A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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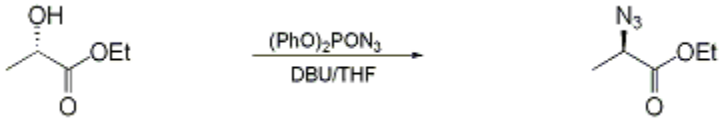
ETHYL (R)-2-AZIDOPROPIONATE

[Propanoic acid, 2-azido-, ethyl ester, (R)-]



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Checked by Christopher L. Lynch and Stephen F. Martin.

1. Procedure

Ethyl (R)-2-azidopropionate . An oven-dried, 500-mL, three-necked flask is equipped with an overhead stirrer, nitrogen inlet, and an immersion thermometer (Note 1). The flask is charged with ethyl S-(−)-lactate (19.2 mL, 0.169 mol) (Note 2), tetrahydrofuran (175 mL) (Note 3), and diphenylphosphoryl azide (40 mL, 0.185 mol) (Note 4). The mixture is cooled to 2°C in an ice-water bath. To the mixture is added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (24 mL, 0.157 mol) (Note 5) dropwise via syringe. *(Caution: The DBU addition causes an exotherm. The reaction temperature is maintained below 5°C by carefully controlling the rate of addition. For this reaction the addition required 35 min).* A thick white precipitate forms during the DBU charge. The reaction is stirred at 1°C for 1 hr, and then it is warmed to room temperature and stirred under nitrogen for 24 hr (Note 6). The resulting homogeneous reaction is diluted with methyl tert-butyl ether (MTBE, 170 mL), and water (100 mL) is added. After the water layer is removed, the organic phase is washed with water (100 mL) and 0.5 M citric acid monohydrate (100 mL). The organic layer is dried (Na_2SO_4) and concentrated under reduced pressure to ca. 40-50 g of a pale yellow oil (Note 7). The product is purified by simple distillation to afford 12.84 g (57%) of a clear, colorless oil, bp 83−88°C/50mm (Note 8), (Note 9) and (Note 10).

2. Notes

1. A Teflon-coated thermocouple of the J-type attached to an Omega model 650 digital thermometer can be substituted for the immersion thermometer.
2. Ethyl lactate was purchased from Aldrich Chemical Company, Inc. , and used without further purification. The water content was 0.8 mg/mL by Karl Fisher titration (Metrohm model 684 KF coulometer).
3. Tetrahydrofuran was purchased from Fisher Scientific Company and dried over 4 Å molecular sieves for 18 hr prior to use. The water content was less than 0.05 mg/mL by Karl Fisher titration.
4. Diphenylphosphoryl azide was 98% as purchased from Aldrich Chemical Company, Inc. , and the water content was less than 0.01 mg/mL by Karl Fisher titration.
5. DBU was 98% as purchased from Aldrich Chemical Company, Inc. , and the water content was 0.5 mg/mL by Karl Fisher titration. The amount of DBU was calculated to be 0.93 equiv of the ethyl lactate charge by assuming a purity of 98% for DBU and 100% purity for ethyl lactate. Amounts of base over 1 equiv resulted in product epimerization.
6. The reaction typically requires 16-24 hr. The progress of the reaction was monitored by capillary GC after diluting a 0.1-mL sample with 1 mL of methyl tert-butyl ether . GC conditions: Hewlett-Packard 5890 series II GC using an Alltech Econo-cap column (30 M × 0.32 mm × 0.25 μM, catalog # 19646). [The submitters used an HP-5 column (25 M × 0.32 mm × 0.52 mm, HP part # 19091J-112)]. Start oven at 50°C, then increase to 250°C at 10°C per min. The reaction was considered complete after 90% conversion; starting material R_t 4.3 min, product R_t 7.0 min.
7. The vacuum was deliberately bled to maintain 120-130 mm to minimize product losses due to volatility.
8. The yield was based on the DBU charge. The product was contaminated with 4-8% of starting material that codistilled with the product. The following characterization data was obtained: ethyl (R)-

