

Regio- and Enantioselective Catalytic Iodoalkoxylation of Styrene Derivatives with Unsaturated C₃-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 C₃-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 (¹H-NMR), (¹³C-NMR) and FTIR spectroscopy. The synthesis followed established methodologies and proceeded without significant complications.

Keywords: Iodoalkoxylation, Unsaturated C₃-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 ¹H and ¹³C substances in CDCl₃ were recorded on the Bruker SF-300 [300.13 (1H), 75(¹³C) MHz] device, the internal standard is GMDS. Elemental analysis was performed on the EURO EA 3000 device.

Preparation of ethers unsaturated C₃-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 Na₂S₂O₃ and extracted with ether. The extract was dried with CaCl₂, the ether was removed, and the reaction mixture was then stirred at room temperature. After the initial material was used up as detected by TLC detection, the reaction mixture was poured into NaCl dissolved in water, and then extracted with CH₂Cl₂ (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 C₃-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 C₃-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. IR spectrum, ν , cm^{-1} : 3308 (C \equiv CH), 2102 (C \equiv C), 1108 (C-O-C), 552 (C-I). NMR spectrum ^1H (CDCl_3), δ , ppm: 2.51 t (1H, $\equiv\text{CH}$, 4J 2 Hz), 3.51-3.55 m (1H, CH), 3.60-3.64 m (1H, CH), 4.01 d (2H, $\equiv\text{CH}_2\text{O}$, 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 ($\equiv\text{C}-\text{CH}_2\text{O}$), 68.35 ($\equiv\text{CH}$), 71.81, 79.45 ($\equiv\text{C}-\text{CH}_2\text{O}$), 126.02, 128.52, 128.71, 139.91. Found, %: C 46.16; H 3.84; I 44.31. $\text{C}_{11}\text{H}_{11}\text{IO}$. Calculated, %: C 46.18; H 3.88; I 44.36.

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

IR spectrum, ν , cm^{-1} : 3081 (C-H), 3064 ($\text{CH}_2=\text{CH}$), 3032 ($\text{CH}_2=\text{CH}$), 3012 ($\text{CH}_2=\text{CH}$), 1642 (C=C), 1491 ($\text{CH}_2=\text{CH}$), 1363 ($\text{CH}_2=\text{CH}$), 1270 ($\text{CH}_2=\text{CH}$), 1102 (C-O-C), 985, 885, 770, 552 (C-I). 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, $\text{H}_2\text{C}=\text{}$, J 9.15, 1.57, 1.23 Hz), 5.31 d.d. (1H, $\text{H}_2\text{C}=\text{}$, J 17.21, 1.57, 1.61 Hz), 5.84 d.d.d. (1H, $\text{OCH}=\text{}$, J 17.21, 9.15, 5.34 Hz), 7.25-7.35 m (5H, Ar). NMR spectrum ^{13}C (CDCl_3), δ_{C} , ppm: 39.52, 56.81, 72.32 ($=\text{C}-\text{CH}_2\text{O}$), 74.01, 110.21, 117.67 ($\text{H}_2\text{C}=\text{}$), 127.32, 131.93, 134.63 ($-\text{HC}=\text{}$), 161.73. Found, %: C 45.81; H 4.53; I 44.07. $\text{C}_{11}\text{H}_{13}\text{IO}$. Calculated, %: C 45.85; H 4.55; I 44.04.

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

IR spectrum, ν , cm^{-1} : 3306 ($\equiv\text{C}-\text{H}$), 2100 (C \equiv C), 1105 (C-O-C), 551 (C-Cl). NMR spectrum ^1H (CDCl_3), δ , ppm: 2.50 t (1H, $\equiv\text{CH}$, 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, $\equiv\text{CH}_2\text{O}$, 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 ($\equiv\text{C}-\text{CH}_2\text{O}$), 68.35 (CH), 72.23, 79.45 ($\equiv\text{C}-\text{CH}_2\text{O}$), 127.42, 128.92, 134.24, 138.81. Found, %: C 41.21; H 3.12; Cl 11.03; I 39.61. $\text{C}_{11}\text{H}_{10}\text{ClIO}$. Calculated, %: C 41.22; H 3.14; Cl 11.06; I 39.59.

