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SHORT COMMUNICATIONS

Unusual Opening of the 1,3-Dioxolane Ring in γ-Hydroxy α,β-Acetylenic Aldehyde Dimers by the Action of Ethylenediamine

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We previously showed that acetylenic γ-hydroxy aldehydes react with ethane-1,2-diamine in polar solvents at room temperature to give 5-hydroxyalkyl-2,3-dihydro-1*H*-1,4-diazepines [1]. Benzodiazepines are widely used for the treatment of neurological and psychical disorders [2], and they also exhibit antidepressant, antiarrhythmic, antiinflammatory, antihistamine [3], antimicrobial, antioxidant [4], and antitumor activity [5].

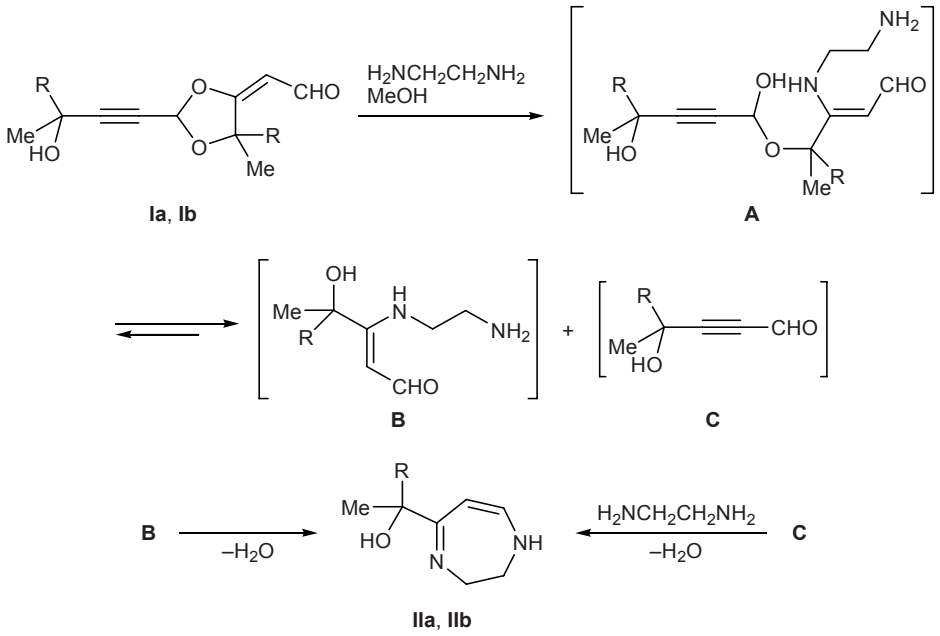
Using 4-hydroxy-4-methylpent-2-ynal as an example we discovered previously unknown base-catalyzed dimerization of γ-hydroxy α,β-acetylenic aldehydes to [2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5,5-dimethyl-1,3-dioxolan-4-ylidene]acetaldehyde [6]. It was surprising that dioxolanes **Ia** and **Ib** reacted with ethane-1,2-diamine at a ratio of 1:2 under mild conditions (methanol, 25°C, 12 h) to give the corresponding 1,4-diazepine derivatives **IIa** and **IIb** in high yield. Previously unknown [5-ethyl-2-(3-hydroxy-3-methylpent-1-yn-1-yl)-5-methyl-1,3-dioxolan-4-ylidene]acetaldehyde (**Ib**) was synthesized in quantitative yield from 4-hydroxy-4-methylhex-2-ynal in the presence of 5 mol % of 1,4-diazabicyclo[2.2.2]octane (DABCO) under microwave activation (reaction time 3 min).

It is known that 1,3-dioxolane protection of carbonyl groups is readily removed by acid hydrolysis [7]. Functionally substituted 1,3-dioxolanes, including those containing a triple bond in the substituent on C^4, are stable under basic conditions, in particular toward triethylamine, organolithium reagents, potassium carbonate in methanol, sodium hydroxide, and potassium fluoride [8]. Presumably, unusually facile opening of the 1,3-dioxolane ring in [2-(3-hydroxy-3-methylalk-1-ynyl)-5,5-dialkyl-1,3-dioxolan-4-ylidene]acetaldehydes is related to the presence of an O–C≡C–CHO "push–pull" fragment.

A probable mechanism of opening of the dioxolane ring includes cleavage of the C–O bond by the action of ethylenediamine with formation of intermediate **A**. Analogous examples of nucleophilic replacement in push–pull systems have been reported in the literature [9]. Decomposition of hemiacetal **A** to β-amino enal **B** and parent γ-hydroxy aldehyde **C**, followed by intramolecular cyclization of the former or addition of ethylenediamine at the triple bond of **C** with subsequent dehydration, leads to the formation of two hydroxyalkyldiazepine molecules **II**.

