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REACTION OF ARENEDIAZONIUM CHLORIDES AND SULFUR(IV) OXIDE WITH (2*E*,6*E*)-2,6-DIBENZYLIDENECYCLOHEXANONE AND (2*E*,2'*E*)-3,3'-BENZENE-1,4-DIYL-BIS(1-PHENYLPROP-2-EN-1-ONE)

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Abstract. It has been established that cuprous catalytic reaction of (2*E*,6*E*)-2,6-dibenzylidenecyclohexanone or (2*E*,2'*E*)-3,3'-benzene-1,4-diyl-bis(1-phenylprop-2-en-1-one) with arenediazonium chloride and sulfur(IV) oxide leads to the formation of arylsulfonylation product by only one double bond. Substituted 2-benzyliden-6-[(arylsulfonyl)(phenyl)methyl]cyclohexanones and 3[4-(1-arylsulfonyl-3-oxo-3-phenylpropyl)phenyl]-1-phenylprop-2-en-1-ones) have been obtained.

Keywords: arylsulfonylation, *a,b*-unsaturated ketones, arenediazonium salts, 2,6-dibenzylidenecyclohexanone, chalcones.

1. Introduction

a,b-Unsaturated ketones are important intermediates also known as chalconic pharmacophores [1]. Pharmacological properties of chalcones are determined by the presence of *a,b*-unsaturated oxo-fragment and aromatic ring [2]. Recent publications emphasize the anti-microbial properties of chalcones, especially of their *p*-nitro-substituted derivatives [3]. Traditional approach to the search of promising biologically active substances is combining several pharmacological fragments in one molecule. From this standpoint chalcone derivatives are interesting due to the presence of arylsulfonylic fragments, which provide different pharmacological properties. A set of biologically active compounds with specific action on some enzymes, including antibiotics [5], cytotoxins [6], *etc.*, were synthesized on the basis of arylsulfones [4]. In the recent years arylsulfones have been widely used in the solid-phase organic synthesis (SPOS) for obtaining linkers [7] for the synthesis of compounds with broad activity spectrum – from optical conductors to inhibitors of human leukocytic elastase. Thus, the question of their effective synthesis is still a topical one.

2. Experimental

2.1. Starting Reagents and Spectral Methods

¹H NMR spectra were recorded on a Varian Mercury instrument (400 MHz) in DMSO-d₆. UV-spectra were measured on Nanodrop ND-1000 Spectrophotometer in ethanol.

(2*E*,6*E*)-2,6-Dibenzylidenecyclohexanone **1** and (2*E*,2'*E*)-3,3'-benzene-1,4-diylbis(1-phenylprop-2-en-1-one) **4** were synthesized as described [4].

2.2. General Procedure for Arylsulfonylation of (2*E*,6*E*)-2,6-Dibenzylidenecyclohexanone **1**

(2*E*)-2-Benzylidene-6-[(arylsulfonyl)(phenyl)methyl]cyclohexanones (**3a-f**) were synthesized as described in [9]. A tree-necked round-bottomed flask is equipped with thermometer, stirrer, dropping funnel, and bubble counter. The flask is charged with 0.01 mol of alkene **1**, 0.3 g of copper chloride and 20 ml of 30 % SO₂ solution in acetone. The 0.01 mole cold diazonium salt solution **2** is added dropwise, and the mixture is stirred until N₂ evolution ceases. Following that the reaction mixture is stirred for additional 3–4 h and diluted with water. The obtained precipitate was washed with water by decanting till neutral reaction, than dried and crystallized from ethanol. The products were purified by repeated crystallization.

(2*E*)-2-Benzylidene-6-[(phenyl)(phenylsulfonyl)methyl]cyclohexanone **3a**. Yield 40 %. Mp 420 K (decomp.). Found: C 74.80; H 5.68; S 7.61. C₂₆H₂₄O₃S. Calc.: C 74.97; H 5.81; S 7.70.

(2*E*)-2-Benzylidene-6-[(4-methylphenylsulfonyl)(phenyl)methyl]-cyclohexanone **3b**. Yield 51 %. Mp 410 K (decomp.). Found: C 75.24; H 6.21; S 7.58.

$C_{27}H_{26}O_3S$. Calc.: C 75.32; H 6.09; S 7.45. UV spectrum, nm: 232. 242. 262. 268. 274. 286. 315.

