ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 10, pp. 1551–1553. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © A.V. Mareev, A.V. Khatashkeev, A.V. Afonin, I.A. Ushakov, A.S. Medvedeva, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 10, pp. 1572–1574.

SHORT COMMUNICATIONS

Dedicated to Full Member of the Russian Academy of Sciences B.A. Trofimov on his 70th anniversary

Detection by ^{1}H NMR of Malonaldehyde as the Key Intermediate in the Trimerization of 3-Trimethylsilylprop-2-ynal to 4-Trimethylsilylethynyl-4*H*-pyran-3,5-dicarbaldehyde

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Received June 2, 2008

DOI: 10.1134/S107042800810028X

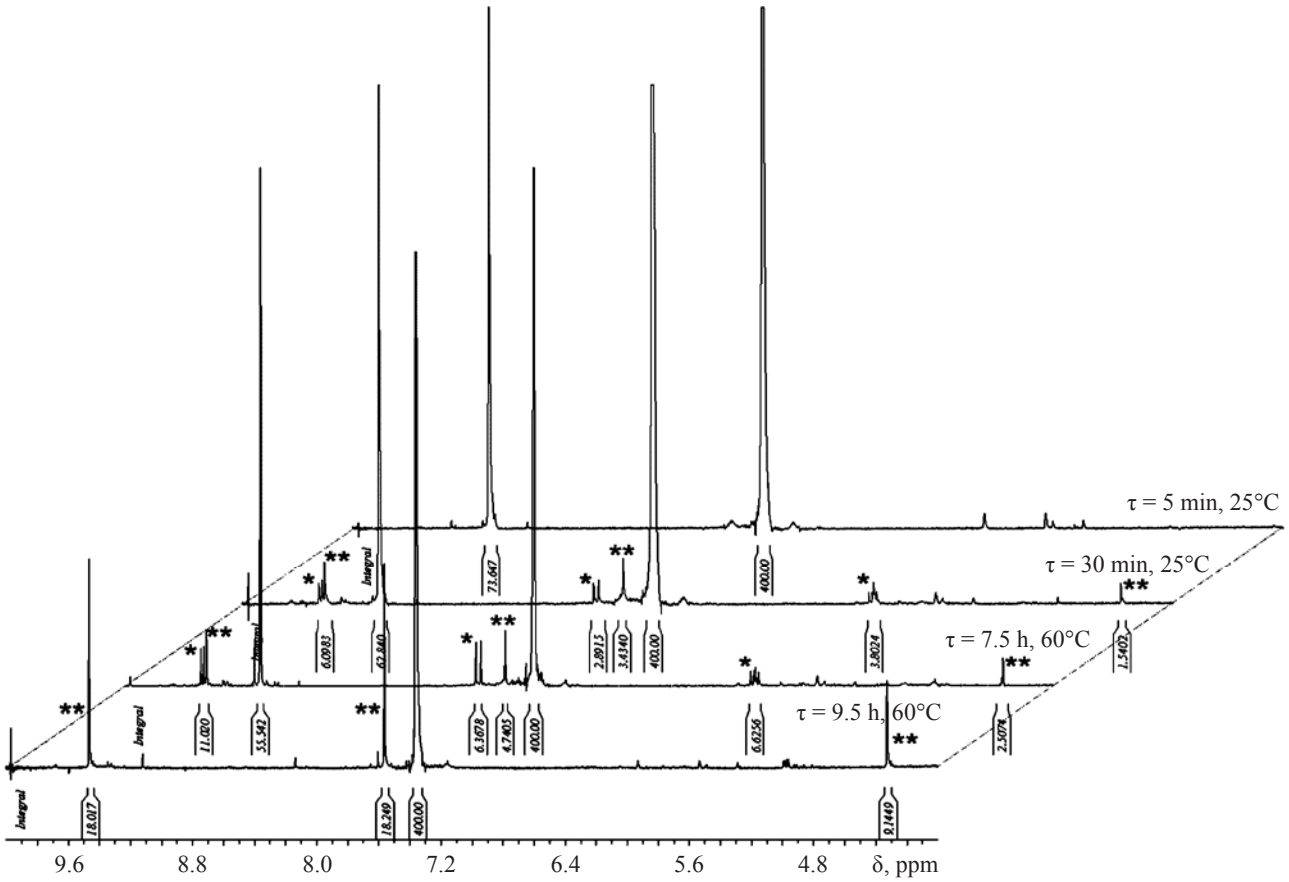
We recently showed that 3-trimethylsilylprop-2-ynal (**I**) in the presence of DABCO (1,4-diazabicyclo-[2.2.2]octane, 5 mol %) undergoes trimerization to give previously unknown 4-trimethylsilylethynyl-4*H*-pyran-3,5-dicarbaldehyde (**III**) [1]. The reaction occurred under mild conditions (25°C, MeCN–H_2O, 2 days), and the yield of dialdehyde **III** was almost quantitative. The proposed mechanism involves formation of malonaldehyde $CH_2(CHO)_2$ as the key intermediate. The possibility for formation of $CH_2(CHO)_2$ in reactions of propynal with nucleophiles was also noted in [2, 3]. Wille and Schwab [3] described the synthesis of 4-ethynyl-4*H*-pyran-3,5-dicarbaldehyde via "polymerization" of propynal by the action of tertiary amines; however, the authors failed to detect intermediate malonaldehyde by ^{1}H NMR spectroscopy.