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

IR spectrum, ν , cm^{-1} : 3083 (C-H), 3064 ($\text{CH}_2=\text{CH}$), 3033 ($\text{CH}_2=\text{CH}$), 3010 ($\text{CH}_2=\text{CHO}$), 1641 (C=C), 1490 ($\text{CH}_2=\text{CH}$), 1360 ($\text{CH}_2=\text{CH}$), 1272 ($\text{CH}_2=\text{CH}$), 1101 (C-O), 985, 885, 771 (C-Cl), 551

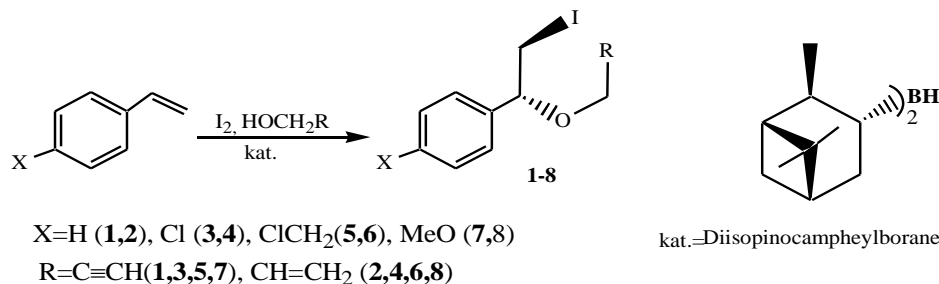
(C-I). NMR spectrum ^1H (CDCl_3), δ , ppm: 3.48 k (1H, CH, J 8.5 Hz, J 10.5 Hz), 3.50 k (1H, CH, J 8.5 Hz, J 10.5 Hz), 4.17 d.d.d. (1H, OCH_2 , J 12.15, 1.61, 1.23 Hz), 4.61 d.d.d. (1H, OCH_2 , J 12.15, 5.34 Hz), 4.86-4.89 m (1H, CH), 5.17 d.dd (1H, $\text{H}_2\text{C}=\text{}$, J 9.15, 1.57, 1.23 Hz), 5.31 d.d.d. (1H, $\text{H}_2\text{C}=\text{}$, J 17.21, 1.57, 1.61 Hz), 5.85 d.d.d. (1H, $\text{OCH}=\text{}$, 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 ($=\text{C}-\text{CH}_2\text{O}$), 117.67 ($\text{H}_2\text{C}=\text{}$), 127.42, 128.91, 134.22, 134.62 ($-\text{HC}=\text{}$), 138.82. Found, %: C 40.91; H 3.77; Cl 10.96; I 39.31. $\text{C}_{11}\text{H}_{12}\text{ClIO}$. Calculated, %: C 40.96; H 3.75; Cl 10.99; I 39.34.

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

IR spectrum, ν , cm^{-1} : 3307 ($\equiv\text{C}-\text{H}$), 2101 (C \equiv C), 1104 (C-O), 550 (C-Cl). ^1H NMR spectrum (CDCl_3), δ , ppm: 2.51 t (1H, $\equiv\text{CH}_2\text{O}$, 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, $\equiv\text{CH}_2\text{O}$, 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} , m. d.: 40.53, 45.72, 56.13 ($\equiv\text{C}-\text{CH}_2\text{O}$), 68.35 ($\equiv\text{CH}$), 73.42, 79.46 ($\equiv\text{C}-\text{CH}_2\text{O}$), 126.41, 128.92, 137.72, 140.52. Found, %: C 43.02; H 3.61; Cl 10.63; I 37.91. $\text{C}_{12}\text{H}_{12}\text{ClIO}$. Calculated, %: C 43.08; H 3.62; Cl 10.60; I 37.93.

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

IR spectrum, ν , cm^{-1} : 3081 (C-H), 3064 ($\text{HC}=\text{CH}_2$), 3030 ($\text{HC}=\text{CH}_2$), 3012 ($\text{HC}=\text{CH}_2$), 1642 ($\text{HC}=\text{CH}_2$), 1493 ($\text{HC}=\text{CH}_2$), 1360 ($\text{HC}=\text{CH}_2$), 1270 ($\text{HC}=\text{CH}_2$), 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, $\text{H}_2\text{C}=\text{}$, J 9.15, 1.57, 1.23 Hz), 5.31 d.d.d. (1H, $\text{H}_2\text{C}=\text{}$, J 17.21, 1.57, 1.61 Hz), 5.85 d.d.d. (1H, $\text{OCH}=\text{}$, 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 ($=\text{C}-\text{CH}_2\text{O}$), 73.43, 117.67 ($\text{H}_2\text{C}=\text{}$), 126.43, 128.92, 134.63 ($-\text{HC}=\text{}$), 137.71, 140.51. Found, %: C 42.79; H 4.16; Cl 10.51; I 37.73. $\text{C}_{12}\text{H}_{14}\text{ClIO}$. Calculated, %: C 42.82; H 4.19; Cl 10.53; I 37.70.



