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for the Preparation
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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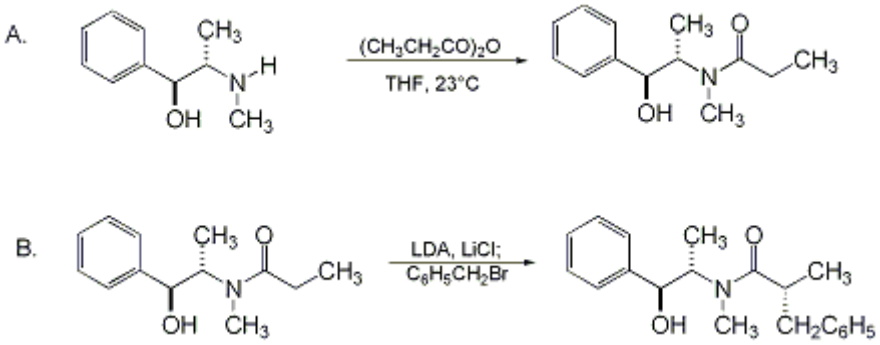
SYNTHESIS AND DIASTEREOSELECTIVE ALKYLATION OF PSEUDOEPHEDRINE AMIDES



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1. Procedure

A. (1S,2S)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N-methylpropionamide, ((1S,2S)-pseudoephedrinepropionamide). A flame-dried, 1-L, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 21.3 g (129 mmol) of (1S,2S)-(+)-pseudoephedrine (Note 1) and 250 mL of tetrahydrofuran (Note 2). The flask is placed in a water bath at 23°C, and to the well-stirred solution, 18.0 g (138 mmol) of propionic anhydride (Note 3) is added by a Pasteur pipette in 1-mL portions over approximately 5 min. The flask is sealed with a rubber septum containing a needle adapter to an argon-filled balloon, and the clear, colorless solution is allowed to stir at 23°C for an additional 10 min. The rubber septum is removed, and the reaction solution is neutralized by the addition of 400 mL of saturated aqueous sodium bicarbonate solution. After thorough mixing (Note 4), the biphasic mixture is poured into a separatory funnel and extracted with three portions of ethyl acetate (250 mL, 150 mL, and 150 mL, respectively). The combined organic extracts are dried over anhydrous sodium sulfate , filtered, and concentrated under reduced pressure to afford a white solid. Residual solvent is removed under vacuum (0.5 mm) for 3 hr. The solid residue is dissolved in 125 mL of hot (110°C) toluene in a 250-mL Erlenmeyer flask, and the flask is placed in a water bath at 80°C. This bath is allowed to cool slowly to 23°C. Extensive crystallization occurs as the solution cools. Crystallization is completed by cooling the flask to −20°C. After 10 hr, the crystals are collected by filtration and rinsed with 100 mL of cold (0°C) toluene . The crystals are dried under reduced pressure (0.5 mm) at 23°C for 3 hr to afford 27.2 g (95%) of the (1S,2S)-pseudoephedrinepropionamide as a white solid (Note 5).

B. [1S(R),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N,2-dimethylbenzenepropionamide, [(1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide]. A flame-dried, 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and an inlet adapter connected to a source of argon is charged with 25.0 g (590 mmol) of anhydrous lithium chloride (Note 6) and sealed with a rubber septum. The inlet adapter is removed and replaced with a rubber septum containing a needle adapter to an argon-filled balloon. The reaction flask is charged with 31.3 mL (223 mmol) of diisopropylamine (Note 7) and 120 mL of tetrahydrofuran (Note 2). The mixture is cooled to −78°C in a dry ice-acetone bath, and 85.1 mL (207 mmol) of a 2.43 M solution of butyllithium in hexanes (Note 8) is added via cannula over 10 min. The resulting suspension is warmed to 0°C in an ice-water bath and is held at that temperature for 5 min, then cooled to −78°C. An ice-cooled solution of 22.0 g (99.4 mmol) of (1S,2S)-pseudoephedrinepropionamide in 300 mL of tetrahydrofuran (Note 2) is transferred to the cold reaction mixture by cannula over 10 min. The reaction mixture is stirred at −78°C for 1 hr, at 0°C for 15 min, at 23°C for 5 min, and finally is cooled to 0°C, whereupon 17.7 mL (149 mmol) of benzyl bromide (Note 9) is added over 3 min via syringe. After 15 min, 5 mL of saturated aqueous ammonium chloride solution is added, and the reaction mixture is poured into a 2-L separatory funnel containing 800 mL of saturated aqueous ammonium chloride solution and 500 mL of ethyl acetate . The aqueous layer is