Taking into account that acetylenic γ-hydroxy aldehydes undergo dimerization on storage or in the presence of bases, the revealed opening of the dioxolane ring by the action of ethylenediamine is very important for studying reactions of polyfunctionalized 1,3-dioxolanes with nucleophiles. Obviously, the stability of compounds like **Ia** and **Ib** toward nucleophiles depends on the nucleophile nature, for dimer **Ia** does not react with 2-amino-2-methylpropan-1-ol [6].

Thus we have shown that [2-(3-hydroxy-3-methylalk-1-yn-1-yl)-5,5-dialkyl-1,3-dioxolan-4-ylidene]acetaldehydes can be used as synthetic equivalents of the corresponding acetylenic γ-hydroxy aldehydes. Studies on the effects of the nucleophile nature and acid conditions on the behavior of the 1,3-dioxolane ring in acetylenic γ-hydroxy aldehyde dimers are now in progress.



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

[5-Ethyl-2-(3-hydroxy-3-methylpent-1-yn-1-yl)-5-methyl-1,3-dioxolan-4-ylidene]acetaldehyde (Ib). A solution of 0.5 g (3.96 mmol) of 4-hydroxy-4-methylhex-2-ynal and 0.022 g (5 mol %) of DABCO in 2 ml of chloroform was placed in a Teflon container and was irradiated for 3 min in a microwave oven at a power of 700 W (in 1-min exposures followed by cooling to room temperature). The mixture was cooled, the solvent was removed, and the residue, 0.53 g, was subjected to column chromatography on silica gel using chloroform–methanol (10:1) as eluent. Yield 0.26 g (50%), oily liquid. IR spectrum, ν, cm^{-1}: 1640 (C=O, C=CH), 2240 (C≡C), 3400 (OH). The product was a mixture of *Z* and *E* isomers at a ratio of 65:35. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: *Z* isomer: 0.7–2.0 m (16H, CH_2, CH_3), 3.45 br.s (1H, OH), 4.93–4.97 d.d (1H, =CH, ^3J = 8.2 Hz), 6.02 s and 6.07 s (1H, 2-H), 9.78–9.82 d.d (1H, CHO); *E* isomer: 5.52–5.56 d.d (1H, =CH, ^3J = 8.2 Hz), 5.99 s and 6.04 s (1H, 2-H), 9.59–9.62 d.d (1H, CHO). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: *Z* isomer: 7.7–24.72 (CH_3), 31.62 and 31.82 (CH_2), 68.22 ($C^{3'}$), 76.05 ($C^{1'}$), 86.80 ($C^{5'}$), 92.38 ($C^{2'}$), 95.91 (C^2), 98.69 (=CH), 174.91 (C^4), 189.46 (C=O); *E* isomer: 31.62 and 31.82 (CH_2), 68.22 ($C^{3'}$), 76.05 ($C^{1'}$), 86.80 ($C^{5'}$), 92.38 ($C^{2'}$), 95.91 (C^2), 98.69 (=CH), 174.91 (C^4), 189.46 (C=O). Found, %: C 66.06; H 7.68. $C_{14}H_{20}O_4$. Calculated, %: C 66.65; H 7.99.

2-(2,3-Dihydro-1*H*-1,4-diazepin-5-yl)propan-2-ol (IIa). A solution of 0.1 g (0.446 mmol) of 1,3-dioxolane **Ia** and 0.053 g (0.892 mmol) of ethane-1,2-diamine in 1 ml of methanol was kept for 12 h at room temperature. The solvent was removed under reduced pressure to leave 0.148 g (97%) of compound **IIa** as a viscous material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 s (6H, CH_3), 3.38 br.s (2H, C**H**$_2$NH), 3.47 br.s (2H, CH_2N=), 3.93 br.s (2H, NH, OH), 4.75 d (1H, =CH, ^3J = 8.8 Hz), 6.51 d (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 30.13 (CH_3), 48.32 (C^2), 53.18 (C^3), 70.74 (COH), 86.11 (C^6), 145.07 (C^7), 173.86 (C^5). The spectral parameters of the product coincided with those reported in [1].

2-(2,3-Dihydro-1*H*-1,4-diazepin-5-yl)butan-2-ol (IIb) was synthesized in a similar way. Yield 98%, viscous oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 t (3H, C**H**$_3$CH$_2$), 1.24 s (3H, C**H**$_3$COH), 1.64 q (2H, CH$_3$C**H**$_2$), 3.40 br.s (2H, C**H**$_2$NH), 3.55 br.s (2H, CH_2N=), 4.30 br.s (2H, OH, NH), 4.68 d (1H, =CH, ^3J = 9.24 Hz), 6.53 d (1H, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.98 (**C**H$_3$CH$_2$), 28.13 (**C**H$_3$COH), 32.47 (CH$_3$**C**H$_2$), 49.11 (C^2), 53.72 (C^3), 74.08 (COH), 88.02 (C^6), 144.45 (C^7), 175.15 (C^5). The spectral parameters of the product coincided with those reported in [1].

The ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer using hexamethyldisiloxane as internal reference. Microwave-assisted reactions were carried out in an LG MS-1904H domestic microwave furnace at a power of 700 W (2450 MHz).

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