(*E*)-2-Benzylidene-6-[(4-methoxyphenylsulfonyl)(phenyl)methyl]-cyclohexanone **3c**. Yield 35 %. Mp 395 K (decomp.). Found: C 72.44; H 5.91; S 7.32. $C_{27}H_{26}O_4S$. Calc.: C 72.62; H 5.87; S 7.18.

(*E*)-2-Benzylidene-6-[(4-nitrophenylsulfonyl)(phenyl)methyl]-cyclohexanone **3d**. Yield 41 %. Mp 427 K (decomp.). Found: C 67.81; H 4.95; N 3.15; S 6.82. $C_{26}H_{23}NO_5S$. Calc.: C 67.66; H 5.02; N 3.03; S 6.95.

(*E*)-2-Benzylidene-6-[(4-bromophenylsulfonyl)(phenyl)methyl]-cyclohexanone **3e**. Yield 43 %. Mp 405 K (decomp.). Found: C 62.91; H 4.81; Br 16.09; S 6.58. $C_{26}H_{23}BrO_3S$. Calc.: C 63.03; H 4.68; Br 16.13; S 6.47. UV spectrum, nm: 229, 242, 265, 274, 289, 298, 315.

(*E*)-2-Benzylidene-6-[(1-naphthylsulfonyl)(phenyl)methyl]-cyclohexanone **3f**. Yield 32 %. Mp 409 K (decomp.). Found: C 77.39; H 5.75; S 6.73. $C_{30}H_{26}O_3S$. Calc.: C 77.22; H 5.62; S 6.87.

2.3. General Procedure for Arylsulfonylation of (*E*,*E'*)-3,3'-Benzene-1,4-diyl-bis(1-phenylprop-2-en-1-one) **4**

(*E*)-3-[4-(1-Arylsulfonyl-3-oxo-3-phenyl-propyl)phenyl]-1-phenylprop-2-en-1-ones **5a, b** were synthesized according to the modified method [9]. A tree-necked round-bottomed flask is equipped with thermometer, stirrer, dropping funnel, and bubble counter. The flask is charged with 0.01 mole of alkene **4**, 0.3 g of copper chloride and 20 ml of 30 % SO_2 solution in acetic acid and heated at 333–348 K. The 0.01 mole diazonium salt solution (**2**) is added dropwise, and the mixture is stirred until N_2 evolution ceases. Following that the reaction mixture is stirred for additional 3–4 h and diluted with water. The obtained precipitate was washed with water by decanting till neutral reaction, than dried and crystallized from ethanol. The products were purified by repeated crystallization.

(*E*)-1-Phenyl-3-[4-[1-(phenylsulfonyl)-3-oxo-3-phenylpropyl]phenyl]prop-2-en-1-one **5a**. Yield 55 %. Mp 452 K (decomp.). Found: C 75.05; H 5.18; S 6.78. $C_{30}H_{24}O_4S$. Calc.: C 74.98; H 5.03; S 6.67. UV spectrum, nm: 234, 244, 337, 346, 358, 366. 1H NMR (DMSO- d_6 , 400 MHz) δ (ppm): 3.90 (two dd, 2H, CH_2); 5.03 (dd, 1H, CH); 7.32 (d, 1H, CH-vinyl), 7.50–7.88 (m, 9H, $C_6H_5+C_6H_4$); 7.90–7.92 (m, 6H, C_6H_5+CH -vinyl); 8.12 (m, 5H, C_6H_5).

(*E*)-1-Phenyl-3-[4-[1-(4-methylphenylsulfonyl)-3-oxo-3-phenylpropyl]phenyl]prop-2-en-1-one **5b**. Yield 68 %. Mp 446 K (decomp.). Found: C 75.16; H 5.21; S 6.39. $C_{31}H_{26}O_4S$. Calc.: C 75.28; H 5.30; S 6.48. UV spectrum, nm: 229, 241, 324, 337, 343, 352, 358.

