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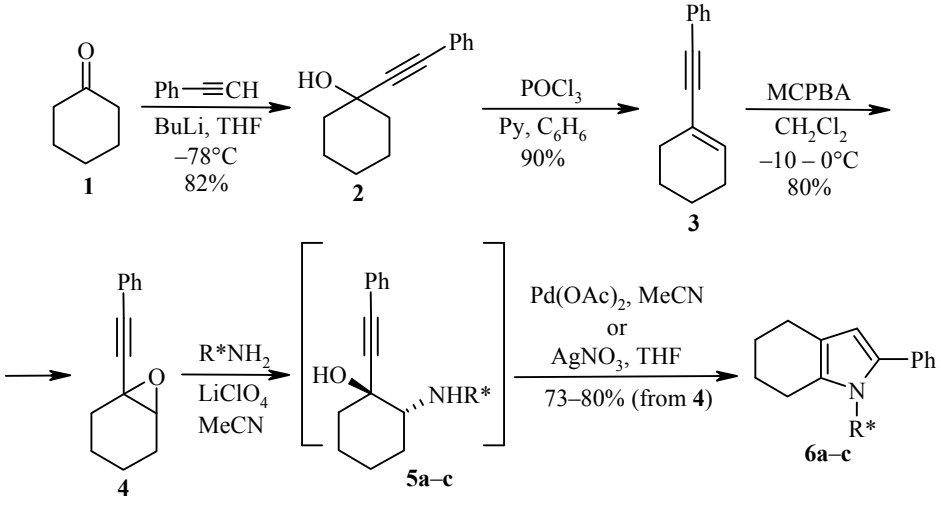
SYNTHESIS OF 2-PHENYL-4,5,6,7-TETRAHYDRO-1*H*-INDOLES WITH A CHIRAL SUBSTITUENT AT THE NITROGEN ATOM

I. A. Andreev[1], I. O. Ryzhkov[1], A. V. Kurkin[1]*, and M. A. Yurovskaya[1]

An efficient method has been developed for the enantioselective synthesis of 2-phenyl-4,5,6,7-tetrahydro-1H-indoles containing chiral substituents at the nitrogen atom. It is based on opening of the epoxide fragment of 1-phenylethynyl-7-oxabicyclo[4.1.0]heptane with chiral amines and/or amino acid esters followed by intramolecular, metal catalyzed cyclization.

Keywords: 2-phenyl-4,5,6,7-tetrahydro-1*H*-indoles, *trans*-amino propargylic alcohols, chiral substituent at nitrogen atom, palladium-catalyzed cyclization.

Current scientific studies in the area of indole chemistry are directed towards the search for convenient and efficient methods to prepare indole derivatives containing a tetrahydroindole fragment in their structure. The increased interest in this heterocyclic system relates to the occurrence of tetrahydroindoles in many natural compounds, e.g. this component occurs in the molecule of the alkaloid dragmacidin F [1-4].



a R = CH(Me)Ph, **b** R = CH(CH$_2$Ph)COOEt, **c** R = CH(CH$_2$Ph)COO-*t*-Bu

*To whom correspondence should be addressed, e-mail: kurkin@direction.chem.msu.ru.

[1]M. V. Lomonosov State University, 1 Build. 3 Leninskie Gory, Moscow 119991, Russia.

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As a result of the synthesis of indole derivatives from amino propargylic alcohols it is possible to obtain *N*-substituted tetrahydroindoles, which contain substituents (of different nature) only in the position 2 of the pyrrole ring. It should be noted that this method has a broad potential for the synthesis of indoles with a chiral substituent at the nitrogen atom.

In this work, we have shown the possibility of using amines containing a chiral substituent at the nitrogen atom (e.g., (*S*)-(1-phenyl)ethylamine or natural amino acid esters) as *N*-nucleophiles for opening an epoxide and for subsequent transformation of the *trans*-aminoethanols thus obtained to tetrahydroindoles. The route presented is an efficient method for the preparation of novel, enantiomerically pure 2-phenyl-4,5,6,7-tetrahydro-1*H*-indoles.

