Regio- and Enantioselective Catalytic Iodoalkoxylation of Styrene Derivatives with Unsaturated C_3-Alcohols

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Summary: The synthesis of unsaturated *β*-iodoethers remains a significant challenge in modern organic chemistry. Three-component synthesis is a highly relevant approach for obtaining these compounds. The primary objective of this study was to develop a process where the triple bond of the reagent is preserved while iodine addition is selectively directed to the double bond of substituted styrenes. This work represents the first successful attempt to perform this reaction in an enantioselective manner. The iodoalkoxylation of substituted styrenes with unsaturated *C*3-alcohols (propargyl and allyl) in the presence of diisopinocampheylborane leads to the formation of regio- and enantiomerically enriched iodoethers with yields of 57–63%. The synthesized compounds were characterized by (^{1}H-NMR), (^{13}C-NMR) and FTIR spectroscopy. The synthesis followed established methodologies and proceeded without significant complications.

Keywords: Iodoalkoxylation, Unsaturated C_3-alcohols, Enantioselectivity, Regioselectivity, Diisopinocampheylborane.

Introduction

Organic compounds containing halogen atoms have played a significant role in pharmaceutical development [1] and organic synthesis [2] over recent decades. Iodine, in particular, is an essential trace element for living organisms, vital for human and animal growth [3] and a key component of the thyroid gland [4]. The *β* - iodoether fragment is a common motif in various medicinal compounds [5,6]. In this study, the reaction was optimized through precise control of parameters, including low temperature and the specific sequence of reagent addition.

Experimental

IR spectra of compounds in a thin layer were recorded on the Specord 75 IR device. NMR spectra of ^{1}H and ^{13}C substances in $CDCl_3$ were recorded on the Bruker SF-300 [300.13 (1H), 75(^{13}C) MHz] device, the internal standard is GMDS. Elemental analysis was performed on the EURO EA 3000 device.

Preparation of ethers unsaturated C_3-alcohols **[7]**

2.6 g (0.009 mol) of diisopinocampheylborane was added to a mixture cooled to (-5÷0°C) and intensively stirred mixture of 14 g (0.25 mol) of substituted styrene, then 2.6 g (0.009 mol) of diisopinocampheylborane was added in portions (0.12 mol) of finely ground crystalline iodine. Stirring continued at room temperature for another 3-4 hours, then the mixture was filtered, the filtrate was washed with a solution of $Na_2S_2O_3$ and extracted with ether. The extract was dried with $CaCl_2$, the ether was removed, and the reaction mixture was then stirred at room temperature. After the initial material was used up us detected by TLC detection, the reaction mixture was poured into NaCl dissolved in water, and then extracted with CH_2Cl_2 (3×10 mL). The combined organic layer was then washed with water (10 mL). The raw product was purified by flash chromatography (silica gel, petroleum ether: ethyl acetate = 6:1). After removing the solvent under reduced pressure, the residue was purified by column chromatography.

One of the rational ways to obtain allyl β-iodides is to alkoxyiodize alkenes with unsaturated C_3-alcohols and iodine [8]. In order to avoid the addition of crystalline iodine to a multiple bond (both to the double bond of allyl alcohol and substituted styrene, and to the triple bond of propargyl alcohol), the temperature of the reaction medium is brought to -5°C and the sequence of supply of the initial compounds is strictly controlled. At (-5 to 0°C) and with intensiv stirring a mixture of unsaturated C_3-alcohols and olefin is added in portions of finely ground crystalline iodine. Yields of methoxy-substituted styrene are higher than those chlorine- and chloromethyl-substituted analogues.

Synthesis of {(2S,3R)-2-Iodo-1-[(prop-2-in-1-yl)oxy]ethyl}benzene (**1**).

