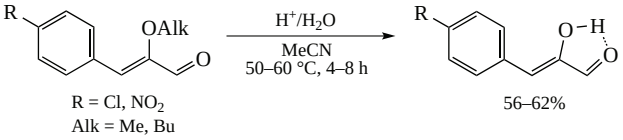
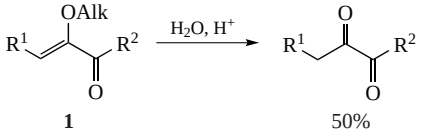
DOI: 10.1016/j.mencom.2016.09.023

Hydrolysis of the C=C bond in 2-alkoxy-3-aryl(hetaryl)-propenals, depending upon substituents in the molecule, can proceed according to Markovnikov or Michael rule or with heterolytic opening of the cycle (in the case of 2-alkoxy-3-furylpropenal). Hydrolysis of 3-phenyl substituted alkoxy-propenals bearing electron-withdrawing substituents (Cl, NO_2) in the *p*-position has allowed a method for the preparation of corresponding benzylglyoxals (stable in enol form) to be developed.



2-Alkoxy(aryloxy)propenals represent a poorly studied, but structurally diverse family of secondary metabolites of plants[1(*a*),(*b*)] and animals.[1(*c*)] Unlike acrolein, 2-alkoxypropenals **1** ($R^1 = R^2 = H$) are capable of adding water molecule according to Markovnikov rule leading finally to methylglyoxal (2-oxopropanal) (Scheme 1).[2] In 1965, it was shown that similar hydrolysis is inherent in β-aryl substituted α-methoxy-α,β-unsaturated ketones and acids **1** (see Scheme 1, R^1, $R^2 \neq H$).[3] However, it remains unclear whether the corresponding β-arylaldehydes (R^1 = Ar, R^2 = H) tolerate this reaction.

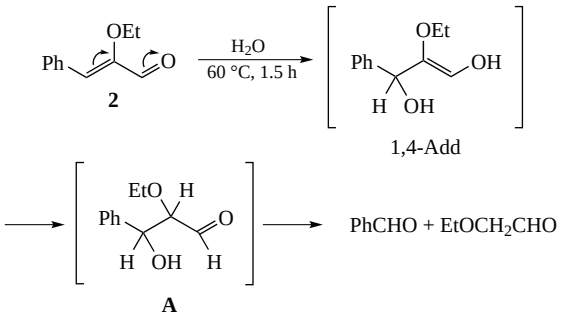


Scheme 1

Earlier we reported[4] that, contrary to compounds **1**, 2-ethoxy-3-phenylpropenal **2** undergoes hydrolysis in acidic medium according to Michael rule (1,4-addition). Subsequent retro-aldol decomposition of the intermediate **A** gives benzaldehyde (^{1}H NMR), whose content in the reaction mixture grows in time (Scheme 2). Similar direction of the C=C bond hydrolysis was observed while attempting to convert 2-methoxy-3-(2-pyridyl)-propenal into its 2,4-dinitrophenylhydrazone in the presence of acids.[4] Eventually, pyridine-3-carbaldehyde hydrazone was obtained in 65% yield. Apparently, the direction of hydration for these reactants is explained by the formation of all-in-one conjugation system between the aliphatic chain and aromatic or heteroaromatic cycle.

The aim of this work was to study the direction of hydrolysis of hitherto unknown 2-alkoxy-3-aryl(hetaryl)propenals in acidic medium as well as to elucidate a possibility to access benzylglyoxals or furylmethylglyoxals by the reaction of the C=C bond hydrolysis according to Markovnikov rule (Schemes 3 and 4).

