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SYNTHESIS OF 2-PHENYLETHYNYL-1,3-DIOXANES AND THEIR HYDROLYSIS

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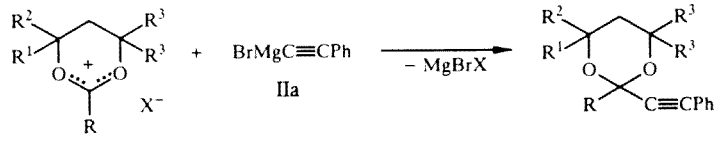
2-Phenylethynyl substituted 1,3-dioxanes were obtained by the reaction of 1,3-dioxanium salts with an Iotsich reagent. It was shown that they are readily hydrolyzed with the formation of α-acetylenic ketones. A simple new method is proposed for the synthesis of the latter without isolating the intermediate 1,3-dioxanes using the reaction of 4 substituted 2-methyl(phenyl, furyl)-1,3-dioxanium salts with hydroxymethyl- and phenylethynylmagnesium bromide as examples.

2-Ethynyl substituted 1,3-dioxanes are uncommon compounds difficult to access [1]. Some are of interest as potentially biologically active substances and as intermediates in organic synthesis [2]. It is therefore expedient to develop a convenient method for the synthesis of 2-ethynyl-1,3-dioxanes.

The present work is a continuation of the investigations published previously on the reaction of 1,3-dioxanium salts with organolithium and organomagnesium compounds [3, 4]. These readily available salts [5-7] possess an electrophilic center at the meso carbon atom in the O=C$^+$=O fragment which actively accepts the attack of nucleophilic reagents. We have established that 1,3-dioxanium salts (I) display analogous properties and on reaction with Iotsich reagents (II) form 1,3-dioxanes (III) with the acetylenic fragment $-C\equiv C-$ at the $C_{(2)}$ atom of the dioxane ring.



Ia-d IIIa-d

I X = ClO_4, $SbCl_6$; I, III a R = R^3 = CH_3, R^1 = R^2 = H; b R = R^1 = R^3 = CH_3, R^2 = H; c R = R^1 = R^2 = R^3 = CH_3; d R = Ph, R^1 = R^3 = H, R^2 = CH_3

The reaction of salts (Ia-d) with the reagent (IIa) occurred in one stage under the mild conditions of organomagnesium synthesis at a ratio of (I):(II) equal to 3:1 and was complete after 3-4 h. The products obtained, the previously unknown 2-ethynyl substituted 1,3-dioxanes (IIIa-d), were colorless, they had the characteristic odor of acetals and were distinguished by good solubility in petroleum ether, hexane, pentane, benzene, CCl_4, $CHCl_3$, CH_2Cl_2, ethanol, acetone, nitromethane, and DMSO, but were poorly soluble in water. Their melting points increased with the growth in the number of substituents and also on replacement of the methyl substituent at the ring $C_{(2)}$ atom by phenyl (Table 1).

The composition and structure of compounds (IIIa-d) are fully in agreement with the results of elemental analysis and with the data of IR, NMR, and mass spectra. There were bands in the IR spectra for the stretching vibrations of $-C\equiv C-$ at 2100-2210 cm^{-1} in addition to a set of 3-4 bands in the 1040-1210 cm^{-1} region characteristic of the O–C–O fragment of 1,3-dioxanes (see Table 1). The PMR spectra were typical of 4,4-, 4,4,6-, and 4,4,6,6-substituted 1,3-dioxanes of the ketal type [4] (Table 2).

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TABLE 1. Characteristics of the Compounds (IIIa-d) Synthesized

Compound	Found, % / Calculated, %		Empirical formula	R_f*	mp, °C	bp, °C (5 mm Hg)	IR spectrum, cm^{-1}	Yield, %
	C	H						
IIIa	78.5 78,3	8.0 7,8	$C_{15}H_{18}O_2$	0,90	20...22	146...148	2100	80
IIIb	78.8 78,7	8.3 8,3	$C_{16}H_{20}O_2$	0,91	27...28	153...154	2200	81
IIIc	79.4 79,6	8.8 8,5	$C_{17}H_{22}O_2$	0,92	53...54	175...177	2210	85
IIId	82.4 82,0	6.5 6,3	$C_{19}H_{18}O_2$	0,86	82...83	215...217	2190	71

*Solvent system, toluene–ethanol 20:3, visualization with I_2 vapor.

