Cyclization of 1-aryl-5-phenylpent-4-en-2-yn-1-ones to 2,3-dihydropyran-2-ones in trifluoromethanesulfonic acid

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Under the action of an excess of trifluoromethanesulfonic acid, 1-aryl-5-phenylpent-4-en-2-yn-1-ones cyclize intramolecularly to 6-aryl-2-phenyl-2,3-dihydropyran-4-ones. The reaction proceeds at room temperature for 1 h with 50–60% yields.

Keywords: conjugated enynones, dihydropyranones, trifluoromethanesulfonic acid, carbocations, cyclization.

Various conjugated enynones are valuable compounds for organic synthesis. Three important linearly or crossconjugated functional fragments are present in their structure (multiple double and triple carbon–carbon bonds, as well as a carbonyl group), that allow them to undergo a variety of synthetic transformations. Nowadays, the number of works devoted to the methods of synthesis of organic compounds based on the enynone transformations has increased.¹ Nevertheless, linearly conjugated pent-4-en-2-yn-1-ones **1** (Scheme 1) remain the least studied among all possible conjugated enynones, probably due to the complicated methods of their synthesis.

It is known from the literature data that 1,5-diarylbut-4-en-2-yn-1-ones interact at the C-3 atom of the acetylenic bond to form dienone structures in reactions with S-nucleophiles (Scheme 1).² Enynones that do not contain aryl substituents at the carbonyl group interact with nucleophiles in a similar way. For example, an intramolecular cyclization with the participation of the alkoxycarbonyl group and the C-3 atom of the triple bond of enynes, catalyzed by gold complexes in the presence of AcOH, has been described^{3,4} (Scheme 1). Nucleophilic silylation of enynones and their carboxy analogs, catalyzed by copper(II) complexes, occurs at the C-3 and C-5 atoms of the enynone system, leading to the corresponding bisilyl derivatives (Scheme 1).⁵ In contrast, the reactions of enynones **1** with electrophilic reagents proceed at the C-2 atom of the acetylene bond. Thus, intramolecular reactions have been presented in which C-2 atom of the triple bond acts as a nucleophilic center, which ultimately leads to various carbocycles⁶ (Scheme 1).

Scheme 1. Literature data on synthetically significant transformations of linearly conjugated pent-4-en-2-yn-1-ones 1



Until now, the conversion of pent-4-en-2-yn-1-ones 1 under the action of various electrophilic reagents, such as Brønsted or Lewis acids, has not been systematically studied. It can be assumed that protonation with Brønsted acids (or coordination with Lewis acids) of the basic centers (multiple carbon–carbon bonds and oxygen atom of the carbonyl group) of conjugated enynones **1** will lead to the generation of highly reactive cationic species with several electrophilic centers. This kind of species can cyclize in superelectrophilic media, which opens up new synthetic routes to practically significant functional derivatives of heterocycles.^{1,7} Therefore, the aim of this work is to study the transformations of 1,5-diarylpent-4-en-2-yn-1-ones **1a**–**d** in strong Brønsted acids H₂SO₄ and TfOH (trifluoromethanesulfonic acid – superacid⁸).

A series of starting 1-aryl-5-phenylpent-4-en-2-yn-1-ones **1a–d** were synthesized in three steps (Scheme 2). In the first step, dibromodiene **2** was formed in Wittig reaction of cinnamaldehyde with CBr_4 and PPh_3 . The subsequent elimination of HBr by BuLi and hydrolysis have led to 1-phenylbut-1-en-3-yn (**3**), which was crosscoupled with aroyl chlorides under the Sonogashira conditions to give the target enynones **1a–d** in 40–61% yields.

Scheme 2. Synthesis of conjugated enynones 1a-d



1a R = H (50%), b R = Me (40%), c R = CI (61%), d R = Br (45%)

We have found that under the action of an excess of TfOH (15 equiv) envnones 1a-d cyclize to 6-aryl-2-phenyl-2,3-dihydropyran-4-ones 4a-d at room temperature within 1 h in 50-60% yields (Scheme 3). The structures of compounds 4a-d were established by ¹H, ¹³C NMR spectroscopy and high-resolution mass spectrometry. The position of the double bond in the dihydropyranone system of compounds 4b-d was additionally confirmed by the NOESY experiment based on the correlations between the vinyl proton of the pyranone ring and the ortho protons of the neighboring aryl substituent. The following characteristic signals of the dihydropyranone fragment are observed in the ¹H NMR spectra of dihydropyranones 4a-d: the 2-CH proton of the CHPh group at 5.56-5.59 ppm, the 5-CH vinyl proton at 6.09-6.13 ppm, as well as two diastereotopic protons of the 3-CH₂ group with a set of signals characteristic for AB system at 2.73-2.75 and 2.96-2.97 ppm. In the ¹³C NMR spectra, signals of carbon atoms of the pyran structure C-2 and C-3 at 81.2 -81.4 and 43.0-43.1 ppm, respectively, and carbonyl carbon atoms C=O at 192.8-193.3 ppm are present.