Unlike well-studied arylglyoxals,[5] the reports on benzylglyoxals, rather promising compounds, remain sporadic.[6–9]



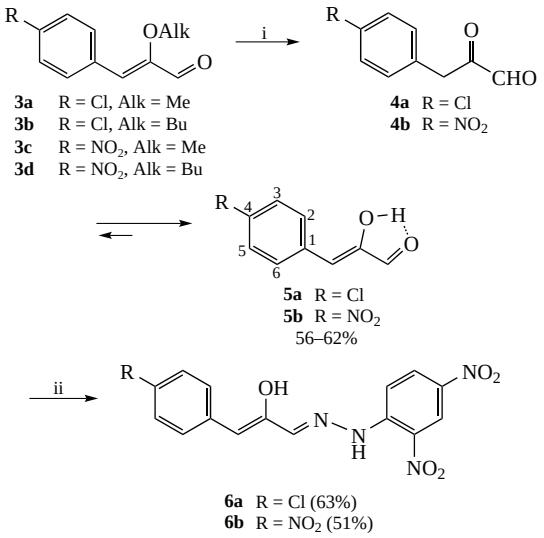
Scheme 2

For example, condensation of 3-(4-acetoxyphenyl)-2-oxopropanal with a pyrazine derivative, coelenteramine, affords coelentrazine, bioluminescent imidazopyrazine.[8] The reaction of benzylglyoxals with a pyridine derivative delivers imidazo-[1,2-*a*]pyridines.[9]

We have found that hydrolysis of 2-alkoxy-3-arylpropenals **3a**–**d**, bearing electron-withdrawing groups in the *p*-position of the aromatic ring, under appropriate conditions (pH 2–3, 50–60 °C, 4–8 h) proceeds in the desired direction giving rise to substituted benzylglyoxals **5a**,**b** in 56–62% yields.[†] Notably,

[†] The ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ at room temperature on Bruker DPX-400 and AV-400 spectrometers (400.13, 100.61 and 40.56 Hz, respectively). Chemical shifts were referred to TMS (^{1}H, ^{13}C) and nitromethane (^{15}N). GC-MS analysis was performed on an Agilent Technologies 5975C (EI, 70 eV, mass-selective detector), AT-6890N chromatograph, Ultra-2 column (5% phenylmethylsilicone), injector temperature 260 °C, column thermostat temperature 70–280 °C, temperature rasing 20 K min^{-1}. IR spectra were recorded on a Bruker IFS25 spectrophotometer. Melting points were determined on a Micro-Hot-Stage Poly Term A instrument. Elemental analysis was performed on a Thermo Finnigan 1112ser analyzer. Column chromatography was carried out on silica gel 60 (70–200 mesh; Merck).

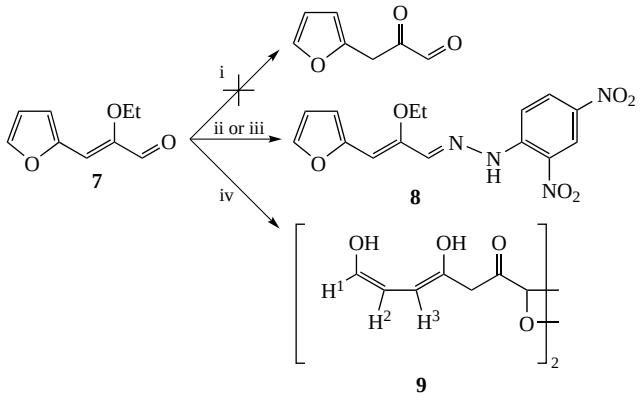
Hydrolysis of (Z)-2-alkoxy-3-(4-chlorophenyl)propenals **3a**,**b** *(general procedure).* To a solution of compound **3a** (1.5 mmol) in 1.5 ml MeCN, H_2O (1.5 mmol) and 28.6% hydrochloric acid (0.55 mmol) (pH 3) were added. The solution was stirred at 50–60 °C for 8 h. The residue was filtered and washed with diethyl ether.



Scheme 3 *Reagents and conditions*: i, H^+/H_2O, MeCN, 50–60 °C, 4–8 h; ii, H^+, 2,4-$(O_2N)_2C_6H_3NHNH_2$.

the precipitated crystals of the compounds do not require additional purification. The ^{1}H NMR study (in $CDCl_3$ and DMSO-d_6) has revealed that the compounds exist in enol form, which is retained even in iminium derivatives **6a** and **6b** obtained from enol aldehydes **5**.‡

Stability of the enol forms is likely due to the formation of strong hydrogen bonding and the prevailing dative effect of the OH group, which is in agreement with electron-withdrawing influence of the Cl and NO_2 substituents.