Eluent – hexane/AsOEt, 4:1 and 4:1. with a yield of **1** (226.9 mg, 93%) as a white liquid – yellow

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oil. İR spectrum, ν, cm^{-1}: 3308 (C≡CH), 2102 (C≡C), 1108 (C-O-C), 552 (C-I). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 2.51 t (1H, ≡CH, ^4J 2 Hz), 3.51-3.55 m (1H, CH), 3.60-3.64 m (1H, CH), 4.01 d (2H, ≡CH_2O, ^4J 2 Hz), 4.90 k (1H, CH, *J* 3.5 Hz, *J* 9.0 Hz), 7.23-7.36 m (5H, Ar). NMR spectrum ^{13}C ($CDCl_3$), δ_C, ppm: 39.61, 56.12 (≡C-CH_2O), 68.35 (≡CH), 71.81, 79.45 (≡C-CH_2O), 126.02, 128.52, 128.71, 139.91. Found, %: C 46.16; H 3.84; I 44.31. $C_{11}H_{11}IO$. Calculated, %: C 46.18; H 3.88; I 44.36.

Synthesis of {(2S,3R)-2-Iodine-1-[(prop-2-en-1-yl)oxy]ethyl}benzene (**2**)

İR spectrum, ν, cm^{-1}: 3081 (C-H), 3064 (CH_2=CH), 3032 (CH_2=CH), 3012 (CH_2=CH), 1642 (C=C), 1491 (CH_2=CH), 1363 (CH_2=CH), 1270 (CH_2=CH), 1102 (C-O-C), 985, 885, 770, 552 (C-l). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 3.50-3.54 m (1H, CH), 3.61-3.64 m (1H, CH), 4.17 d.d.d. (1H, OCH_2, *J* 12.15, 1.61, 1.23 Hz), 4.88 d.d.d. (1H, OCH_2, *J* 12.15, 5.34 Hz), 4.91 k (1H, CH, *J* 3.5 Hz, *J* 9.0 Hz), 5.17 d.d (1H, H_2C=, *J* 9.15, 1.57, 1.23 Hz), 5.31 d.d (1H, H_2C=, *J* 17.21, 1.57, 1.61 Hz), 5.84 d.d.d. (1H, OCH=, *J* 17.21, 9.15, 5.34 Hz), 7.25-7.35 m (5H, Ar). NMR spectrum ^{13}C ($CDCl_3$), δC, ppm: 39.52, 56.81, 72.32 (=C-CH2O), 74.01, 110.21, 117.67 (H_2C=), 127.32, 131.93, 134.63 (-HC=), 161.73. Found, %: C 45.81; H 4.53; I 44.07. $C_{11}H_{13}IO$. Calculated, %: C 45.85; H 4.55; I 44.04.

Synthesis of 1-Chloro-4-{(2S,3R)-2-iodine-1-[(prop-2-in-1-yl)oxy]ethyl}benzene (**3**).

IR spectrum, ν, cm-^{1}: 3306 (≡C-H), 2100 (C≡C), 1105 (C-O-C), 551 (C-Cl). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 2.50 t (1H, ≡CH, ^4J 2 Hz), 3.60 k (1H, CH, *J* 8.5 Hz, *J* 10.5 Hz), 3.59 k (1H, CH, *J* 8.5 Hz, *J* 10.5 Hz), 4.01 d (2H, ≡CH_2O, ^4J 2 Hz), 4.88-4.88 m (1H, CH), 7.25-7.34 (4H, Ar). NMR spectrum ^{13}C ($CDCl_3$), δ_C, ppm: 41.41, 56.10 (≡C-CH2O), 68.35 (CH), 72.23, 79.45 (≡C-CH_2O), 127.42, 128.92, 134.24, 138.81. Found, %: C 41.21; H. 3.12; Cl 11.03; I 39.61. $C_{11}H_{10}ClIO$. Calculated, %: C 41.22; H. 3.14; Cl 11.06; I 39.59.

Synthesis of 1-Chloro-4-{(2S,3R)-2-iodine-1-[(prop-2-en-1-yl)oxy]ethyl}benzene (**4**).

