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CONDENSATION OF STEREOISOMERIC 2-ACETYL-2,3-DIPHENYLOXIRANES WITH ETHYL TRIFLUOROACETATE

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The reaction of E-2-acetyl-2,3-diphenyloxirane with ethyl trifluoroacetate in the presence of sodium isopropoxide leads to 3-hydroxy-2,3-diphenyl-6-trifluoromethyl-2,3-dihydro-4H-pyran-4-one. Under the same conditions Z-acetyloxirane forms 3-hydroxy-2-phenyl-5-trifluoromethylfuran as a result of retroaldol cleavage of the initial cyclocondensation product.

Keywords: *E*- and *Z*-2-acetyl-2,3-diphenyloxiranes, ethyl trifluoroacetate.

Substituted α- and γ-pyrones and also various furanones containing a *cis*-stilbene fragment in the molecule are of interest as substances susceptible to photoinitiated transformations. Such compounds exhibit photochromic characteristics [1] and can be used in the synthesis of derivatives of phenanthrene [1-3] and pentahelicene [4]. At the same time it is known that the introduction of perfluoroalkyl groups into pyran systems and particularly coumarins, which have been used successfully for the generation of radiation in lasers [5-7] and also as fluorescent markers for biochemical investigations [8, 9], leads to an increase in resistance to photooxidation and affects the solubility and spectral characteristics of the dyes [7, 10].

We have shown that various 2-perfluoroalkyl-4H-pyran-4-ones can be obtained by the reaction of 2-acetyloxiranes with perfluoroalkanoic esters followed by dehydration of the reaction products [11]. In the present work in order to study the applicability of this approach to the synthesis of the compounds containing two vicinal phenyl groups we realized the condensation of the stereoisomeric 2-acetyl-2,3-diphenyloxiranes (*E*-, *Z*-**1**) with ethyl trifluoroacetate.

As expected [11, 12], the reaction of the oxirane *E*-**1** with ethyl trifluoroacetate in the presence of sodium isopropoxide led to the hydroxydihydropyranone **2a** with a yield of 80%. The relative arrangement of the hydroxyl group and the 2-H atom in compound **2a**, due to the *trans*-opening of the oxirane ring on the side of the β-carbon atom in the intermediate **A**, is confirmed by the significant downfield shift of the signal of this proton in the ^{1}H NMR spectrum of the acetate **2b** (Δδ 0.93 ppm), which is typical of related systems, including flavanonol systems [12, 13]. The absorption bands of the carbonyl group and of the double bond conjugated with it, observed in the IR spectrum of compound **2a** at 1695 and 1640 cm^{-1} respectively, and also the retrodiene fragmentation of the molecular ion, deduced from the appearance of a strong peak for the deoxybenzoin radical-cation (*m*/*z* 196) in the mass spectrum, indicate the formation of a six-membered dihydropyran ring during cyclization [12, 14] (Scheme 1).

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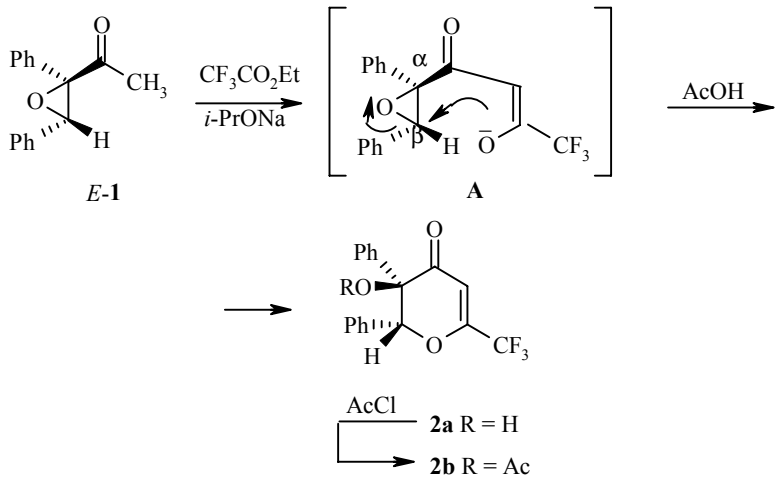
Scheme 1