TABLE 2. PMR Spectra of Compounds (IIIa-d) in $CDCl_3$, δ, ppm, Coupling Constants (J), Hz

Compound	R	Ph, m (5H)*	R^1, R^2	5-H_aH_e (2H)	R^3
IIIa	1,63 (3H)	7,18	4,33 m (1H), 3.73 m (1H), $^3J_{Aa}$ 11.7, $^3J_{Ar\,(Be)}$ = 3.1, $^2J_{(AB}$ = −11,7	1.45 m, 1.79 m, $^2J_{ae}$ = −13.5	1.50 s (3H) 1.16 s (3H)
IIIb	1,65 s (3H)	7,26	1.15 d (3H), $^3J_{HCH3}$ = 7, 4.30 m (1H)	1.38 d, 1.63 d, $^2J_{ae}$ = −13.5	1.53 s (3H), 1.15 s (3H)
IIIc	1,61 s (3H)	7,22	1.43 s (3H), 1.28 s (3H)	1,55 d, 2.27 d $^2J_{ae}$ = −13.5	1.43 s (3H), 1.28 s (3H)
IIId	7,85 m (5H)	7,22	4.35 m (1H), 1.15 d (3H), $^3JH_{CH3}$ = 7	1.35 m	3.85 m (2H)

*Centers of multiplets are given.

TABLE 3. Mass Spectra of 1,3-Dioxanes (IIIa-c)

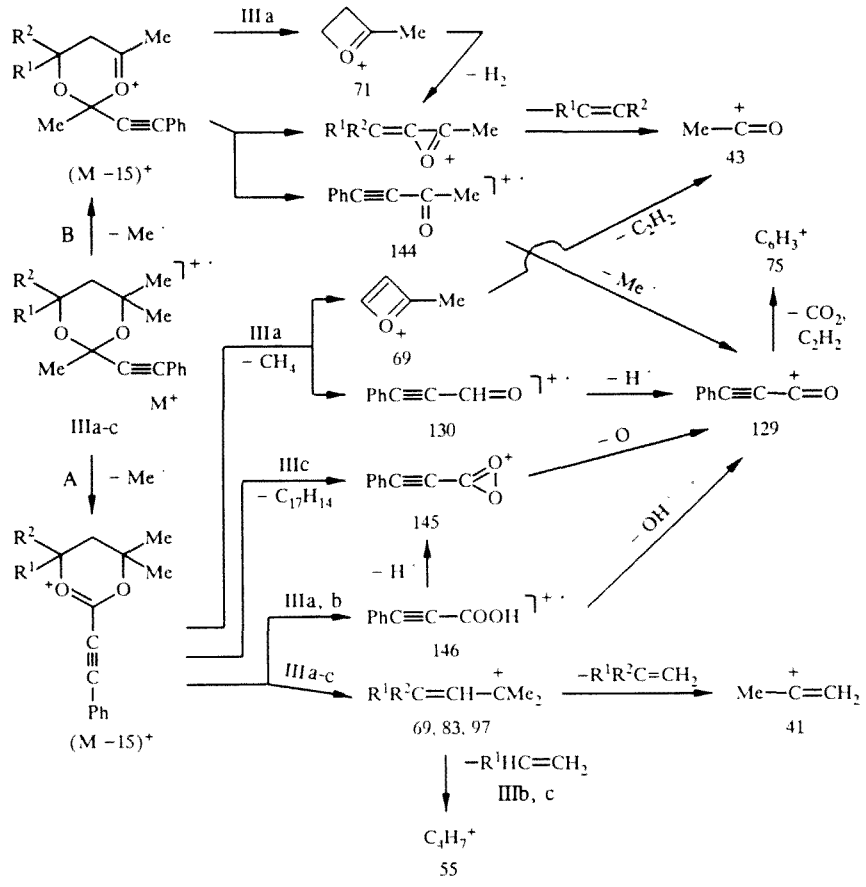
Compound	Value of *m/z* (I_{rel}, %)*
IIIa	230 (1,1), 215 (39,8), 146 (5,8), 145 (42,4), 144 (12,0), 130 (10,1), 129 (100), 75 (10,6), 71 (30,5), 69 (64,5), 43 (55,8), 41 (16,8)
IIIb	244 (1,5), 229 (26,4), 146 (27,1), 145 (90,9), 144 (17,9), 129 (100), 83 (71,1), 75 (13,2), 55 (14,7), 43 (72,7), 41 (16,5)
IIIc	258 (2,1), 243 (26,7), 162 (21,3), 145 (77,4), 144 (22,8), 129 (100), 97 (82,6), 56 (16,8), 55 (22,4), 43 (84,3), 41 (23,2)