Scheme-1: Regio- and enantioselective catalytic iodoalkoxylation of substituted styrene with unsaturated C₃-alcohols.

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

IR spectrum, ν , cm⁻¹: 3307 (≡C-H), 2103 (C≡C), 1100 (C-O), 551(C-I). NMR spectrum ¹H (CDCl₃), δ , ppm: 2.51 t (1H, ≡CH, ⁴J 2 Hz), 3.51-3.60 m (2H, CH₂), 3.81 s (3H, CH₃), 4.01 d (2H, ≡CH₂O, ⁴J 2 Hz), 4.87 d (1H, CH₂O, *J* 9.0 Hz), 7.25 d (2H, Ar, *J* 8.5 Hz), 7.36 d (2H, Ar, *J* 8.5 Hz). NMR spectrum ¹³C (CDCl₃), δ_c , ppm: 39.55, 56.11 (≡C-CH₂O), 56.83, 68.35 (CH), 74.02, 79.46 (≡C-CH₂O), 110.22, 127.33, 131.91, 161.71. Found, %: C 45.55; H 4.17; I 40.11. C₁₂H₁₃IO₂. Calculated, %: C 45.59; H 4.14; I 40.14.

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

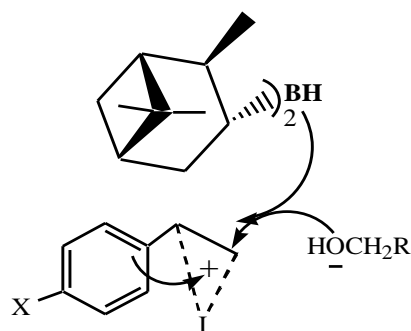
IR spectrum, ν , cm⁻¹: 3081 (C-H), 3063 (HC=CH₂), 3030 (HC=CH₂), 3012 (HC=CH₂), 1642 (C=C), 1491, 1360, 1271, 1101 (C-O), 985, 884 (HC=CH₂), 552 (C-I). NMR spectrum ¹H (CDCl₃), δ , ppm: 3.50-3.61 m (2H, CH₂), 3.80 s (3H, CH₃), 4.17 d.d.d (1H, OCH₂, *J* 12.15, 1.61, 1.23 Hz), 4.61 d.d. (1H, OCH₂, *J* 12.15, 5.34 Hz), 4.87 d (1H, CH, *J* 9.0 Hz), 5.17 d.d (1H, H₂C=, *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 ¹³C (CDCl₃), δ_c , ppm: 41.41, 68.12, 72.32 (=C-CH₂O), 117.67 (H₂C=), 126.02, 128.52, 128.71, 134.63 (-HC=), 139.92. Found, %: C 45.35; H 4.73; I 39.81. C₁₂H₁₃IO₂. 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 alkoxyhalogenylation of actively substituted styrenes (Scheme-2).



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

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 IR 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, ¹³C and IR spectroscopy, as well as elemental analysis data.

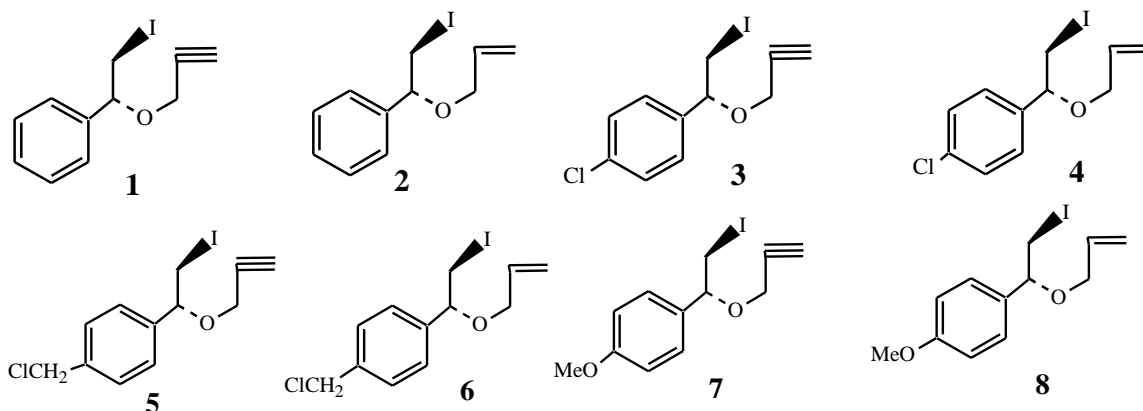


Fig. 1: The structures of synthesized compounds.

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 iodohalogenation of the double bond of substituted styrenes with unsaturated C₃-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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