The first stage of the synthesis was the addition of lithium acetylide (prepared *in situ* from phenylacetylene and butyl lithium) to cyclohexanone (**1**). Cerium acetylides have been used previously [5] in the preparation of tertiary alcohols, but in our case the reaction occurs with the more readily available lithium phenylacetylide to give the tertiary alcohol **2** in high yield (82%).

We used the system $POCl_3$–pyridine [6] for the dehydration of the tertiary alcohol **2**. The absence of heating and the weak acidity of the medium allows to avoid possible side processes, e.g. isomerization of a propargylic cation to an allene system.

In our case, a most convenient reagent for preparation of epoxide **4** proved to be *m*-chloroperbenzoic acid (*m*-CPBA) [7]. The epoxidation was carried out under standard conditions using a 20-30% excess of *m*-CPBA. It should be noted that commercially available *m*-CPBA contains traces of water, hence we initially dissolved the acid in methylene chloride and dried it using anhydrous sodium sulfate. The solution obtained was added to the alkene with stirring below 0ºC. Ignoring this simple operation lowered the yields by 10-20%. It was important to maintain the temperature conditions when carrying out the reaction since the *m*-chlorobenzoic acid (pK_a 3.82) present as an admixture in the *m*-CPBA is a much stronger acid than the *m*-CPBA itself (pK_a 7.57), and this can lead to an undesired rearrangement of the carbon framework. Despite the possibility of the epoxidation of acetylenes to oxirenes [8], the products of epoxidation at the triple bond (or the corresponding ketone products of their rearrangement) were not observed.

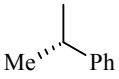
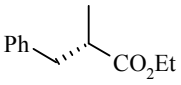
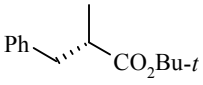
Subsequent synthetic use of the epoxide **4** obtained was based on its opening by (*S*)-(1-phenyl)-ethylamine and amino acid esters. Several efficient methods for such conversion under mild conditions have recently been developed using Lewis acids (to increase the electrophilicity of the epoxide) [9] or with the initial generation of anions from amines (to increase the nucleophilicity of the amine) [10]. Thus, we have employed lithium perchlorate [9] as a catalyst for the nucleophilic opening of the obtained epoxide **4**.

Under the influence of the nucleophiles the opening of the ring occurs by a bimolecular nucleophilic substitution mechanism (S_N2 mechanism). With the presence of the phenylethynyl substituent in the epoxide ring, the nucleophilic attack is directed to the less substituted carbon atom, and the reaction occurs stereoselectively with retention of configuration. The nucleophilic addition to the epoxide was carried out at 60-65ºC in acetonitrile, in the presence of 1.5 to 2.0 equivalents of the amine (or amino acid ester) and 1.5 equivalents of lithium perchlorate. The reaction of epoxide **4** with natural amino acid esters or with (*S*)-(1-phenyl)ethylamine gave a 1:1 ratio mixture of the diastereomers **5a-c** (determined by ^{1}H NMR spectroscopy). If needed, this mixture can be separated chromatographically. In our case, the separation of the diastereomeric mixture was not required, since the metal-catalyzed cyclization gave a single tetrahydroindole with a chiral substituent at the nitrogen atom.

Methods for the cyclization of amino propargylic and related systems to pyrroles using mercury salts [11] and catalysts based on gold [12], copper [13], silver [14], and palladium [15] have been reported in the literature.

As catalysts, we have used palladium acetate or silver nitrate. In the case of the palladium acetate, the reaction mixture was refluxed in acetonitrile for 2 h, while with silver nitrate it was refluxed in THF for 1 h. The course of the reaction was monitored by TLC. The yields of the obtained tetrahydroindoles **6a-c** are given in Table 1 and are based on compound **4** (opening of the epoxide with a nucleophile and the subsequent cyclization to the corresponding tetrahydroindole **6**).