*Peaks of M^+ and the ten most intense ions are given.

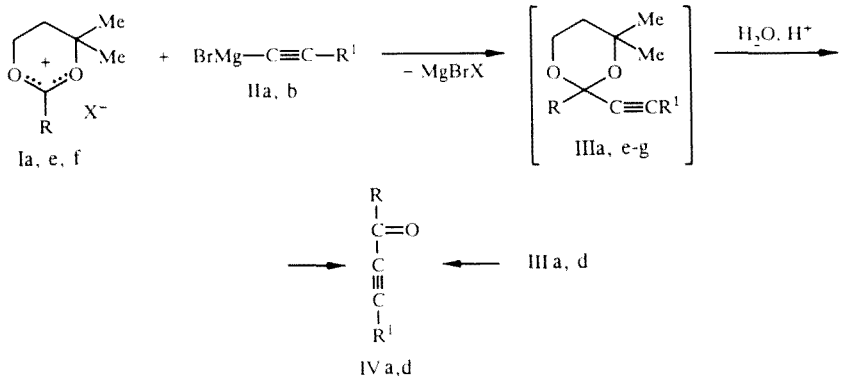
The molecular ions of the 1,3-dioxanes determined by mass spectrometry were in agreement with calculated values (Table 3) and their fragmentation patterns may be represented as in Scheme 1. The presence in the mass spectra of all the samples investigated of weak intensity peaks for the molecular ions M^+ is a characteristic of 2,4,6-substituted 1,3-dioxanes, which readily split off a methyl group from position 2 or 4 of the ring [8]. The $(M-15)^+$ ions are also unstable and their subsequent decomposition occurs by two pathways (A and B). According to pathway A, they eliminate phenylpropiolic acid and ion homologs of masses 69, 83, and 97 respectively, the peaks of which are highly intense in the spectrum (Table 3). The decomposition of 4,4-dimethyl-1,3-dione (IIIa) occurs analogously to the 1,3-dioxane unsubstituted at positions 5 and 6, with elimination of methane and the molecular ion of phenylpropiolic aldehyde [8]. In the case of compound (IIIc) the $(M-15)^+$ ion eliminates the hydrocarbon portion of the 4,4,6,6-tetramethyl substituted dioxacycle and forms a stable ion of *m/z* 145. When $(M-15)^+$ ions decompose by pathway B, the molecular ion of methyl phenylethynyl ketone and the homologs of the oxonium

ions are formed. Subsequent fragmentation of the molecular ions of phenylpropiolic acid with elimination of $H^{\cdot}$, $CH_3^{\cdot}$, and $OH^{\cdot}$ leads to an ion peak of maximum intensity and mass 129 [9]. It is evident from Scheme 1 that the character of the decomposition of the molecular ions is in agreement with the structure proposed.