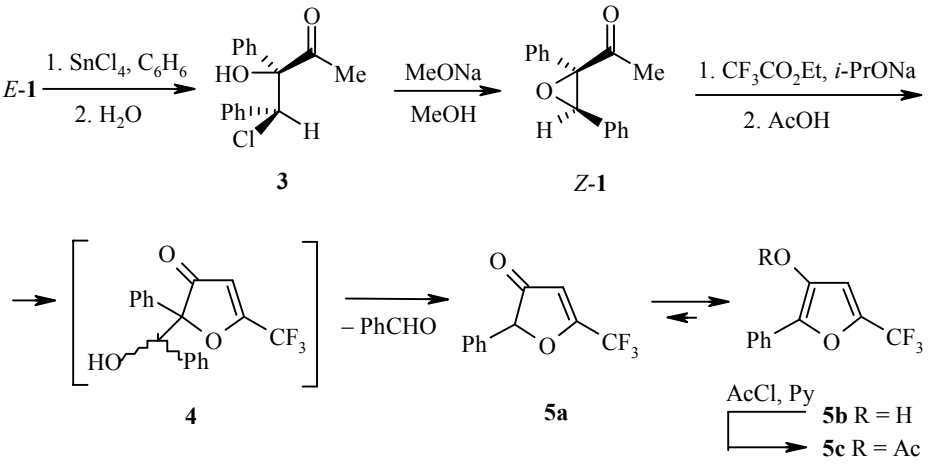
An attempt to dehydrate the hydroxypyranone **2a** by the action of thionyl chloride in pyridine and also by *p*-toluenesulfonic acid in boiling toluene, which was undertaken with a view to forming a *cis*-stilbene fragment, did not lead to the desired result. This may be due to the *cis* arrangement of the hydroxy group and the hydrogen atom of the pyran ring unfavorable for elimination [11].

In order to obtain the hydroxypyranone stereoisomeric with compound **2a** we investigated the reaction of the acetyloxirane *Z*-**1** with ethyl trifluoroacetate. We obtained the oxirane *Z*-**1**, previously synthesized by a four-stage method [15], with an overall yield of 79% by a simpler and more effective method from its isomer *E*-**1** by reaction with $SnCl_4$ in benzene followed by cyclization of the obtained chlorohydrin **3** with sodium methoxide. The structure and relative configuration of the asymmetric atoms of compound **3** shown in the scheme are presented on the basis of the known *cis*-opening of the three-membered ring in aryl-substituted acyloxiranes on the side of the β-C atom by the action of Lewis acids in aprotic solvents [16]. The transformation of this product into the oxirane *Z*-**1** in a basic medium takes place in the usual way with inversion of the configuration at the halogen-bearing carbon atom [17, 18]. In the ^{1}H NMR spectrum of the oxirane *Z*-**1** compared with the spectrum of the *E*-isomer the hydrogen atoms of the acetyl group are 0.12 ppm upfield on account of the screening by the *cis*-located phenyl ring, the hydrogen atoms of which are nonequivalent on account of the effect of the carbonyl group and give a multiplet signal. The singlet of the 3-H proton is also shifted upfield by 0.27 ppm on account of the absence of the descreening effect of the acetyl group, characteristic of the *E*-isomer [19].

The condensation of the oxirane *Z*-**1** with ethyl trifluoroacetate in the presence of sodium isopropoxide led unexpectedly to the 3(2H)-furanone **5a** with a yield close to quantitative. This is the product from cyclization of an intermediate of type *A* at the α-C atom and subsequent retroaldolization of the obtained compound **4**, which was detected by TLC at the initial stages of the process but was easily converted into the furanone **5a** during an attempt at isolation. The benzaldehyde released as a result of retroaldol cleavage was identified by means of its 2,4-dinitrophenylhydrazone (Scheme 2).