TABLE 1. Yields of the Cyclization Products of the Amino Propargylic Alcohols to Tetrahydroindoles

Compound	R	Yield*, %	*ee**[2], %
6a		75 (64)	99 (98)
6b		80 (66)	70 (67)
6c		73	98

* Cyclization yield using silver nitrate as a catalyst is reported in the brackets.

*[2] Enantiomeric excess when cyclized using silver nitrate as a catalyst is reported in the brackets.

The obtained tetrahydroindole derivatives showed optical activity. An HPLC analysis with a chiral stationary phase showed that the enantiomeric excess of compounds **6a,c** at the final stage was greater than 98%, while that of compound **6b** did not exceed 70%. Racemization depends on the nature of the functional groups bonded to the asymmetric carbon atom [16]. Hence an explanation of the partial loss of enantiomeric purity in the tetrahydroindole derivative with the ethyl phenylalanine ester fragment can be related to the previously reported observation that ethyl esters of amino acid derivatives are more readily racemized than *tert*-butyl esters [17].

Thus, we have found an optimal approach to the synthesis of enantiomerically pure 2-phenyl-4,5,6,7-tetrahydro-1*H*-indoles, which contain a chiral substituent at the nitrogen atom.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 and 100 MHz respectively) using $CDCl_3$ with TMS as internal standard. Chromatography and mass spectrometry studies were performed using an Agilent 1200 chromatograph with fluorimetric and diode array detectors (Chiralcel OD-RH column (4.6×150 mm), UV detector (250 nm), mobile phase H_2O–MeCN, 2:3, 1 ml/min), and with an ITD-700 mass spectrometric detector (Finnigan MAT, electron impact ionization, ionization energy 70 eV, mass range *m/z* 35-400 Da). The specific rotation was measured on Perkin Elmer 241 (589 nm) and Jasco DIP-360 (589 nm) polarimeters in 5 and 10 cm cuvettes. Methanol (c = 1.0 M) was used as solvent. The reaction course and the purity of the obtained compounds was monitored by TLC, using petroleum ether and ethyl acetate as eluent in different ratios and iodine vapor or $KMnO_4$ solution for visualization. The commercially available (*S*)-(1-phenyl)ethylamine, (*S*)-phenylalanine, phosphoryl chloride, and *m*-chloroperbenzoic acid were used without purification. The (*S*)-phenylalanine ethyl ester hydrochloride was obtained using a standard method by refluxing in ethanol in the presence of $SOCl_2$ and converted to the free base before being used in the reaction. The *tert*-butyl ester of (*S*)-phenylalanine was prepared as the free base according to a known method [16]. Commercially available cyclohexanone and phenylacetylene were distilled *in vacuo* before use.

1-(Phenylethynyl)cyclohexanol (2). A 2.5 M solution of BuLi (40 ml, 0.010 mol) in hexane was added over 15 min to a solution of the phenylacetylene (10.7 g, 0.105 mol) in THF (70 ml) at -78ºC. The reaction mixture was stirred at this temperature for 15 min. Cooling was stopped and the temperature of the reaction mixture was gradually raised to 20ºC over 1 h. The reaction mixture was maintained for 10 min at room temperature, then cooled to -78ºC, and a solution of cyclohexanone (**1**) (10.8 g, 0.110 mol) in THF (20 ml) was added dropwise over 10 min and then stirred for a further 30 min. The reaction temperature was again slowly raised to ambient, 0.1 M aqueous solution of NH_4Cl (200 ml) was added to the reaction mixture, and the product was extracted with CH_2Cl_2 (3×100 ml). The extract was dried over anhydrous sodium sulfate, and the solvent was evaporated *in vacuo*. Yield 17.2 g (82%); mp 60-61ºC (petroleum ether) (mp 59-60ºC [18]). The ^1H and ^{13}C NMR spectroscopic parameters were in agreement with the literature [19].