separated and extracted further with two 150-mL portions of ethyl acetate . The combined organic extracts are dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford a yellow solid. Residual solvent is removed under vacuum (0.5 mm) for 3 hr. The solid residue is dissolved in 100 mL of hot (110°C) toluene in a 250-mL Erlenmeyer flask, and the flask is placed in a water bath at 80°C. The bath is allowed to cool slowly to 23°C. Extensive crystallization occurs as the solution cools. Crystallization is completed by cooling the flask to −20°C. After 10 hr, the crystals are collected by filtration and are rinsed with 100 mL of cold (0°C) toluene . The crystals are dried under reduced pressure (0.5 mm) at 23°C for 3 hr to afford 27.8 g (90%) of the desired (1S,2S)-pseudoephedrine-(R)-2-methylhydrocinnamamide as a white solid (Note 10). The diastereomeric excess (de) of this product is determined to be ≥99% (Note 11).

2. Notes

1. (1S,2S)-(+)-Pseudoephedrine was obtained from Aldrich Chemical Company, Inc. , and was used without further purification.
2. Tetrahydrofuran was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen.
3. Propionic anhydride was obtained from Aldrich Chemical Company, Inc. , and used without further purification.
4. Because of the large volume of CO_2 released during the neutralization of propionic acid, care should be taken that the propionic acid is quenched before the reaction mixture is sealed and shaken inside a separatory funnel.
5. The product exhibits the following properties: mp 114-115°C; ^{1}H NMR (300 MHz, C_6D_6) δ: 0.53 (d, J = 6.7), 0.9-1.1 (m), 1.22 (t, J = 7.3), 1.73 (m), 2.06 (s), 2.40 (m), 2.77 (s), 3.6-3.75 (m), 4.0-4.2 (m), 4.51 (t, J = 7.2), 4.83 (br), 6.95-7.45 (m) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.0, 9.4, 14.2, 15.2, 26.6, 27.3, 27.6, 32.1, 57.7, 58.1, 75.0, 76.1, 126.3, 126.7, 127.4, 127.9, 128.1, 128.3, 141.5, 142.2, 174.8, 175.8 (The ^{1}H and ^{13}C NMR spectra are complex due to amide geometrical isomerism); IR (neat) cm^{-1}: 3380 (OH), 2979, 1621 (C=O), 1454, 1402, 1053, 702 ; HRMS (FAB) m/z 222.1490 [(M+H)$^+$ calcd. for $C_{13}H_{20}NO_2$: 222.1495]. Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.55; H, 8.50; N, 6.35.
6. Anhydrous lithium chloride (99+%, A.C.S. reagent grade) was purchased from Aldrich Chemical Company, Inc. , and was further dried as follows. The solid reagent is transferred to a flask fitted with a vacuum adapter. The flask is evacuated (0.5 mm) and immersed in an oil bath at 150°C. After heating for 12 hr at 150°C, the flask is allowed to cool to 23°C and is flushed with argon for storage.
7. Diisopropylamine was distilled from calcium hydride under an atmosphere of nitrogen.
8. Butyllithium (2.5 M solution in hexanes) was purchased from Aldrich Chemical Company, Inc. , and was titrated against diphenylacetic acid .[2]
9. Benzyl bromide was obtained from Aldrich Chemical Company, Inc. , and purified by passage through 5 g of activated basic aluminum oxide .
10. The product exhibits the following properties: mp 136-137°C; ^{1}H NMR (300 MHz, C_6D_6) δ: 0.59 (d, J = 6.8), 0.83 (d, J = 7.0), 1.02 (d, J = 6.5), 1.05 (d, J = 7.0), 2.08 (s), 2.45-2.59 (m), 2.70 (s), 2.75 (m), 3.01 (m), 3.36 (dd, J = 13.1, 6.92), 3.80 (m), 3.96 (m), 4.25 (br), 4.45 (m), 6.9-7.4 (m) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 15.5, 17.4, 17.7, 27.1, 32.3, 38.1, 38.9, 40.0, 40.3, 58.0, 75.2, 76.4, 126.2, 126.4, 126.8, 127.5, 128.26, 128.31, 128.6, 128.9, 129.2, 139.9, 140.5, 141.1, 142.3, 177.2, 178.2 (The ^{1}H and ^{13}C NMR spectra are complex due to amide geometrical isomerism); IR (neat) cm^{-1}: 3384 (OH), 3027, 2973, 2932, 1617 (C=O), 1493, 1453, 1409, 1080, 1050, 701 ; HRMS (FAB) m/z 312.1972 [(M+H)$^+$ calcd. for $C_{20}H_{26}NO_2$: 312.1965]. Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.14, H, 8.09, N, 4.50. Found: C, 76.87, H, 8.06, N, 4.50.
11. The diastereomeric excess (de) of the product was determined as follows. A 10-mL round-bottomed flask equipped with a Teflon-coated magnetic stirring bar is charged with 30 mg (0.096 mmol) of (S,S)-pseudoephedrine-(R)-2-methylhydrocinnamamide and 1.0 mL of dichloromethane . To the clear, colorless solution is added 49 µL (0.35 mmol) of triethylamine and 34 µL (0.27 mmol) of chlorotrimethylsilane . After 10 min, the cloudy reaction mixture is quenched with 5 mL of water, and the mixture is transferred to a 125-mL separatory funnel with 50 mL of 50% ethyl acetate-hexanes . The organic layer is separated and extracted further with 5 mL of water followed by 5 mL of brine . The organic layer is dried over anhydrous sodium sulfate, filtered, and concentrated. The oily residue is dissolved in ethyl acetate for capillary gas chromatographic analysis. The analysis is carried out using a Chirasil-Val capillary column (25 m × 0.25 mm × 0.16 µm, Alltech, Inc.) under the following