The difference in the regioselectivity of the cyclization stage in our investigated condensation of the isomeric oxiranes *E*-, *Z*-**1** has an analogy with the problem of obtaining six-membered flavanonols and five-membered aurones in the course of the oxidation of *o*'-hydroxychalcones by hydrogen peroxide [the Algar–Flynn–Oyamada (AFO) reaction] and related processes [20-22]. However, the formation of the intermediate compound **4** is probably due to steric hindrances for cyclization at the β-C atom, created in the respective intermediate by the phenyl group in the *cis* position to the acyl fragment and not by effects of the substituents in the aromatic rings, as in the case of the AFO reaction.

Scheme 2



Compound **5a**, which proved labile in air both during storage in the crystalline state and during chromatographic isolation, exists predominantly in the tautomeric hydroxyfuran form **5b**, as shown by the ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum the signal of the proton of the hydroxyl group appears in the form of a broad singlet in a relatively upfield position for such systems at 4.56 ppm. This is typical of the enolic forms of compounds in which a strong intramolecular hydrogen bond cannot form and, in particular, 3-hydroxythiophenes like compound **5b** [23]. With the addition of DMSO-d_6 to the solution of the hydroxyfuran **5b** in deuterochloroform used for recording the spectrum the signal is strongly shifted downfield (9.5 ppm). The ^{13}C NMR spectrum does not contain signals in the region of more than 180 ppm, specific for the carbon atoms of the carbonyl group, and this also indicates a significant preference for the tautomer **5b**. At the same time in addition to the strong absorption band of the OH group there is a weak band at 1740 cm^{-1}, corresponding to the stretching vibrations of the C=O group, and in comparison with hydroxydihydropyranone **2a** the carbonyl absorption has higher frequency, which is typical of 3(2H)-furanones [24]. In order to confirm the structure of compound **5b** we obtained its more stable acetate **5c**, the spectral characteristics of which agreed with published data for related derivatives of furan: In the IR spectrum of this compound the maximum of the band for the carbonyl absorption of the acetoxyl group is observed at 1785 cm^{-1}, which is typical of 3-acetoxyfurans [25].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200 MHz (solvent deuterochloroform, internal standard TMS) and a Tesla BS-467A spectrometer at 60 MHz (for solutions of compounds **1** and **3** in carbon tetrachloride with HMDS as internal standard). The ^{13}C NMR spectra were obtained on a Bruker AC-200 spectrometer at 50.3 MHz for solutions in deuterochloroform. The chemical shifts were measured with reference to TMS. The IR spectra were recorded on a Specord 75IR spectrophotometer in carbon tetrachloride, and the mass spectra were obtained on a Shimadzu QP-5000 instrument (70 eV ionizing electrons). The reactions and the purity of the obtained compounds were monitored by TLC on Silufol plates with development with aqueous potassium permanganate solution.

***E*-2-Acetyl-2,3-diphenyloxirane (*E*-1).** The compound was obtained by oxidation of *E*-3,4-diphenyl-3-buten-2-one with an alkaline solution of hydrogen peroxide by the method in [15]. Yield 90%; mp 63-64°C (aqueous methanol) [15]. ^{1}H NMR spectrum, δ, ppm: 7.01 (5H, s, Ph); 6.88 (5H, s, Ph); 4.18 (1H, s, 3-H); 2.05 (3H, s, CH_3).

3-Hydroxy-2,3-diphenyl-6-trifluoromethyl-2,3-dihydro-4H-pyran-4-one (2a). The compound was obtained by the condensation of acetyloxirane *E*-**1** with ethyl trifluoroacetate by the method in [12]. Yield 80%; mp 73.5-74°C (hexane). IR spectrum, ν, cm^{-1}: 1640 (C=C), 1695 (C=O), 3495 (OH). ^{1}H NMR spectrum, δ, ppm: 7.33-7.05 (10H, m, 2Ph); 6.36 (1H, s, 5-H); 5.63 (1H, s, 2-H); 4.05 (1H, bs, OH). ^{13}C NMR spectrum, δ, ppm, *J* (Hz): 194.41 (C=O); 161.19 (q, $^2J_{C–F}$ = 38, $\underline{C}CF_3$); 135.20 (C_{quat}, Ph); 132.38 (C_{quat}, Ph); 128.95 (C, Ph); 128.68 (C, Ph); 128.20 (2C, Ph); 127.67 (2C, Ph); 127.62 (2C, Ph); 126.16 (2C, Ph); 118.53 (q, $^1J_{C–F}$ = 275, CF_3); 104.45 ($\underline{C}H=CCF_3$); 88.92 (CHO); 76.12 (COH). Mass spectrum (*m/z*) (I_{rel}, %): 335 (M^+ + 1, 20), 334 (M^+, 100), 229 (37), 228 (77), 196 (58), 165 (17), 131 (94), 118 (27), 105 (90), 91 (17), 90 (28), 89 (20), 77 (65), 53 (17), 51 (14). Found, %: C 64.85; H 4.13. $C_{18}H_{13}F_3O_3$. Calculated, %: C 64.67; H 3.92.