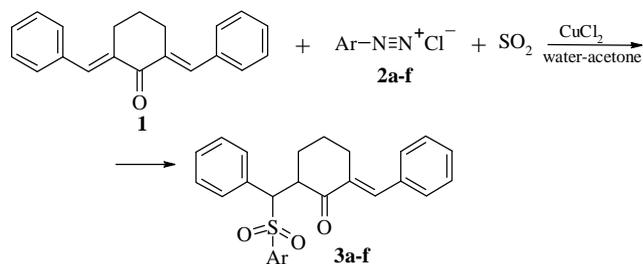
3. Results and Discussion

Cuprocatalytic interaction of *a,b*-unsaturated ketones with arenediazonium salts in the presence of SO_2 may be treated as “one pot” multicomponent reaction, allowing to obtain complex functionalized compounds, containing sulfo-group, without isolation of intermediary products. It is known, that arylsulfonylation of *a, b*-unsaturated ketones with arenediazonium salts results in a high yields and is quite defined, as opposed to similar reactions without SO_2 [8].

Earlier we have described cuprous catalytic arylsulfonylation of (*E*,*4E*)-1,5-diphenylpenta-1,4-dien-3-one [9]. The task of the current work was to further investigate arylsulfonylation of bis-*a,b*-unsaturated ketones using as example (*E*,*6E*)-2,6-dibenzylidenecyclohexanone and (*E*,*2'E*)-3,3'-benzene-1,4-diylbis(1-phenylprop-2-en-1-one) with arenediazonium chlorides and sulfur(IV) oxide; another task was to obtain arylsulphones containing chalcone fragment in the molecule, as compounds combining arylsulfonyl and chalconic fragments are promising candidates for biologically active compounds.

The study of reaction of (*E*,*6E*)-2,6-dibenzylidenecyclohexanone **1** with arenediazonium salts **2** and SO_2 (25–30 % acetone solution) was performed under cuprous catalytic conditions ($CuCl_2$). Water-acetone 1:1 medium was used as a solvent. The reaction was carried out at room temperature. Reaction products were obtained as precipitates, which were further purified by crystallization from different solvents or by washing with diethyl ether, hexane, or CCl_4 . Unsaturated compound and arenediazonium salt were taken in the ratio 1:1, despite the fact that unsaturated compound has two double bonds. It was planned to obtain arylation compounds by one double bond with preserving of another one for formation of chalconic fragment in the molecule.

We have found that the reaction occurs as arylsulfonylation by one C=C bond:

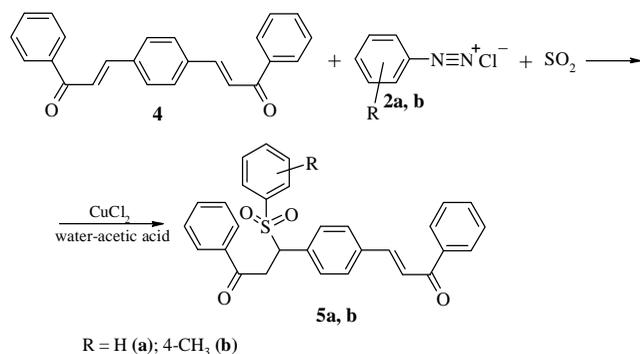


Ar = C_6H_5 (a), $C_6H_4-CH_3-p$ (b), $C_6H_4-OCH_3-p$ (c), $C_6H_4-NO_2-p$ (d), C_6H_4-Br-p (e), α -naphthyl (f)

Reaction of (*E*,*2'E*)-3,3'-benzene-1,4-diylbis(1-phenylprop-2-en-1-one) **4** with arenediazonium salts and sulfur(IV) oxide was carried out as in the previous

reaction, but acetic acid-water 1:1 was used as the reactive medium was. The reaction was carried at 338–343 K for full dissolving of unsaturated compound in the acetic acid medium.

Reaction of **4** with arenediazonium salts and SO₂ also results in the formation of the product by one double bond:



The structure of compounds **5a, b** was confirmed by elemental analysis, ¹H NMR, and UV spectral data. During identification of compounds we proved the presence of the double bond in the molecule (decolorizing of bromine water and potassium permanganate solution). The presence of a conjugated system of double bonds in compounds **3** and **5** is verified by UV spectra, taken for alcohol solutions. In the NMR ¹H spectrum of compound **5a** we have identified signals characteristic of AMX spin system (CH₂CH). Chemical shifts are (*d*, ppm): 3.90 (two dd, 2H, CH₂); 5.03 (dd, 1H, CH); 7.32 (d, 1H, CH-vinyl); 7.50–7.88 (m, 9H, C₆H₅+C₆H₄); 7.90–7.92 (m, 6H, C₆H₅+CH-vinyl) and 8.12 (m, 5H, C₆H₅).