Scheme 1



Confirmation of the structures of compounds (IIIa, d) is afforded by their facile hydrolysis in acid media (method A) proceeding in 80-85% yield to the difficultly available α-acetylenic ketones (IVa, b) which are not obtained from the corresponding 2,4,4,5,5-penta-methyl-2-ethynyl-1,3-dioxolanes due to steric hindrance [10]. Ketones (IVa-d) were also obtained by us in 42-84.4% yield from the 1,3-dioxanium salts (Ia, e, f) and the Iotsich reagent (IIa, b) without isolating the intermediate 1,3-dioxanes (IIIa, e-g) by decomposing the reaction mixture with 10% HCl solution (method B) [11].



Ie R = Ph, f R = furyl, IIb $R^1 = CH_2OH$; IIIe R = CH_3, $R^1 = CH_2OH$, f R = R^1 = Ph, g R = furyl, R^1 = Ph; IVa R = CH_3, R^1 = Ph, b R = R^1 = Ph, c R = CH_3, $R^1 = CH_2OH$, d R = furyl, R^1 = Ph

The physicochemical constants of the products (IVa-d) corresponded to literature data (see Experimental section).

It should be mentioned that in spite of adequate information on the synthesis of α-acetylenic ketones [12] the generally accepted methods are not always suitable for obtaining their functionally substituted analogs due to the high reactivity of the ethynylcarbonyl group $-C\equiv C-C=O$. Side reactions frequently occur on protecting the carbonyl group and these lower or reduce to zero the yield of the desired product [13]. The use of 1,3-dioxanes under the conditions of organomagnesium synthesis enabled us to avoid side reactions to a significant extent, since the carbonyl group is already protected in the initial compounds.

The preparation of ketones (IVa-d) from dioxanium salts and Iotsich reagents described in the present study represents a new one-stage route for the synthesis of α-acetylenic ketones in high yield.

EXPERIMENTAL

The IR spectra were drawn on a Specord 71 instrument at room temperatures for liquids in thin films and for solids in Nujol suspensions. The ^1H NMR spectra were obtained on a Tesla BS 467 instrument (60 MHz). The internal standard was HMDS. The ^{13}C NMR spectra were drawn on a Bruker AC 80 spectrometer (20 MHz) at room temperature in impulse accumulation mode with subsequent Fourier transformation with full decoupling from protons. The internal standard was TMS. The mass spectra were recorded on a ZKB 2091 instrument using direct insertion of substances into the ion source, the ionization energy being 70 eV, and temperature 50, 100, and 140°C.

The purity of the 1,3-dioxanes (IIIa, b) and of ketones (IVa-d) was determined on a Chrom 5 instrument with DIP on a column of length 2.5 m (15% PMFS-4 on Chromaton N-AW DMCS), carrier gas (nitrogen) flow rate was 32 cm^3/min, evaporator temperature 250°C, column and detector temperature 210°C, sensitivity $32\cdot10^{-9}$, recorder tape rate 0.6 cm/min, and volume of sample introduced 0.1 μl.

The 1,3-dioxanium salts (Ia-f) were obtained by the procedures in [5-7].

2-R^1-4R^2-6,6-di-R^3-4-methyl-2-phenylethynyl-1,3-dioxanes (IIIa-d). Salts (Ia-d) (0.13 mole) were added during 20 min at 20°C to the Iotsich reagent (IIa) obtained from magnesium (9.5 g, 0.40 mole), ethyl bromide (47.9 g, 31.5 ml, 0.44 mole) in ether (150 ml) and phenylacetylene (40.8 g, 43 ml, 0.40 mole) in ether (40 ml). The mixture was stirred until complete solution of the salt and then slowly decomposed with saturated ammonium chloride solution (150 ml) while cooling with ice–salt. The organic layer was separated and the aqueous layer extracted with ether (2 × 50 ml). The combined ether extract was dried with anhydrous Na_2SO_4, and the solvent distilled off on the water bath. The reaction product was isolated from the residue either by distillation under reduced pressure (IIIa, b) or by crystallization of the oily product from hexane or 50% aqueous alcohol (IIIc, d). ^{13}C NMR spectrum (CCl_4) of compound (IIIa): 25.77 and 32.92 [4-$(CH_3)_2$], 34.61 (2-CH_3), 37.31 ($C_{(5)}$), 60.38 ($C_{(6)}$), 73.51 ($C_{(4)}$), 90.00 (C=C), 125.00, 129.61, 132.91 ppm (C_{ph}).