Earlier, structurally similar 2,3-dihydropyran-4-ones were obtained by us as a result of cyclization of cross-conjugated 1,5-diarylpent-1-en-4-yn-3-ones (Ar–CH=CH–CO–C=C–Ar') in $H_2SO_{4.7}^{7}$ However, in the present work, the reactions of

environmes 1a-d in H_2SO_4 led to the formation of complex mixtures possibly containing secondary products of subsequent aromatic sulfonation.

Scheme 3. Cyclization of enynones 1a-d into dihydropyranones 4a-d in TfOH



4a R = H (50%), b R = Me (50%), c R = Cl (60%), d R = Br (50%)

Additionally, we have studied the reaction of enynone **1b** with less amount of TfOH (1.5 equiv). In this case, the product of the Kucherov reaction – hydration of the acetylene bond – enolic form of the corresponding β -diketone **5a** was isolated after chromatographic separation on silica gel (Scheme 4). Apparently, compound **5a** is formed as a result of the hydrolysis of the intermediate vinyl triflate generated by the addition of TfOH to the acetylene bond of the starting enynone **1b**.

Scheme 4. Conversion of enynone 1b into compound 5a under the action of 1.5 equiv of TfOH



The complex of the experimental data obtained in this work, together with the results of our previous study on the conversion of cross-conjugated environmes in acids⁷, suggests possible mechanisms for the cyclization of envnones 1a-d to dihydropyranones 4a-d (Scheme 5). The initial protonation of the oxygen atom of the carbonyl group of substrates 1 in TfOH leads to cations $A \leftrightarrow A'$, which, in turn, can be protonated at the acetylene bond in the superacid TfOH with the formation of dications **B**. Both species A and B can form O-protonated forms of vinyl triflates C as a result of interaction with triflate anions TfO⁻. In the case of small amounts of TfOH, the reaction stops at this stage. Subsequent hydrolytic treatment of the reaction mixtures leads to vinyl triflates D. The latter are, apparently, unstable and hydrolyze rather rapidly to the enol forms of diketones 5 upon storage in air or chromatographic separation on silica gel (Scheme 4). In the case when excess of TfOH is used, the reaction proceeds further and cyclization of cations C to pyrans E occurs, subsequent hydrolysis of which leads to the formation of dihydropyranones 4. According to the literature data,^{7,9,10} cyclization of *O*-protonated enol forms $C \leftrightarrow C'$ (or similar enol structures) into pyrans E can proceed by two alternative mechanisms: as coordinated 6*π*-electrocyclization (resonance form C) or nucleophilic addition Ad_N (resonance form C') (Scheme 5). At this stage of the study, it is difficult to postulate which mechanism is





followed in this cyclization. However, consideration that to achieve the cyclization of cations C into pyrans E an excess of the superacid TfOH is required, which promotes the solvation of the intermediate cationic species, may indicate the ionic nature of the key cyclization intermediates, which possibly occurs in the case of the Ad_N reaction.

It is known that 2,3-dihydropyran-4-one fragment is included into the structure of many natural and biologically active compounds,^{11–13} therefore the development of the methods for the preparation of 2,3-dihydropyran-4-one derivatives is a promising trend of organic chemistry.

Thus, as a result of the study, a new method for the synthesis of 2,3-dihydropyran-4-one derivatives by cyclization of 1,5-diarylpent-4-en-2-yn-1-ones in trifluoro-methanesulfonic acid has been developed.

Experimental

¹H and ¹³C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz, respectively) in CDCl₃. Residual solvent signals (7.26 ppm for ¹H nuclei and 77.0 ppm for ¹³C nuclei) were used as internal standard. High-resolution mass spectra were recorded on a Bruker micrOTOF instrument, electrospray ionization. The reaction progress was monitored by TLC on Alugram SIL G UV-254 plates. The reaction mixtures were separated by column chromatography (on Merck 60 silica gel) or by preparative TLC (on LS 5/40 silica gel plates), eluent petroleum ether (fraction with bp 40–70°C) – EtOAc.