1-(Phenylethynyl)cyclohexene (3). A solution of $POCl_3$ (57 ml, 0.710 mol) in benzene (750 ml) was added over 30 min to a solution of compound **2** (50 g, 0.284 mol) and pyridine (119 g, 1.700 mol) in benzene (500 ml) and stirred for 48 h at room temperature. A saturated aqueous solution of $NaHCO_3$ (750 ml) was added, the organic phase was separated, and the aqueous phase was extracted with additional benzene (500 ml). The combined organic extracts were dried over anhydrous Na_2SO_4, the solvent was evaporated *in vacuo*, and the residue was distilled *in vacuo*. Yield 41 g (90%); bp 126-130ºC (1 mm Hg) (bp 106ºC (0.6 mm Hg) [20]). The ^1H and ^{13}C NMR spectroscopic parameters agreed with the literature [20].

1-Phenylethynyl-7-oxobicyclo[4.1.0]heptane (4) was prepared according to a known method [20].

Opening of the Epoxide 4 by Amines (General Method). The amine (37.7 mmol) and $LiClO_4$ (4.01 g, 37.7 mmol) were added to a solution of the epoxide **4** (4.96 g, 25.0 mmol) in MeCN (25 ml). The reaction mixture was held for 16 h at 65ºC, cooled, poured into water (100 ml), and extracted with CH_2Cl_2 (3×100 ml). The organic extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was separated by chromatography on a silica gel column using petroleum ether–ethyl acetate (10:1). The mixture of diastereomers **5a-c** was obtained and used in the subsequent cyclization without separation.

Metal-Catalyzed Cyclization of the Amino Propargyl Alcohols 5a-c to 4,5,6,7-tetrahydroindoles (General Method). A. $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) was added to a solution of the amino propargylic alcohol derivative **5a-c** (1.00 mmol) in MeCN (10 ml), and the reaction mixture was refluxed for 2 h. The course of the reaction was monitored by TLC. The catalyst was filtered off, the organic solvent was removed *in vacuo*, and the residue was separated by chromatography on a silica gel column using petroleum ether–ethyl acetate (100:1) as eluent.

B. $AgNO_3$ (1.70 mg, 0.01 mmol) was added to a solution of the amino propargylic alcohol derivative **5a-b** (1.00 mmol) in THF (10 ml). The reaction mixture was refluxed for 1 h. The course of the reaction was monitored by TLC. The organic solvent was removed *in vacuo* and the residue was separated by chromatography on a silica gel column using petroleum ether–ethyl acetate (100:1) as eluent.

2-Phenyl-1-[(1*S*)-1-phenylethyl]-4,5,6,7-tetrahydro-1*H*-indole (6a). Yield 75% (method A), 64% (method B). $[\alpha]_D^{20}$ +8.4º, *ee* 99% (HPLC, τ_S 24.5 min, τ_R 27.8 min). IR spectrum, ν, cm^{-1}: 3054, 2931, 2856, 1490, 1444, 1371, 1108, 1056. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.53-1.65 (1H, m) and 1.66-1.82 (3H, m, 5,6-CH_2); 1.86 (3H, d, *J* = 7.1, C<u>H</u>$_3$CH); 1.92-2.06 (1H, m) and 2.42-2.53 (1H, m, 4-CH_2); 2.53-2.68 (2H, m, 7-CH_2); 5.59 (1H, q, *J* = 7.1, CH_3C<u>H</u>); 6.07 (1H, s, H-3); 7.04-7.11 (2H, m, H Ph); 7.21-7.44 (8H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 19.8; 23.4; 23.6; 23.7; 24.4; 52.9; 107.5; 118.6; 126.0 (2C); 126.7; 126.7; 128.3 (2C); 128.4 (2C); 129.2; 129.3 (2C); 134.5; 134.7; 142.9. Mass spectrum, *m/z* (I_{rel}, %): 301 $[M]^+$ (48), 197 (100), 196 (26), 169 (53), 105 (87), 79 (19), 77 (29), 65 (11). Found, %: C 87.69; H 7.77; N 4.59. $C_{22}H_{23}N$. Calculated, %: C 87.66; H 7.69; N 4.65.