Scheme 4 *Reagents and conditions*: i, H_3O^+; ii, 2,4-$(O_2N)_2C_6H_3NHNH_2$, HCl, H_2O, pH 3, 20 °C, 10 min, 75%; iii, H_3O^+, MeCN, 55 °C, 6 h, then 2,4-$(O_2N)_2C_6H_3NHNH_2$, 20 °C, 24 h, 29%; iv, H_3O^+, pH 3, 60 °C.

In contrast to 2-alkoxypropenals **1**, which are quantitatively transformed to methylglyoxal in acidic medium for 1 h at 50–60 °C,[2] 2-ethoxy-3-furylpropenal **7** is more resistant to hydrolysis at heating under acidic aqueous (H_2O/MeCN) conditions at 55 °C for > 6 h that is confirmed by consequent formation of hydrazone **8** (Scheme 4).§ Note that alkenal **7** also does not decompose to furfural and ethoxyacetic aldehyde for 10 min as it is observed

(*Z*)-*3-(4-Chlorophenyl)-2-hydroxypropenal* **5a**: yield 59%, mp 161 °C (*cf.* ref. 10). IR (ν/cm^{-1}): 3192, 1643, 1586, 1489, 1417, 1360, 1289, 1158, 925, 858, 724. ^{1}H NMR ($CDCl_3$) δ: 6.10 (s, 1H, =CH), 6.72 (s, 1H, OH), 7.36 (d, 2H, H^3, H^5, *J* 8.2 Hz), 7.75 (d, 2H, H^2, H^6, *J* 8.2 Hz), 9.24 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 121.2 (=C), 129.1 (C^3, C^5), 131.7 (C^2, C^6), 132.15 (C^1), 135.3 (C^4), 149.0 (COH), 188.0 (CHO). GC-MS, *m*/*z* (%): 182 (47) [M]$^+$, 165 (2) [M–OH]$^+$, 147 (23) [M–Cl]$^+$, 125 (100), 89 (36) [C_6H_4CH]. Found (%): C, 59.43; H, 3.81; Cl, 19.35. Calc. for $C_9H_7ClO_2$ (%): C, 59.20; H, 3.86; Cl, 19.41.

Hydrolysis of (*Z*)-2-butoxy-3-(4-chlorophenyl)propenal **3b** was carried out as above, the same product **5a** was obtained in 62% yield.

Hydrolysis of (*Z*)-2-methoxy-3-(4-nitrophenyl)propenal **3c** was carried out similarly, but reaction time was 4 h. (*Z*)-2-Hydroxy-3-(4-nitrophenyl)-propenal **5b** was obtained in 56% yield, mp 175 °C (*cf.* ref. 10). IR (ν/cm^{-1}): 3074, 2919, 1676, 1594, 1515, 1344, 1160, 1105, 926, 865, 693. ^{1}H NMR ($CDCl_3$) δ: 6.20 (s, 1H, =CH), 7.95 (d, 2H, H^2, H^6, *J* 8.8 Hz), 8.24 (d, 2H, H^3, H^5, *J* 8.8 Hz), 9.33 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$) δ: 119.2 (=C), 123.55 (C^3, C^5), 130.4 (C^2, C^6), 140.5 (C^1), 146.7 (C^4), 152.0 (COH), 188.6 (CHO). ^{15}N NMR ($CDCl_3$) δ: –10.0. GC-MS, *m*/*z* (%): 193 (100) [M]$^+$, 176 (45) [M–OH]$^+$, 164 (55) [M–CHO]$^+$, 147 (34) [M–NO_2]$^+$, 136 (86), 118 (38) [M–NO_2–CHO]$^+$, 89 (72) [C_6H_4CH]. Found (%): C, 55.81; H, 3.72; N, 6.98. Calc. for $C_9H_7NO_4$ (%): C, 55.96; H, 3.65; N, 7.25.

Hydrolysis of (*Z*)-2-butoxy-3-(4-nitrophenyl)propenal **3d** was carried out as described for **3c**, the product **5b** was obtained in 56% yield.