UV spectra of compounds **3b, e** are characterized by the presence of absorption lines at 232 and 229 nm (Ar), at 242 nm (Ar–SO₂), 262–274 nm (Ar–SO₂–CH=C), 286–298 nm (C=C–C=O), and 315–318 nm (characteristic of a longer conjugation chain). The less intense absorption lines are the two last ones.

UV spectra of compounds **5a, b** are characterized by the presence of absorption lines at 229 and 234 nm (Ar), at 241 and 244 nm (Ar–SO₂), 270–300 nm (Ar–SO₂–CH=C, C=C–C=O), and the most intense lines with fine structure in the region of 325–370 nm with the maxima at 352 and 358 nm, characterizing low-energy electron transition, caused by relatively long conjugation chains containing chalcon fragment.

The differences in spectral properties of compounds **3** and **5** are most probably caused by the plane location of central benzene ring in **5**, and by the possibility of existing

of central cyclohexane ring in different conformations for compounds **3**.

Thus, multicomponent arylsulfonation reaction of bis-α,β-unsaturated ketones results in high yield of arylsulfones with chalcone core in the molecule, which, based on the analysis of the literary data, have potentially high pharmacological activity.

4. Conclusions

It was shown that the reaction of (2*E*,6*E*)-2,6-dibenzylidenecyclohexanone and (2*E*,2'*E*)-3,3'-benzene-1,4-diyl-bis(1-phenylprop-2-en-1-one) with aryldiazonium chlorides and sulfur dioxide under cuprous(II) catalytic conditions occurs as arylation only by one double bond. The (2*E*)-2-benzylidene-6-[(arylsulfonyl)(phenyl)methyl]cyclohexanones and (2*E*)-3[4-(1-arylsulfonyl-3-oxo-3-phenyl-propyl)phenyl]-1-phenylprop-2-en-1-ones are formed.

References

- [1] Srikanth G. and Castle S.: Tetrahedron, 2005, **61**, 10377.
- [2] Kempin U., Hennig L., Knoll D. *et al.*: Tetrahedron, 1997, **53**, 17690.
- [3] Ardia R. and Rao J.: Asian J. Chem., 2004, **16**, 1194.
- [4] Desenko S. and Orlov V.: Azogeterocykly Nenasychenyh Aromatycheskih Khalkonov. Folio. Kharkov 1998.
- [5] Dhar D.: The Chemistry of Chalcones and Related Compounds. John Wiley & Sons, New York 1981.
- [6] Boyd M.: Cancer: Principles and Practice of Oncology Updates. Lippincott, Philadelphia 1989.
- [7] Chen Yu., Lam Yu. and Yee-Hing L.: Org. Lett., 2003, **5**, 1067.
- [8] Bila E. and Ganschak M.: Proceedings of the Shevchenko Scientific Society, 2003, **10**, 76.
- [9] Bila E.: Visnyk Lvivskogo Universytetu, 2008, **49**, 2.

ВЗАЄМОДІЯ ХЛОРИДІВ АРЕНДІАЗОНІЮ ТА ОКСИДУ СУЛЬФУРУ(IV) З (2*E*,6*E*)-2,6-ДИБЕНЗИЛІДЕНЦИКЛОГЕКСАНОНОМ ТА (2*E*,2'*E*)-3,3'-БЕНЗЕН-1,4-ДІЛ-БІС(1-ФЕНІЛПРОП-2-ЕН-1-ОНОМ)

Анотація. Встановлено, що купрокаталітична взаємодія (2*E*,6*E*)-2,6-добензиліденциклогексанону та (2*E*,2'*E*)-3,3'-бензен-1,4-ділбіс(1-фенілпроп-2-ен-1-ону) з хлоридами арендіазонію та оксидом сульфуру(IV) приводить до утворення продуктів арилсульфонілювання лише за одним подвійним зв'язком. Отримані заміщені (2*E*)-2-бензиліден-[6-(арилсульфоніл)(феніл)метил]циклогексанони та (2*E*)-3[4-(1-арилсульфоніл-3-оксо-3-фенілпропіл)феніл]-1-фенілпроп-2-ен-1-они.

Ключові слова: арилсульфонілювання, а,в-ненасичені кетони, солі арендіазонію, 2,6-добензиліденциклогексанон, 3,3'-бензен-1,4-ділбіс(1-фенілпроп-2-ен-1-он), халкони.