The synthesis and properties of the following compounds were described previously: 1,1-dibromo-4-phenylbuta-1,3-diene (2),¹⁴ 1-phenylbut-1-en-3-yne (3),¹⁵ 1,5-diphenylpent-4-en-2-yn-1-one (1a),¹⁶ 1-(4-methylphenyl)-5-phenylpent-4-en-2-yn-1-one (1b),¹⁶ 1-(4-chlorophenyl)-5-phenylpent-4-en-2-yn-1-one (1c).¹⁶

(4*E*)-1-(4-Bromophenyl)-5-phenylpent-4-en-2-yn-1-one (1d). Yield 200 mg (45%). Pale-yellow needles. Mp 89.5–

90.0°C (EtOH–H₂O). ¹H NMR spectrum, δ , ppm (*J*, Hz): 6.38 (1H, d, ³*J* = 16.2, =CH); 7.34–7.40 (4H, m, H Ph, =CH); 7.47–7.49 (2H, m, H Ph); 7.65 (2H, d, *J* = 8.6, H Ar); 8.03 (2H, d, *J* = 8.6, H Ar). ¹³C NMR spectrum, δ , ppm: 88.8; 93.7; 105.3; 127.2; 129.1; 129.6; 130.4; 131.1; 132.1; 135.2; 135.9; 148.4; 176.8. Found, *m/z*: 311.0073 [M+H]⁺. C₁₇H₁₂BrO. Calculated, *m/z*: 311.0066.

Synthesis of 2,6-diaryl-2,3-dihydro-4*H*-pyran-4-ones 4a–d from enynones 1a–d in TfOH (General method). TfOH (0.11 ml, 1.29 mmol) was added with vigorous stirring at room temperature to a solution of enynone 1a–d (0.086 mmol) in CH₂Cl₂ (0.1 ml), the mixture was stirred for 1 h. The reaction mixture was poured into H₂O (50 ml), extracted with CHCl₃ (3×25 ml). The combined extracts were washed with H₂O (50 ml), aqueous NaHCO₃ solution (25 ml), again with H₂O (25 ml) and dried with Na₂SO₄. The solvent was removed under reduced pressure, the product was isolated by preparative TLC on LS 5/40 µm silica gel plates, eluent petroleum ether – EtOAc, 95:5. The separated fractions were washed off from the sorbent with CH₂Cl₂.

2,6-Diphenyl-2,3-dihydro-4*H***-pyran-4-one (4a).⁷ Yield 11 mg (50%). Pale-yellow solid. Mp 94–95°C. ¹H NMR spectrum, \delta, ppm (***J***, Hz): 2.75 (1H, AB system, ddd, ²***J* **= 16.9, ³***J* **= 3.4, ⁴***J* **= 0.8, CH₂); 2.97 (1H, AB system, dd, ²***J* **= 16.9, ³***J* **= 14.1, CH₂); 5.59 (1H, dd, ³***J* **= 14.1, ³***J* **= 3.4, CHPh); 6.13 (1H, d, ⁴***J* **= 0.8, =CH); 7.41–7.47 (4H, m, H Ph); 7.48–7.52 (3H, m, H Ph); 7.77–7.80 (2H, m, H Ph). ¹³C NMR spectrum, \delta, ppm: 43.1 (3C); 81.2 (2C); 102.5; 126.3; 126.8; 128.9; 129.0 (2C); 131.9; 132.7; 138.5; 170.5; 193.1 (C=O). Found,** *m***/***z***: 251.1073 [M+H]⁺. C₁₇H₁₅O₂. Calculated,** *m***/***z***: 251.1067.**

6-(4-Methylphenyl)-2-phenyl-2,3-dihydro-4H-pyran-4-one (4b). Yield 10 mg (50%). Oil. ¹H NMR spectrum, δ , ppm (*J*, Hz): 2.40 (1H, s, CH₃); 2.73 (1H, AB system, ddd, ²*J* = 16.9, ³*J* = 3.4, ⁴*J* = 0.9, CH₂); 2.96 (1H, AB system, dd, ²*J* = 16.9, ³*J* = 14.1, CH₂); 5.56 (1H, dd, ³*J* = 14.1, ${}^{3}J = 3.4$, CHPh); 6.12 (1H, d, ${}^{4}J = 0.9$, =CH); 7.25–7.27 (2H, m, H Ar); 7.39 (2H, d, J = 8.0, H Ar); 7.42–7.44 (2H, m, H Ar); 7.47–7.51 (2H, m, H Ar); 7.76–7.79 (2H, m, H Ar). 13 C NMR spectrum, δ , ppm: 21.4; 43.0 (3C); 81.2 (2C); 102.4; 126.4; 126.8; 128.8; 129.7; 131.9; 132.8; 135.4; 139.0; 170.6; 193.3 (C=O). Found, *m*/*z*: 265.1230 [M+H]⁺. C₁₈H₁₇O₂. Calculated, *m*/*z*: 265.1223.