‡ *(Z)-3-(4-Chlorophenyl)-2-hydroxypropenal 2,4-dinitrophenylhydrazone* **6a**. To a solution of compound **3a** (0.38 g, 1.93 mmol) in 2 ml of MeCN, H_2O (0.035 g, 1.93 mmol) and 28.6% HCl (0.072 g, 0.56 mmol) (pH 3) were added. The solution was stirred at 50–60 °C for 8 h. Then 2,4-dinitrophenylhydrazine (0.35 g, 1.76 mmol) dissolved in ethanol was added, the solution was stirred at room temperature for 1 h. Compound **6a** (0.4 g, 63%) was obtained after recrystallization from ethanol, mp 186 °C. IR (KBr, ν/cm^{-1}): 3404, 3373, 3250, 1619, 1594, 1521, 1502, 1414, 1343, 1319, 1280, 1213, 1135. ^{1}H NMR (DMSO-d_6) δ: 5.75 (s, 1H, =CH), 7.40 (d, 2H, H^3, H^5, *J* 8.6 Hz), 7.80 (d, 2H, H^2, H^6, *J* 8.6 Hz), 8.29 (s, 1H, HC=N), 8.36 (dd, 1H, H$^{5'}$, ^3J 9.6 Hz, ^4J 2.4 Hz), 8.50 (d, 1H, H$^{6'}$, ^3J 9.6 Hz), 8.85 (d, 1H, H$^{3'}$, ^4J 2.4 Hz), 9.53 (s, 1H, OH), 11.71 (s, 1H, NH). ^{13}C NMR (DMSO) δ: 112.6 (C=), 118.4 (C$^{6'}$), 123.3 (C$^{3'}$), 128.7 (C=N), 128.9 (C^3, C^5), 130.8 (C^2, C^6), 131.3 (C^1), 132.1 (C$^{5'}$), 135.4 (C^4), 137.8 (C$^{2'}$), 144.8 (C^4), 146.7 (C$^{1'}$), 149.2 (COH). ^{15}N NMR (DMSO) δ: –11.2 (*p*-NO_2), –28.4 (*o*-NO_2), –67.1 (C=N), –222.8 (NH). Found (%): C, 49.74; H, 3.07; N, 15.70; Cl, 9.61. Calc. for $C_{15}H_{11}N_4ClO_5$ (%): C, 49.67; H, 3.06; N, 15.45; Cl, 9.77.

(Z)-2-Hydroxy-3-(4-nitrophenyl)propenal 2,4-dinitrophenylhydrazone **6b** was prepared as above. Yield 0.24 g, 51%, mp 191 °C (ethanol). ^{1}H NMR (DMSO-d_6) δ: 5.91 (s, 1H, =CH), 8.01 (d, 2H, H^2, H^6, *J* 8.8 Hz), 8.21 (d, 2H, H^3, H^5, *J* 8.8 Hz), 8.33 (s, 1H, HC=N), 8.38 (dd, 1H, H$^{5'}$, ^3J 9.7 Hz, ^4J 2.5 Hz), 8.52 (d, 1H, H$^{6'}$, ^3J 9.7 Hz), 8.86 (d, 1H, H$^{3'}$, ^4J 2.5 Hz), 10.12 (s, 1H, OH), 11.78 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 111.8 (C=), 117.3 (C$^{6'}$), 121.2 (C$^{3'}$), 128.4 (C=N), 127.9 (C^3, C^5), 130.3 (C^2, C^6), 129.6 (C^1), 132.31 (C$^{5'}$), 137.8 (C$^{2'}$), 144.8 (C^4), 145.4 (C^4), 146.8 (C$^{1'}$), 151.4 (COH). ^{15}N NMR (DMSO-d_6) δ: –10.3 (PhNO$_2$), –12.3 (*p*-NO_2), –27.8 (*o*-NO_2), –61.4 (C=N), –224.6 (NH). Found (%): C, 48.06; H, 2.98; N, 18.41. Calc. for $C_{15}H_{11}N_5O_7$ (%): C, 48.26; H, 2.97; N, 18.77.

§ *2-Ethoxy-3-(2-furyl)propenal 2,4-dinitrophenylhydrazone* **8** was obtained from 2-ethoxy-3-(2-furyl)propenal **7**.