(+)-2-azidopropionate : $[\alpha]_D^{25}$ +14.8° (hexane , *c* 1.00); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.28 (t, 3 H, J = 7.2), 1.43 (d, 3 H, J = 7.1), 3.89 (q, 1 H, J = 7.1), 4.21 (q, 2 H, J = 7.2) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 16.7, 57.3, 61.8, 170.9 ; IR (thin film) cm^{-1}: 2120, 1743 .
9. Optical purity can be quantitatively assayed by HPLC after reducing a sample to the amine with triphenylphosphine . A 50-mg sample was diluted with 10:1 THF:water (1 mL in a screw cap vial) and treated with triphenylphosphine (190 mg). Gas evolution begins within 5 min; once this subsides the reaction is sealed and placed in an oil bath at 50°C for 30 min. The mixture is diluted with $HClO_4$ (pH 1.0, 1 mL) and washed with dichloromethane (2 × 1 mL). The acidic water phase contains the salt of the amine. A 200-µL sample was diluted to 1 mL and assayed by HPLC using a Crownpak CR(+) column (Diacel Chemical Industries): HPLC conditions; aqueous pH 1.0 $HClO_4$, flow 0.5 mL/min, UV detection at 210 nm. The product had an enantiomeric excess of 96%, major enantiomer, R_t 3.4 min, and minor enantiomer, R_t 5.0 min.
10. The product from the distillation was analyzed by drop weight testing and differential scanning calorimetry (DSC). The drop weight test indicated that the product was not shock sensitive. By DSC, there was a 400 cal/g release of energy which initiated at 135°C. The pot residue showed a slow release of energy which was estimated to be ca. 100 cal/g and initiated at 150°C.

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

Asymmetric introduction of azide to the α-position of a carbonyl has been achieved by several methods. These include amine to azide conversion by diazo transfer,[2] chiral enolate azidation,[3 4] and displacement of optically active trifluoromethanesulfonates,[5] p-nitrobenzenesulfonates,[6] or halides.[7 8] Alkyl 2-azidopropionates have been prepared in optically active form by diazo transfer,[2] p-nitrobenzenesulfonate displacement,[6] and the Mitsunobu displacement using zinc azide .[9] The method presented here is the simplest of the displacement methods since alcohol activation *and* displacement steps occur in the same operation. In cases where the α-hydroxy esters are available, this would be the simplest method to introduce azide.

In addition to α-hydroxy carbonyl compounds, the method can be generally applied for alcohol to azide displacements. This method has been successfully demonstrated on fourteen optically active alcohols.[10] Mechanistically, this reaction proceeds in two stages. The first is alcohol activation via formation of the corresponding phosphate, and the second stage is the azide displacement step. The method is most useful for azide displacements of alcohols which tend to racemize using highly reactive groups for activation (e.g., sulfonate formation or Mitsunobu conditions[11]). When diphenylphosphoryl azide and DBU are used, the alcohol is only mildly activated for displacement as a phosphate. Use of the phosphate thus provides access to azide displacements of alcohols that are too sensitive using standard activation techniques. However, since the phosphate is only mildly activating, the alcohol undergoing displacement should be benzylic, allylic, or as in the present case, α to a carbonyl.

Certain classes of compounds are too reactive for the present method. Ethyl mandelate produced a racemic, protected phenyl glycine derivative. Benzylic alcohols with two methoxy groups (directly conjugating in the 2 and 4 positions) gave azide of 50% e.e.

Other classes of alcohols are unreactive. Ethyl 3-hydroxybutyrate (a β-hydroxy ester) went to the phosphate stage, but would not undergo azide displacement. In this example about 30% of the crotonate was formed because of β-elimination.

References and Notes

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

Ethyl (R)-2-azidopropionate:
Propanoic acid, 2-azido-, ethyl ester, (R)- (12); (124988-44-9)

Ethyl (S)-(−)-lactate:
Lactic acid, ethyl ester, L- (8);
Propanoic acid, 2-hydroxy-, ethyl ester, (S)- (9); (687-47-8)

Diphenylphosphoryl azide:
Phosphorazidic acid, diphenyl ester (8, 9); (26386-88-9)

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU):
Pyrimido[1,2-a]azepine, 2,3,4,6,7,8,9,10-octahydro- (8, 9); (6674-22-2)

Methyl tert-butyl ether:
Ether, tert-butyl methyl (8);
Propane, 2-methoxy-2-methyl- (9); (1634-04-4)

Citric acid monohydrate (8);
1, 2, 3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate (9); (5949-29-1)