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ENANTIOSELECTIVE CATALYTIC THREE-COMPONENT SYNTHESIS OF OPTICALLY ACTIVE PROPARGYL AMINO ETHERS

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Catalytic enantioselective three-component aminomethylation of benzaldehyde as well as its methoxy-substituted derivatives and propargyl ethers with aniline in the presence of a chiral catalyst – pseudoephedrine – yielded previously unknown optically active propargyl amino ethers with high yields and a high degree of enantioselectivity. This reaction can also be used to form both C-C and C-N bonds.

Keywords: enantioselective aminomethylation, enantioselectivity, asymmetric catalysis, three-component reaction

1. Introduction

Optically active propargylamines are important synthetic intermediates for the preparation of various natural products [1],[2] and biologically active compounds [3]-[5].

Many Mannich bases have a number of useful pharmacological properties, for example, antimicrobial, cytotoxic, antitumor and analgesic activity [6],[7].

Propargyl-containing chiral organic compounds can act as synthons for the targeted synthesis of many natural nitrogen-containing compounds as well as optically active drugs [8]-[11]. To achieve this goal, the catalytic asymmetric Mannich reaction is carried out efficiently. This is one of the most convenient methods for synthesizing chiral nitrogen-containing compounds [12]. Although three-component syntheses of amino ethers involving various compounds are found in the literature [11], the synthesis of novel compounds No. 1-7 is the first time that propargyl ethers have been used. Enantioselective reactions using pseudoephedrine as a chiral catalyst also exist [12],[13].

2. Experimental

The general methodology for synthesizing target compounds was as follows: a mixture of 0.1 mmol of aromatic aldehyde, 0.3 mmol of propargyl ether, 0.1 mmol of aniline as well as 1.5 mg of pseudoephedrine and 0.8 mg of CuCl in 18 ml of dry CH_2Cl_2 was stirred at 25°C before being heated for 4 hours at 80-90°C. Next, 3 ml of isopropyl alcohol was added before the precipitate was filtered off then washed with water (3 ml) and isopropyl alcohol (3 ml).

The purity of the compounds obtained was monitored by TLC on Silufol UV-254 plates with a 1:1 ratio of eluent acetone to hexane. Their melting points were determined using a Melting Point M-565 instrument. The specific optical rotation [α]D20 was measured using a Perkin Elmer-341 polarimeter. HPLC was performed by a Thermo Scientific TSQ Quantum Access™ instrument with a Zorbax CB-C18 (150mm x 2.1mm, 1.8 μm) designed to carry out reversed phase HPLC.

^{1}H and ^{13}C NMR spectra of the resulting compounds in a solution of $CDCl_3$ were recorded by a Bruker SF-300 spectrometer with operating frequencies of 300 (^{1}H) and 75 MHz (^{13}C) as well as an internal standard - HMDS.The data of ^{1}H NMR, ^{13}C NMR ($CDCl_3$) and IR spectra can be found in the Supplement.

In the synthesis described, the following novel compounds were obtained:

No. 1:
N-[(1R,4R)-4-phenoxy-1-phenylpent-2-yn-1-yl]-aniline

Yield: 45%. Light yellow powder, m.p.: 156–157°C (with decomposition), [α]D22 +55.4 (with 0.1, $CHCl_3$). Observed composition (%): C 84.32; H 6.51; N 4.22 - $C_{23}H_{21}NO$. Calculated composition (%): C 84.37; H 6.46; N 4.28.

No. 2:
N-[(1R,5R)-4-phenoxy-1-phenylhex-2-yn-1-yl]-aniline

Yield: 54%. Light yellow powder, m.p.: 158–159°C (with decomposition), [α]D22 +56.8 (with 0.1, $CHCl_3$). Observed composition (%): C 84.32; H 7.11; N 3.84 -

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$C_{25}H_{25}NO$. Calculated composition (%): C 84.47; H 7.09; N 3.94.

No. 3:
N-[(1R)-4-(Cyclohexyloxy)-1-phenylbut-2-yn-1-yl]-aniline

Yield: 51%. Light yellow powder, m.p.: 124–125°C (with decomposition), [α]D22 +36.4 (with 0.1, $CHCl_3$). Observed composition (%): C 82.22; H 8.14; N 4.51 - $C_{21}H_{25}NO$. Calculated composition (%): C 82.04; H 8.20; N 4.56.

No. 4:
N-[(1R)-4-(Cyclopentyloxy)-1-phenylbut-2-yn-1-yl]-aniline

Yield: 56%. Light yellow powder, m.p.: 121–122°C (with decomposition), [α]D22 +34.9 (with 0.1, $CHCl_3$). Observed composition (%): C 81.23; H 8.21; N 4.87 - $C_{19}H_{23}NO$. Calculated composition (%): C 81.10; H 8.24; N 4.98.

No. 5:
N-[(1R,4R)-4-phenoxy-1-(2-(methoxy-phenylpent-2-in-1-yl]-aniline

Yield: 53%. Light yellow powder, m.p.: 161–162°C (with decomposition), [α]D22 +66.8 (with 0.1, $CHCl_3$). Observed composition (%): C 83.87; H 7.21; N 4.21 - $C_{24}H_{25}NO$. Calculated composition (%): C 83.93; H 7.34; N 4.08.

No. 6:
N-[(1R,4R)-4-phenoxy-1-(3-(methoxy-phenylpent-2-yn-1-yl]-aniline

Yield: 56%. Light yellow powder, m.p.: 160–161°C (with decomposition), [α]D22 +64.8 (with 0.1, $CHCl_3$). Observed composition (%): C 83.66; H 7.14; N 4.14 - $C_{24}H_{25}NO$. Calculated composition (%): C 83.93; H 7.34; N 4.08.