conditions: oven temp. 200°C, injector temp. 250°C, detector temp. 275°C. The following retention times were observed: 8.60 min (minor diastereomer), 9.27 min (major diastereomer). It should be noted that the retention times can vary greatly depending on the age and condition of the column. Dichloromethane was purchased from EM Science and was distilled from calcium hydride under an atmosphere of nitrogen. Triethylamine and chlorotrimethylsilane were purchased from Aldrich Chemical Company, Inc. , and were distilled from calcium hydride under an atmosphere of nitrogen.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This procedure describes the use of pseudoephedrine as a chiral auxiliary for the asymmetric alkylation of carboxylic acid amides. In addition to the low cost and availability in bulk of both enantiomeric forms of the chiral auxiliary, pseudoephedrine, a particular advantage of the method is the facility with which the pseudoephedrine amides are formed. In the case of carboxylic acid anhydrides, the acylation reaction occurs rapidly upon mixing with pseudoephedrine. Because pseudoephedrine amides are frequently crystalline materials, the acylation products are often isolated directly by crystallization, as illustrated in the procedure above.

Pseudoephedrine amides undergo highly diastereoselective and efficient alkylation reactions. Like the alkylation substrates, the alkylation products are frequently crystalline compounds, and can often be isolated in ≥99% de by direct crystallization from the crude reaction mixture. The procedure described above is representative of this methodology and can be generally employed with a wide range of pseudoephedrine amides and alkylating agents.[3,4] The transformation of the alkylation products into highly enantiomerically enriched alcohols, aldehydes, and ketones, provides access to a large number of useful intermediates for organic synthesis, as described in the accompanying procedure.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1S,2S)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N-methylpropionamide:
Propanamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl-, [R-(R,R)]- (14); (192060-67-6); [S-(R,R)]- (13); (159213-03-3)

(1S,2S)-(+)-Pseudoephedrine:
Pseudoephedrine, (+)- (8);
Benzenemethanol, α-[1-(methylamino)ethyl]-, (R,S)-(±)- (9); (90-82-4)

Propionic anhydride (8);

Propanoic acid, anhydride (9); (123-62-6)

[1S(R),2S]-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N, 2-dimethylbenzenepropionamide:
(1S,2S)-Pseudoephedrine-(R)-2-methylhydrocinnamide:
Benzenepropanamide, N-(2-hydroxy-1-methyl-2-phenylethyl)-N, α-dimethyl-, [1S-[1R(R),2R]]- (13); (159345-08-1); [1S-[1R(S),2R]]- (13); (159345-06-9)

Lithium chloride (8,9); (7447-41-8)

Diisopropylamine (8);
2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Benzyl bromide:
Toluene, α-bromo- (8);
Benzene, (bromomethyl)- (9); (100-39-0)