6-(4-Chlorophenyl)-2-phenyl-2,3-dihydro-4H-pyran-4-one (4c). Yield 13 mg (60%). Oil. ¹H NMR spectrum, δ , ppm (*J*, Hz): 2.75 (1H, AB system, ddd, ²*J* = 16.9, ³*J* = 3.4, ⁴*J* = 0.9, CH₂); 2.96 (1H, AB system, dd, ²*J* = 16.9, ³*J* = 14.1, CH₂); 5.58 (1H, dd, ³*J* = 14.1, ³*J* = 3.4, CHPh); 6.09 (1H, d, ⁴*J* = 0.9, =CH); 7.41 (2H, d, *J* = 8.8, H Ar); 7.44–7.48 (5H, m, H Ph); 7.71 (2H, d, *J* = 8.8, H Ar). ¹³C NMR spectrum, δ , ppm: 43.1 (3C); 81.4 (2C); 102.6; 126.4; 128.1; 129.0; 129.1; 129.2; 131.2; 138.1; 138.3; 169.2; 192.8 (C=O). Found, *m*/*z*: 285.0683 [M+H]⁺. C₁₇H₁₄ClO₂. Calculated, *m*/*z*: 285.0677.

6-(4-Bromophenyl)-2-phenyl-2,3-dihydro-4H-pyran-4-one (4d). Yield 10 mg (50%). Oil. ¹H NMR spectrum, δ , ppm (*J*, Hz): 2.75 (1H, AB system, ddd, ²*J* = 17.0, ³*J* = 3.4, ⁴*J* = 0.9, CH₂); 2.96 (1H, AB system, dd, ²*J* = 17.0, ³*J* = 14.1, CH₂); 5.58 (1H, dd, ³*J* = 14.1, ³*J* = 3.4, CHPh); 6.10 (1H, d, ⁴*J* = 0.9, =CH); 7.42–7.50 (5H, m, H Ph); 7.57 (2H, d, *J* = 8.8, H Ar); 7.64 (2H, d, *J* = 8.8, H Ar). ¹³C NMR spectrum, δ , ppm: 43.0 (3C); 81.4 (2C); 102.6; 126.4; 126.6; 128.3; 129.1 (2C); 132.2; 138.2; 169.4; 192.9 (C=O). Found, *m/z*: 329.0180 [M+H]⁺. C₁₇H₁₄BrO₂. Calculated, *m/z*: 329.0172.

(2*Z*,4*E*)-3-Hydroxy-1-(4-methylphenyl)-5-phenylpenta-2,4-dien-1-one (5a) was synthesized according to the general method for the preparation of compounds 4a–d from enynone 1b (20 mg, 0.08 mmol) and TfOH (18 mg, 1.2 mmol) in CH₂Cl₂ (0.1 ml). The product was isolated by column chromatography on silica gel, eluent petroleum ether – EtOAc, 99:1. Yield 14 mg (67%). Oil. ¹H NMR spectrum, δ , ppm (*J*, Hz): 2.39 (3H, s, CH₃); 6.34 (1H, s, =CH); 6.62 (1H, d, ³*J* = 15.8, =CH); 7.21 (2H, d, *J* = 8.0, H Ar); 7.46–7.50 (4H, m, H Ar); 7.53–7.57 (1H, m, H Ar); 7.68 (1H, d, ${}^{3}J = 15.8$, =CH); 7.94–7.97 (2H, m, H Ar). 13 C NMR spectrum, δ , ppm: 21.6; 97.6; 122.5; 127.5; 128.2; 128.8; 129.8; 132.5; 132.6; 136.5; 140.3; 140.6; 180.1; 189.1. Found, *m*/*z*: 265.1227 [M+H]⁺. C₁₈H₁₇O₂. Calculated, *m*/*z*: 265.1223.

Supplementary information file containing ¹H and ¹³C NMR spectra of all synthesized compounds, as well as NOESY spectra of compounds **4c,d** is available at the journal website at http://link.springer.com/journal/10593.

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