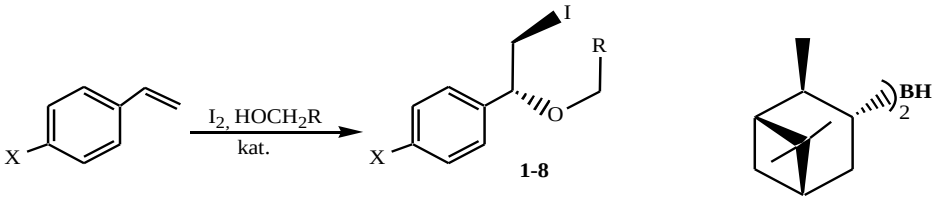
İR spectrum, ν, cm^{-1}: 3083 (C-H), 3064 (CH_2=CH), 3033 (CH_2=CH), 3010 (CH_2=CHO), 1641 (C=C), 1490 (CH_2=CH), 1360 (CH_2=CH), 1272 (CH_2=CH), 1101 (C-O), 985, 885, 771 (C-Cl), 551 (C-l). NMR spectrum 1H ($CDCl_3$), δ, ppm: 3.48 k (1H, CH, *J* 8.5 Hz, *J* 10.5 Hz), 3.50 k (1H, CH, *J* 8.5 Hz, *J* 10.5 Hz), 4.17 d.d.d (1H, OCH_2, *J* 12.15, 1.61, 1.23 Hz), 4.61 d.d.d (1H, OCH_2, *J* 12.15, 5.34 Hz), 4.86-4.89 m (1H, CH), 5.17 d.dd (1H, H_2C=, *J* 9.15, 1.57, 1.23 Hz), 5.31 d.d.d (1H, H_2C=, *J* 17.21, 1.57, 1.61 Hz), 5.85 d.d.d (1H, OCH=, *J* 17.21, 9.15, 5.34 Hz), 7.25-7.35 m (4H, Ar). NMR spectrum ^{13}C ($CDCl_3$), δ_C, ppm: 41.42, 72.23, 72.31 (=C-CH_2O), 117.67 (H2C=), 127.42, 128.91, 134.22, 134.62 (-HC=), 138.82. Found, %: C 40.91; H 3.77; Cl 10.96; I 39.31. $C_{11}H_{12}ClIO$. Calculated, %: C 40.96; H 3.75; Cl 10.99; I 39.34.

Synthesis of 1-(Chloromethyl)-4-{(2S,3R)-2-iodine-1-[(prop-2-in-1-yl)oxy]ethyl}benzene (**5**).

IR spectrum, ν, cm^{-1}: 3307 (≡C-H), 2101 (C≡C), 1104 (C-O), 550 (C-Cl). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.51 t (1H, ≡CH_2O, ^4J 2Hz), 3.50 k (^1H, CH, *J* 9.0 Hz, *J* 11.0 Hz), 3.62 k (^1H, CH, *J* 3.5 Hz, *J* 10.5 Hz, 1H), 4.02 d (2H, ≡CH_2O, ^4J 2 Hz), 4.56 s (2H, CH2), 4.92 k (1H, CH, *J* 3.5 Hz, *J* 9.0 Hz), 7.25-7.36 m (4H, Ar). NMR spectrum ^{13}C ($CDCl_3$), δ_C, м. д.: 40.53, 45.72, 56.13 (≡C-CH_2O), 68.35 (≡CH), 73.42, 79.46 (≡C-CH_2O), 126.41, 128.92, 137.72, 140.52. Found, %: C 43.02; H 3.61; Cl 10.63; I 37.91. $C_{12}H_{12}ClIO$. Calculated, %: C 43.08; H 3.62; Cl 10.60; I 37.93.

Synthesis of 1-(chloromethyl)-4-{(2S,3R)-2-iodine-1-[(prop-2-en-1-yl)oxy]ethyl}benzene (**6**).