Method A. To a mixture of aldehyde **7** (0.2 g, 1.2 mmol), H_2O (1.7 ml) and DMF (6 ml), conc. HCl was slowly added (pH 3). Then, 2,4-dinitrophenylhydrazine (0.22 g, 1.1 mmol) in EtOH was added within 10 min. The solution was stirred at room temperature for 24 h to give 0.31 g (75%) of compound **8**, mp 210 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.47 (t, 3H, Me, *J* 7.0 Hz), 4.28 (q, 2H, OCH_2, *J* 7.0 Hz), 6.27 (s, 1H, =CH), 6.51 (dd, 1H, H^4, ^3J 3.4 Hz, ^4J 1.7 Hz), 6.97 (d, 1H, H^3, ^3J 3.4 Hz), 7.45 (d, 1H, H^5, ^4J 1.7 Hz), 7.64 (s, 1H, HC=N), 7.92 (d, 1H, H$^{6'}$, ^3J 9.6 Hz), 8.33 (dd, 1H, H$^{5'}$, ^3J 9.6 Hz, ^4J 2.4 Hz), 9.12 (d, 1H, H$^{3'}$, ^4J 2.4 Hz), 11.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 16.2 (Me), 67.5 (OCH_2), 104.4 (=CH), 108.7 (C$^{6'}$), 113.1 (C^4), 117.1 (C^3), 124.1 (C$^{3'}$), 128.1 (C=N), 132.6 (C$^{5'}$), 136.1 (C$^{2'}$), 138.8 (C$^{4'}$), 146.8 (C^5), 148.7 (C$^{1'}$), 149.2 (C^2), 150.1 (COH). Found (%): C, 51.73; H, 4.06; N, 16.01. Calc. for $C_{15}H_{14}N_4O_6$ (%): C, 52.02; H, 4.05; N, 16.18.

Method B. The solution of aldehyde **7** (0.1 g, 0.6 mmol) in 1 ml of MeCN, H_2O (0.01 g, 0.6 mmol) and HCl (0.021 g, 0.16 mmol) (pH 3) was heated on stirring at 50–60 °C for 6 h. Then 2,4-dinitropenylhydrazine (0.12 g, 0.6 mmol) in EtOH was added and the mixture was left at room temperature for 24 h. Product **8** (0.06 g, 29%) was obtained. In addition, black powder **9**, insoluble in water and organic solvents, was also formed. IR (KBr, ν/cm^{-1}): 3434, 2922, 1708, 1628, 1393, 1236, 1089. Hourly monitoring of the liquid phase of the reaction mixture (^{1}H NMR) confirms the increase of dimer **9** concentration (up to 1:4 molar ratio for **7**:**9**, CH_2Br_2 as internal standard). ^{1}H NMR ($CDCl_3$) δ: 4.11 (s, 2H, CH_2), 5.1 (d, 1H, H^3, *J* 10.5 Hz), 5.23 (d, 1H, H^1, *J* 17.1 Hz), 5.98 (m, 1H, H^2), 6.65 (s, 1H, CH). Found (%): C, 53.66; H, 5.32. Calc. for $C_7H_8O_4$ (%): C, 53.85; H, 5.13.

in the case of 2-methoxy-3-(2-pyridyl)propenal (*cf*. ref. 4). The prolongation of the reaction or raising the temperature to 70 °C in the case of aldehyde **7** results in precipitation of black powder insoluble in water and organic solvents. The structure of its dimer or oligomer with chemical composition $(C_7H_8O_4)_n$ may be assigned to product **9** according to data of elemental analysis, mass spectrometry ($[M^+ - 1] = 311$) and ^{1}H NMR spectroscopy.

In conclusion, we have found that hydrolysis of 2-alkoxy-3-aryl(hetaryl)propenals is substrate dependent and is affected by the nature of substituents in the aromatic ring as well as structure of the 3-positioned heteroaromatic moiety. Combination of capto-dative effect of the substituents in 2-alkoxy-3-phenylpropenals with electron-withdrawing substituents (Cl, NO_2) promotes hydration of the C=C bond according to Markovnikov rule. This effect allows hydrolysis of these aldehydes to be considered as a convenient access to the corresponding benzylglyoxals.

The main results were obtained using the equipment of Baikal Analytical Center of Collective Use of the Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.09.023.

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Received: 10th February 2016; Com. 16/4841