3-Acetoxy-2,3-diphenyl-6-trifluoromethyl-2,3-dihydro-4H-pyran-4-one (2b). The compound was synthesized by the acylation of compound **2a** with an excess of acetyl chloride [12]. Yield 81%; mp 90-91°C (hexane). IR spectrum, ν, cm^{-1}: 1645 (C=C), 1705, 1750 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.37-6.80 (10H, m, 2Ph); 6.56 (1H, s, 2-H); 6.38 (1H, s, 5-H); 2.28 (3H, s, CH_3). Found, %: C 63.99; H 4.21. $C_{20}H_{15}F_3O_4$. Calculated, %: C 63.83; H 4.02.

4-Chloro-3-hydroxy-3,4-diphenylbutan-2-one (3). To a solution of acetyloxirane *E*-**1** (4.0 g, 16.8 mmol) in dry benzene (100 ml) with stirring we added dropwise $SnCl_4$ (4.2 ml, 36.0 mmol), while keeping the temperature at 18-20°C. The reaction mixture was stirred for a further 2 h and poured onto ice. The benzene layer was separated, washed with dilute hydrochloric acid and then with water, and dried with sodium sulfate. Crystallization of the residue after removal of the benzene gave 4.0 g (87%) of chlorohydrin **3**; mp 95-96°C (hexane–isopropanol, 5:1). IR spectrum, ν, cm^{-1}: 1720 (C=O), 3425, 3545 (OH). ^{1}H NMR spectrum, δ, ppm: 7.36-6.84 (10H, m, 2Ph); 5.77 (1H, s, CHCl); 4.03 (1H, s, OH); 2.17 (3H, s, CH_3). Found, %: C 70.23; H 5.69. $C_{16}H_{15}ClO_2$. Calculated, %: C 69.95; H 5.50.

***Z*-2-Acetyl-2,3-diphenyloxirane (*Z*-1).** To a solution of chlorohydrin **3** (3.0 g, 10.9 mmol) in absolute methanol (20 ml) while stirring and cooling with iced water we added dropwise a solution of sodium methoxide, obtained from sodium (0.25 g, 10.9 mmol) and absolute methanol (25 ml). After stirring for 3 h methanol was evaporated at reduced pressure, water (5 ml) was added to the residue, and the mixture was extracted with methylene chloride. The extract was washed with water and dried with sodium sulfate. The methylene chloride was distilled, and 2.3 g (89%) of oxirane *Z*-**1** was obtained by crystallization of the residue; mp 70°C (hexane) [15]. ^{1}H NMR spectrum, δ, ppm: 7.57-7.06 (5H, m, Ph); 7.17 (5H, s, Ph); 3.91 (1H, s, 3-H); 1.93 (3H, s, CH_3).