Ethyl (2*S*)-3-Phenyl-2-(2-phenyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl)propionate (6b). Yield 80% (method A), 66% (method B). $[\alpha]_D^{20}$ +6.9º, *ee* 70% (HPLC: τ_S 19.5 min, τ_R 17.6 min). IR spectrum, ν, cm^{-1}: 3109, 2940, 2875, 1750, 1507, 1420, 1380, 1110, 1052. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.2, CH_2C<u>H</u>$_3$); 1.75-1.90 (3H, m) and 1.90-2.02 (1H, m, 5,6-CH_2); 2.49-2.64 (3H, m) and 2.71-2.82 (1H, m, 4,7-CH_2); 3.12 (1H, dd, *J* = 13.9, *J* = 9.5) and 3.37 (1H, dd, *J* = 13.9, *J* = 5.5, CH_2Ph); 4.21-4.35 (2H, m,

$CH_3C\underline{H}_2$); 4.94 (1H, dd, J = 9.5, J = 5.7, $C\underline{H}CH_2$); 5.84 (1H, s, H-3); 6.74-6.80 (2H, m, H Ph); 6.88-6.97 (2H, m, H Ph); 7.10-7.20 (3H, m, H Ph); 7.20-7.27 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.4; 23.4; 23.8; 23.9; 24.0; 37.7; 59.4; 61.8; 107.8; 119.0; 126.7; 126.9; 128.0 (2C); 128.4 (2C); 128.6; 129.3 (2C); 129.7 (2C); 133.7; 135.3; 137.4; 171.2. Mass spectrum, *m/z* (I_{rel}, %): 373 $[M]^+$ (88), 300 (28), 208 (26), 197 (39), 196 (100), 169 (29), 91 (57). Found, %: C 80.42; H 7.21; N 3.62. $C_{25}H_{27}NO_2$. Calculated, %: C 80.40; H 7.29; N 3.75.

***tert*-Butyl (2*S*)-3-phenyl-2-(2-phenyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl)propionate (6c)**. Yield 73% (method A). $[\alpha]_D^{20}$ +5.1°, *ee* 98% (HPLC: τ_R 26.8 min, τ_S 27.9 min). IR spectrum, ν, cm^{-1}: 3087, 2940, 2864, 1748, 1510, 1430, 1364, 1140, 1034. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.48 (9H, s, $(CH_3)_3C$); 1.74-1.93 (3H, m) and 1.93-2.04 (1H, m, 5,6-CH_2); 2.57-2.72 (3H, m) and 2.78-2.88 (1H, m, 4,7-CH_2); 3.19 (1H, dd, J = 14.1, J = 9.7) and 3.36 (1H, dd, J = 14.1, J = 5.6, CH_2Ph); 4.79-4.86 (1H, m, $C\underline{H}CH_2$); 5.84 (1H, s, H-3); 6.83-6.95 (4H, m, H Ph); 7.15-7.27 (6H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 23.5; 23.8; 24.0; 24.3; 28.0 (3C); 37.4; 60.3; 82.1; 107.8; 118.9; 126.6; 126.7; 128.1 (2C); 128.4 (2C); 128.7; 129.3 (2C); 129.7 (2C); 134.0; 135.7; 137.8; 170.0. Mass spectrum, *m/z* (I_{rel}, %): 401 $[M]^+$ (49), 346 (23), 345 (91), 344 (22), 300 (26), 209 (18), 208 (23), 197 (38), 196 (81), 194 (21), 180 (21), 169 (45), 91 (88), 77 (29), 57 (100), 41 (56). Found, %: C 80.71; H 7.73; N 3.44. $C_{27}H_{31}NO_2$. Calculated, %: C 80.76; H 7.78; N 3.49.

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