Malonaldehyde is the simplest 1,3-dialdehyde; it is widespread in the nature as the product of peroxide oxidation of lipids and biosynthesis of prostaglandins [4]. This natural metabolite is present in mammalian and human tissues and foods [5] and is capable of modifying nucleic acids [6, 7], so that it exhibits mutagenic activity toward bacteria and mammalian cells. Malonaldehyde as difunctional electrophile reacts with nucleophilic centers of proteins and is thus a highly efficient cross-linker [8, 9].

A certain relation between the biological activities of malonaldehyde and propynal must be noted. The formation of propynal *in vivo* has been reported [10], and its participation in the reversible inhibition of some enzymes was rationalized by reactions with nucleophilic centers in the latter. Unlike nonmutagenic propynenitrile and ethyl propynoate, strong mutagenic activity of propynal [11] is likely to result from formation of malonaldehyde *in vivo* due to catalysis by nucleobases.

Up to now, no data have been reported on the formation of malonaldehyde in reactions of 3-trimethylsilylprop-2-ynal or other heteroelement-containing analogs with nucleophiles. We were the first to prove by ^{1}H NMR spectroscopy that malonaldehyde is formed as intermediate in the base-catalyzed trimerization of 3-trimethylsilylprop-2-ynal to 4-trimethylsilylethynyl-4*H*-pyran-3,5-dicarbaldehyde.

A mixture of equimolar amounts of aldehyde **I** and water and 10 mol % of DABCO in CD_3CN contained (in 5 min after mixing the reactants at room temperature) only the initial aldehyde (δ_{CHO} 9.13 ppm, s; see figure). After 30 min, signals assignable to malonaldehyde (**II**) [δ, ppm: 5.95 d.d (2-H, $^3J_{1,2}$ = 7.9, $^3J_{2,3}$ = 12.2 Hz), 7.27 d (3-H), 9.50 (1-H); these signals are marked with an asterisk in figure] and 4-trimethylsilylethynyl-4*H*-pyran-3,5-dicarbaldehyde (**III**) [δ, ppm: 4.37 s (4-H), 7.55 s (2-H, 6-H), 9.48 s (CHO); the signals are marked with a double asterisk] appeared in the ^{1}H NMR spectrum of the mixture. During the next 7 h at 60°C, gradual accumulation of pyran **III** and malonaldehyde **II** was observed, and aldehyde **II** then rapidly disappeared, the trimerization process being complete in 9.5 h after the reaction started. The ^{1}H NMR spectrum of the final mixture contained only singlets from pyran **III**, while those corresponding to



^{1}H NMR monitoring of the trimerization of 3-trimethylsilylprop-2-ynal (**I**) into 4-trimethylsilylethynyl-4*H*-pyran-3,5-dicarbaldehyde (**III**); for comments, see text.