1-Phenyl-1-butyn-3-one (IVa). Method A. A 10% HCl solution (10 ml) was added to a solution of 1,3-dioxane (IIIa) (4.6 g, 0.02 mole) in ether (50 ml). The mixture obtained was stirred at room temperature for 2 h. The ether layer was separated and the aqueous layer extracted three times with ether. The total ether extract was washed sequentially with 5% aqueous $NaHCO_3$ solution and with water, and dried with anhydrous Na_2SO_4. After distilling off the ether on the water bath, ketone (IVa) (2.53 g: 88%) was isolated by distillation under vacuum, bp 115-116°C (8 mm Hg). Literature data, bp 101-102°C (3 mm Hg) [14]. IR spectrum: 3080, 2200, 1686, 1600, 1580, 1500, 1450, 1280, 1150, 1020, 980 cm^{-1}. PMR spectrum (CCl_4): 2.17 (3H, s, CH_3), 7.16 ppm (5H, s, H_{ph}).

Method B. Water (50 ml) and 10% HCl (75 ml) were added with ice-cooling to the reaction mixture obtained from reagent (IIa) and salt (Ia) as described above [see synthesis of compounds (IIIa-d)]. The mixture was stirred for 2 h and then treated as in Method A. Ketone (IVa) was obtained identical with a sample synthesized by Method A (bp, IR spectrum, GLC). Yield was 84.4%.

1,3-Diphenyl-1-propyn-3-one (IVb). Method A. Ketone (IVb) was obtained in 80% yield by the hydrolysis of dioxane (IIId) as described above for dioxane (IIIa) [see synthesis of ketone (IVa)], bp 168-170°C (5 mm Hg). IR spectrum: 2200 (C≡C), 1640 (C=O), 1600, 1580 cm^{-1} (C=C). Literature data, bp 176°C (7 mm Hg). IR spectrum: 2200, 1650 cm^{-1} [16].

Method B. Ketone (IVb) (55% yield) was obtained from (Ie) hexachloroantimonate and reagent (IIa) by the procedure described above [see synthesis of ketone (IVa) by Method B]. It was identical with a sample obtained by Method A.

1-Hydroxy-2-pentyn-4-one (IVc). Salt (Ia) (22.8 g, 0.1 mole) was added during 30 min at 15°C to the Iotsich reagent (IIb), obtained from magnesium (4.8 g, 0.2 mole), ethyl bromide (29.1 g, 20 ml, 0.27 mole) in ether (70 ml), and propargyl

alcohol (5.65 g, 0.1 mole) in ether (30 ml), similarly to the synthesis of ketone (IVa) by Method B. Ketone (IVc) (8.2 g, 83.6%) was obtained after hydrolysis with aqueous HCl. bp 109°C (50 mm Hg). IR spectrum: 3400 (OH), 2200 (C≡C), 1680 (C=O), 1590, 1580, 1480, 1250, 1050, 1010, 950, 810, 730 cm^{-1}. Literature data, bp 60-63°C (0.5 mm Hg). IR spectrum: 3400, 2200, 1670 cm^{-1} [15].

3-Furyl-1-phenyl-1-propyn-3-one (IVd). Ketone (IVd) (50% yield) was obtained from Iotsich reagent (IIa) and (If) hexachloroantimonate by Method B, bp 50-51°C. IR spectrum: 2200 (C≡C), 1635 cm^{-1} (C=O). Literature data, bp 51-52°C. IR spectrum: 2200 (C≡C), 1636 cm^{-1} (C=O) [17].

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