No. 7:
N-[(1R,4R)-4-phenoxy-1-(4-(methoxy-phenylpent-2-yn-1-yl]-aniline

Yield: 50%. Light yellow powder, m.p.: 158–159°C (with decomposition), [α]D22 +61.8 (with 0.1, $CHCl_3$). Observed composition (%): C 83.83; H 7.17; N 4.11 - $C_{24}H_{25}NO$. Calculated composition (%): C 83.93; H 7.34; N 4.08.

3. Results and analysis

For the first time, the highly enantioselective three-component reaction of aldehydes, aniline and propargyl ethers was investigated using the chiral catalyst pseudoephedrine, where the degree of diastereomeric excess (de) was as high as 96 % (*Figure 1*).

The starting propargyl ethers were obtained in advance [14].

Since the methylene protons in compound No. 2 are diastereotopic, they exhibit different singlet signals at 3.46 d (1H, OCH_2, J=9.4 Hz), 3.75 d (1H, OCH_2, J=9.4 Hz).

In the case of R^2=Me for compounds No. 1-2 and 5-7, diastereomers were obtained. The ratio of these diastereomeric isomers was determined by ^{1}H NMR spectroscopy after the reaction had finished and a thermodynamic equilibrium between the diastereoisomers (before chromatography) established according to the ratio of the integration of doublet signals of methine protons 1-2 and 5-7 at 3.46-3.75 ppm. To determine the absolute configuration of amino ethers 1-2 and 5-7, the polarimetric method was used whereby similar compounds had previously been studied [15],[16]. Therefore, the measured positive optical rotation of the synthesized diastereoisomers indicates their (R,R)-absolute configuration.

Reactions of benzaldehyde as well as its methoxy-substituted derivatives and propargyl ethers with aniline in the presence of a chiral catalyst – pseudoephedrine – proceeded smoothly to produce the corresponding

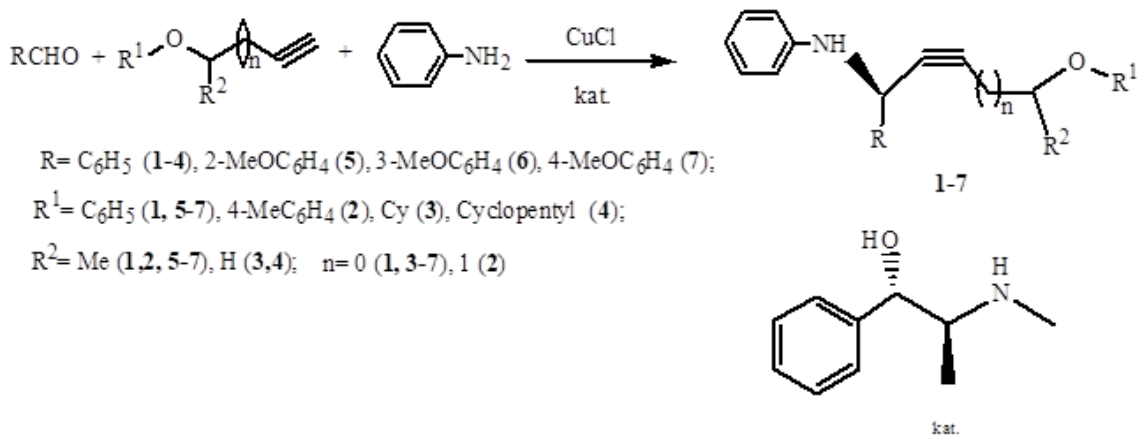

Figure 1: Reaction scheme

Table 1: Enantioselective reactions of benzaldehyde as well as its methoxy-substituted derivatives and propargyl ethers with aniline in the presence of a chiral catalyst – pseudoephedrine

Entry	Time (h)	Yield (%)	de (%)
1	1	45	93
2	1	54	94
3	1	51	90
4	1	56	95
5	1	53	94
6	1	56	94
7	1	50	96

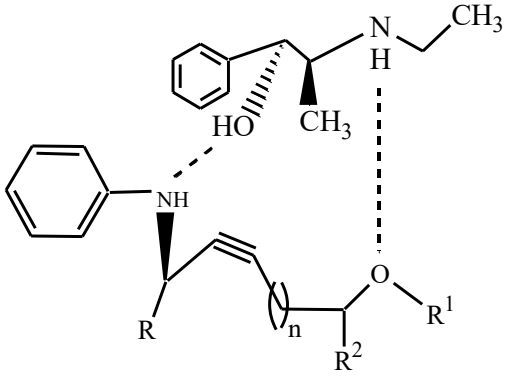

Figure 2: Scheme of how the protons of pseudoephedrine interact with the hydrogen bonds of propargyl amino ethers

products in yields of 45-56% and with enantioselectivities of 90-96% (*Table 1*).

The protons of pseudoephedrine interact with the hydrogen bonds of propargyl amino ethers, leading to its activation (*Figure 2*).

The structure and composition of the obtained target compounds No. 1-7 were confirmed by ^{1}H and ^{13}C NMR spectroscopy as well as elemental analysis (The spectra can be found in the Supplementary information, available in the Editorial office.).

4. Conclusions

Based on the experimental results, the catalytic enantioselective three-component synthesis of benzaldehyde as well as its methoxy-substituted derivatives and propargyl ethers with aniline in the presence of a chiral catalyst with high yields and a high degree of enantioselectivity was achieved.

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