3-Hydroxy-2-phenyl-5-trifluoromethylfuran (5b). To a solution of sodium isopropoxide, obtained from sodium (0.23 g, 10 mmol) and absolute isopropyl alcohol (7 ml) we added absolute diethyl ether (35 ml). With vigorous stirring we then added dropwise a solution of oxirane *Z*-**1** (1.2 g, 5 mmol) and ethyl trifluoroacetate (1.2 ml, 10 mmol) in ether (5 ml), while keeping the temperature between -10 and -12°C (cooling with ice and salt). The reaction mixture was stirred for 6 h, neutralized to pH 6-7 with acetic acid, kept at 18-20°C for 5 h, and washed with water. The ether layer was extracted with a saturated solution of $NaHSO_3$ until the smell of benzaldehyde had disappeared (monitored by TLC, development with an alcohol solution of 2,4-dinitrophenylhydrazine in the presence of sulfuric acid), washed again with water, and dried with sodium sulfate. After evaporation of the ether we obtained 1.1 g (95%) of furan **5b**; mp 96-97°C (carbon tetrachloride). IR spectrum, ν, cm^{-1}: 1635 (C=C), 1745 (C=O), 3595 (OH). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 7.83-7.25 (5H, m, Ph); 6.64 (1H, q, $J_{H–F}$ = 1.0, 4-H); 4.56 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm, *J*, Hz: 141.47 (COH); 137.17 (q, $^2J_{C–F}$ = 43, $\underline{C}CF_3$); 130.10 (C–Ph); 128.50 (2C, Ph); 127.05 (C_{quat}, Ph); 126.50 (C, Ph); 123.33 (2C, Ph); 119.19 (q, $^1J_{C–F}$ = 266, CF_3); 108.22 ($\underline{C}H=CCF_3$). Mass spectrum, *m/z* (I_{rel}, %): 228 (M^+, 100), 131 (41), 105 (42), 103 (23), 90 (19), 89 (21), 77 (81), 75 (14), 69 (21), 57 (23), 53 (35), 51 (48), 50 (23), 44 (45), 43 (62), 41 (31). Found, %: C 58.11; H 3.29. $C_{11}H_7F_3O_2$. Calculated, %: C 57.90; H 3.09.

In a similar experiment the reaction mixture, obtained from oxirane *Z*-**1** (0.3 g, 1.3 mmol) without treatment with $NaHSO_3$ solution, was chromatographed on a column of silica gel with chloroform as eluent. Benzaldehyde was obtained, and its treatment with an excess of an alcohol solution of 2,4-dinitrophenylhydrazine in ethanol in the presence of sulfuric acid gave 0.2 g (56%) of benzaldehyde 2,4-dinitrophenylhydrazone; mp 233°C [26]. We also obtained 0.19 g (66%) of hydroxyfuran **5b**.

3-Acetoxy-2-phenyl-5-trifluoromethylfuran (5c). To a solution of hydroxyfuran **5b** (0.28 g, 1.2 mmol) in dry pyridine (1 ml) while stirring and cooling with iced water we added dropwise acetyl chloride (0.18 ml, 2.5 mmol). After stirring for 2 h the reaction mixture was decomposed by the addition of water (5 ml) and extracted with methylene chloride. The extract was washed with water and dried with sodium sulfate. The residue after removal of the solvent was chromatographed on a column of silica gel with a 3:1 mixture of hexane and ether as eluent. We isolated 0.23 g (69%) of acetate **5c**; mp 36°C (pentane). IR spectrum, ν, cm^{-1}: 1635 (C=C), 1785 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.78-7.26 (5H, m, Ph); 7.06 (1H, s, 4-H); 2.35 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm, *J*, Hz: 167.70 ($\underline{C}OCH_3$); 143.17 ($\underline{C}$–$OCOCH_3$); 138.40 (q, $^2J_{C-F}$ = 43, $\underline{C}CF_3$); 134.10 (C–Ph); 128.86 (2C, Ph); 128.74 (C, Ph); 128.18 (C_{quat}, Ph); 124.89 (2C, Ph); 118.93 (q, $^1J_{C-F}$ = 267, CF_3); 110.04 (q, $^3J_{C-F}$ = 2, $\underline{C}H$=CCF_3); 20.92 ($CO\underline{C}H_3$). Mass spectrum, *m/z* (I_{rel}): 270 (M^+, 9), 229 (14), 228 (100), 227 (20), 131 (14), 105 (18), 77 (19), 51 (8), 43 (19). Found, %: C 57.98; H 3.57. $C_{13}H_9F_3O_3$. Calculated, %: C 57.79; H 3.36.

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