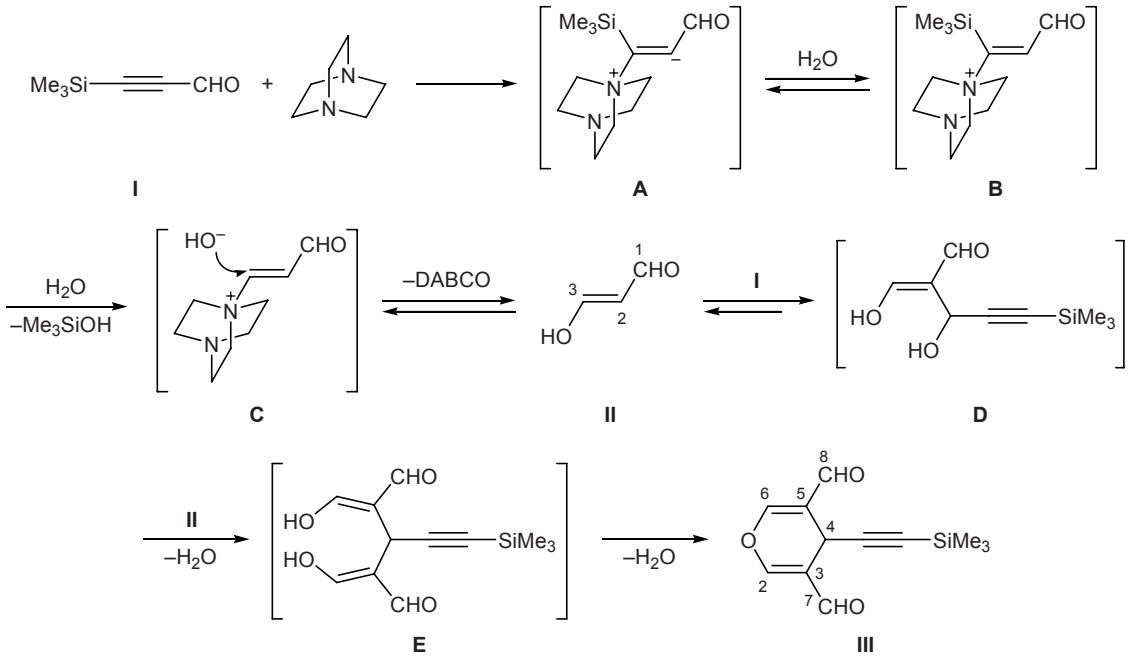
initial aldehyde **I** and malonaldehyde (**II**) were absent. It should be noted that malonaldehyde (**II**) exists in the enol form. The vicinal ^{1}H–^{1}H coupling constant for the olefinic fragment (^3J = 12.2 Hz) indicates that enol **II** has *trans* configuration. Heating of the mixture accelerates the heterocyclization process which takes 48 h at room temperature.

Our data are consistent with the proposed mechanism of trimerization of 2-trimethylsilylprop-2-ynal (**I**) (Scheme 1), which includes formation of zwitterionic intermediate **A** as a result of addition of DABCO at the triple bond of **I**, successive desilylation of intermediate **B** and hydrolysis of intermediate **C** to give malonaldehyde (**II**), and subsequent cascade assembly of 4*H*-pyran **III** via formation of two C–C bonds by reaction of two molecules **II** at the aldehyde group of propynal **I** and intramolecular cyclization of intermediate **E** with elimination of water.

Thus we were the first to confirm intermediate formation of malonaldehyde in the base-catalyzed transformation of 3-trimethylsilylprop-2-ynal using ^{1}H NMR spectroscopy. Malonaldehyde resulting from addition of water to 3-trimethylsilylprop-2-ynal, catalyzed by DABCO, and subsequent desilylation, acts as the key intermediate in the cascade assembly of 4-trimethylsilylethynyl-4*H*-pyran-3,5-dicarbaldehyde. We demonstrated that silicon-containing analogs of propynal can be used as synthetic equivalents of extremely unstable and readily polymerizable malonaldehyde [12] in the design of polyfunctional heterocyclic compounds.

An ampule was charged at 25°C with 0.2879 g (7.28 mmol) of 3-trimethylsilylprop-2-ynal (**I**), 0.013 g (0.11 mmol) of DABCO, 0.04 ml of distilled water, and 5.0 ml of acetonitrile-d_3. The mixture was thoroughly stirred, a sample was withdrawn and transferred into an NMR ampule, and the reaction ampule was sealed and frozen with liquid nitrogen. The first two ^{1}H NMR spectra were recorded in a 5-min interval, and the spectra were then recorded every 10 min. After 30 min, the ampule was heated to 60°C, and the spectra were recorded at that temperature every 30 min until the reaction was complete.

Scheme 1.



The ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer using benzene as internal reference (solvent CD_3CN).

This study was performed under financial support by the Siberian Division, Russian Academy of Sciences (Lavrent'ev Competition of Young Scientists Projects, project no. 75, 2006) and by the Foundation for Support of the Russian Science.

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