IR spectrum, ν, cm^{-1}: 3081 (C-H), 3064 (HC=CH_2), 3030 (HC=CH_2), 3012 (HC=CH_2), 1642 (HC=CH_2), 1493 (HC=CH_2), 1360 (HC=CH_2), 1270 (HC=CH_2), 1101(C-O), 985, 885, 772, 551(C-Cl). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 3.52 k (1H, CH, *J* 9.0 Hz, *J* 11.0 Hz), 3.62 k (1H, CH, *J* 3.5 Hz, *J* 10.5 Hz), 4.17 d.d.d. (1H, OCH_2, *J* 12.15, 1.61, 1.23 Hz), 4.58 s (2H, CH2), 4.61 d.d (1H, OCH_2, *J* 12.15, 5.34 Hz), 4.92 k (1H, CH, *J* 3.5 Hz, *J* 9.0 Hz), 5.17 d.d.d (1H, H_2C=, *J* 9.15, 1.57, 1.23 Hz), 5.31 d.d.d (1H, H_2C=, *J* 17.21, 1.57, 1.61 Hz), 5.85 d.d.d (1H, OCH=, *J* 17.21, 9.15, 5.34 Hz), 7.25-7.32 m (4H, Ar). NMR spectrum ^{13}C ($CDCl_3$), δ_C, ppm: 40.51, 45.72, 72.32 (=C-CH_2O), 73.43, 117.67 (H_2C=), 126.43, 128.92, 134.63 (-HC=),137.71, 140.51. Found, %: C 42.79; H 4.16; Cl 10.51; I 37.73. $C_{12}H_{14}ClIO$. Calculated, %: C 42.82; H 4.19; Cl 10.53; I 37.70.



X=H (**1,2**), Cl (**3,4**), $ClCH_2$(**5,6**), MeO (**7,**8)
R=C≡CH(**1,3,5,7**), $CH=CH_2$ (**2,4,6,8**)

kat.=Diisopinocampheylborane

Scheme-1: Regio- and enantioselective catalytic iodoalkoxylation of substituted styrene with unsaturated C_3-alcohols.

Synthesis of 1-{(2S,3R)-2-Iodine-1-[(prop-2-in-1-yl)oxy]ethyl}-4-methoxybenzene (**7**).

IR spectrum, ν, cm^{-1}: 3307 (≡C-H), 2103 (C≡C), 1100 (C-O), 551(C-l). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 2.51 t (1H, ≡CH, ^4J 2 Hz), 3.51-3.60 m (2H, CH_2), 3.81 s (3H, CH_3), 4.01 d (2H, ≡CH_2O, ^4J 2 Hz), 4.87 d (1H, CH_2O, *J* 9.0 Hz), 7.25 d (2H, Ar, *J* 8.5 Hz), 7.36 d (2H, Ar, *J* 8.5 Hz). NMR spectrum ^{13}C ($CDCl_3$), δ_C, ppm: 39.55, 56.11 (≡C-CH_2O), 56.83, 68.35 (CH), 74.02, 79.46 (≡≡C-CH_2O), 110.22, 127.33, 131.91, 161.71. Found, %: C 45.55; H 4.17; I 40.11. $C_{12}H_{13}IO_2$. Calculated, %: C 45.59; H 4.14; I 40.14.

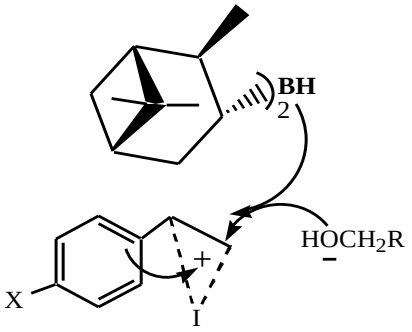
Synthesis of 1-{(2S,3R)-2-Iodine-1-[(prop-2-en-1-yl)oxy]ethyl}-4-methoxybenzene (**8**).

IR spectrum, ν, cm^{-1}: 3081 (C-H), 3063 (HC=CH_2), 3030 (HC=CH_2), 3012 (HC=CH_2), 1642 (C=C), 1491, 1360, 1271, 1101 (C-O), 985, 884 (HC=CH_2), 552 (C-l). NMR spectrum ^1H ($CDCl_3$), δ, ppm: 3.50-3.61 m (2H, CH_2), 3.80 s (3H, CH_3), 4.17 d.d.d (1H, OCH_2, *J* 12.15, 1.61, 1.23 Hz), 4.61 d.d. (1H, OCH_2, *J* 12.15, 5.34 Hz), 4.87 d (1H, CH, *J* 9.0 Hz), 5.17 d.d (1H, H_2C=, *J* 9.15, 1.57, 1.23 Hz), 5.31 d.d (1H, H2C=, *J* 17.21, 1.57, 1.61 Hz), 5.85 d.d.d (1H, OCH=, *J* 17.21, 9.15, 5.34 Hz), 7.16 in (2H, Ar, *J* 8.5 Hz), 7.31 in (2H, Ar, *J* 8.5 Hz). NMR spectrum ^{13}C ($CDCl_3$), δ_C, ppm: 41.41, 6812, 72.32 (=C-CH_2O), 117.67 (H_2C=), 126.02, 128.52, 128.71, 134.63 (-HC=), 139.92. Found, %: C 45.35; H 4.73; I 39.81. $C_{12}H_{15}IO_2$. Calculated, %: C 45.30; H 4.75; I 39.89.

Results and Discussions

We found that the replacement of the latter with diisopinocampheylborane contributes to the process involving a safer and more non-toxic catalyst. Substituted styrene were used as substituted alkenes, as a result of alkoxyhalogenation of which iodine ethers (Scheme-1) are obtained with a yield of up to 80% (**1-8**) (Fig. 1)

The chiral catalyst plays an active role in the enantioselective alkooxyhalogenylation of actively substituted styrenes (Scheme-2).



Scheme-2: The effect of a chiral catalyst on enantioselective alkooxyhalogenylation.

Regioselective alkoxyiodination of the substituted styrene double bond is evidenced by the presence of methylene proton signals at ~3.51-3.55 m (1H, CH) and ~3.60-3.64 m (1H, CH), in the ^1H NMR spectra of reaction products (**1-8**), as well as the presence in the İR spectra of the absorption band of valence oscillations of the C-I bond in the region of 545-560 cm^{-1}.

It is worth noting that the yields of compounds (**1-8**) correlate with the electronic influence of substituents in the benzene nucleus.

The structure and purity of the obtained substances are confirmed by physicochemical methods and TLC.

The structure of synthesized β-halogen ethers (**1-8**) is confirmed by NMR data of ^1H, ^{13}C and İR spectroscopy, as well as elemental analysis data.

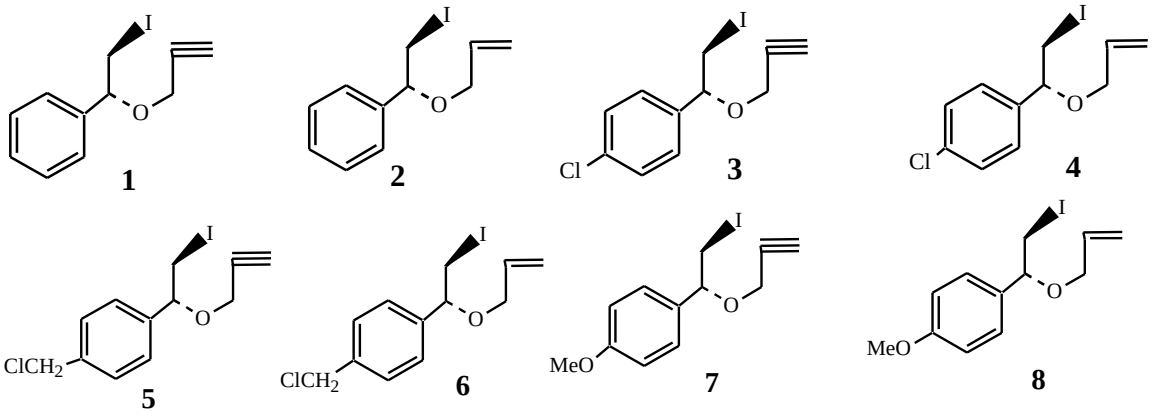


Fig. 1: The structures of synthesized compounds.

Conclusion

Regioselective and vicinal double bond functionalization is an important process in synthetic organic chemistry. In particular, the selective introduction of an alkoxy group and a halogen atom with high region- and stereoselectivity have important and complex tasks. The introduction of such groups not only improves the synthetic potential (multiple bond, halogen) of the products obtained, but also plays an important role in the synthesis of pharmaceuticals, dyes, flame retardants, agrochemicals, additives, plasticizers and special chemicals.

For the first time, the reaction of iodhalosilation of the double bond of substituted styrenes with unsaturated C_3-alcohols (propargyl and allyl) in the presence of diisopinocampheylborane leads to the formation of enantio- and regioselective iodoethers with high yields. The synthesized compounds may be of interest in medicinal chemistry due to the presence of heteroatoms in their structure, including the iodine atom.

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