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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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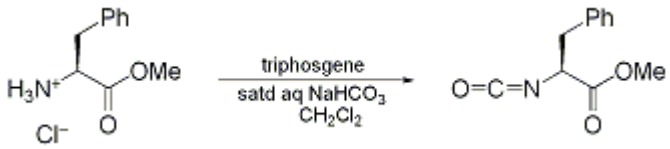
SYNTHESIS OF AMINO ACID ESTER ISOCYANATES: METHYL (S)-2-ISOCYANATO-3-PHENYLPROPANOATE

[Benzenepropanoic acid, α-isocyanato-, methyl ester, (S)]



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Checked by Adam Charnley and Steven Wolff.

1. Procedure

A 250-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer and charged with 100 mL of methylene chloride , 100 mL of saturated aqueous sodium bicarbonate , and 5.50 g (25.5 mmol) of L-phenylalanine methyl ester hydrochloride (Note 1). The biphasic mixture is cooled in an ice bath and stirred mechanically while 2.52 g (8.42 mmol) of triphosgene (Note 2) is added in a single portion. The reaction mixture is stirred in the ice bath for 15 min and then poured into a 250-mL separatory funnel. The organic layer is collected, and the aqueous layer is extracted with three 15-mL portions of methylene chloride . The combined organic layers are dried ($MgSO_4$), vacuum filtered, and concentrated at reduced pressure using a rotary evaporator to give a colorless oil. The oil is purified by Kugelrohr distillation (130°C, 0.05 mm) to afford 5.15 g (98%) of methyl (S)-2-isocyanato-3-phenylpropanoate as a colorless oil (Notes 3-6).

2. Notes

1. L-Phenylalanine methyl ester hydrochloride was purchased from Bachem California Inc.
2. Triphosgene was purchased from Aldrich Chemical Company, Inc.
3. The product has the following properties: $[\alpha]_D^{25}$ −83.8° (neat); IR ($CHCl_3$) cm^{-1}: 2260, 1747 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.03 (dd, 1 H, ABX pattern, J_{AB} = 13.8, J_{BX} = 7.8), 3.16 (dd, 1 H, ABX pattern, J_{AB} = 13.6, J_{AX} = 4.8), 3.81 (s, 3 H), 4.27 (dd, 1 H, J = 7.8, 4.6), 7.18-7.21 (m, 2 H), 7.27-7.36 (m, 3 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 39.6, 52.8, 58.3, 126.7, 127.2, 128.4, 129.1, 135.4, 170.7 . Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.18; H, 5.40; N, 6.70.
4. The yield is typically 4.97-5.15 g (95-98%).
5. The submitters previously reported an optical rotation of $[\alpha]_D^{22}$ +71.9° (neat) for methyl (S)-2-isocyanato-3-phenylpropanoate .[2] This value does not match the current value of $[\alpha]_D^{25}$ −83.8° (neat) and is in error. The origin of this discrepancy involves the path length of the polarimeter cell. With a 5-cm cell, a correct α value of −48.15° is obtained. If a 10-cm cell is used, a spurious positive α value is obtained, which gives rise to a erroneous positive value of $[\alpha]_D$.
6. The optical purity of the product was determined to be >99.5% by trapping with (S)-1-phenylethylamine and ^1H NMR analysis of the resulting urea adduct, as described in reference 2.

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 provides a convenient, rapid, high yielding route to amino acid ester isocyanates.. It is based upon procedures the submitters have previously reported for the preparation of both amino acid ester isocyanates[2] and peptide isocyanates.[3,4] These procedures use either triphosgene or a solution of

phosgene in toluene as a one-carbon electrophile and either pyridine or aqueous sodium bicarbonate as a base. The current procedure uses triphosgene and sodium bicarbonate to minimize the hazard and toxicity of the reagents and waste products. These mild reaction conditions are superior to alternative methods for the preparation of amino acid ester isocyanates, which include refluxing the amino acid ester hydrochloride in toluene for several hours while purging with gaseous phosgene,[5] or treating the amino acid ester hydrochloride with di-tert-butyl dicarbonate and 4-dimethylaminopyridine (DMAP).[6]

Amino acid ester isocyanates are produced cleanly by this method and can often be used without purification. If desired, volatile amino acid ester isocyanates, such as the title compound, can be purified to analytical purity by Kugelrohr distillation. The amino acid ester isocyanates generated by this method are formed without detectable racemization (>99.5% ee); the enantiomeric purity of the isocyanates can be checked by trapping with (S)-1-phenylethylamine, followed by ^{1}H NMR analysis of the resulting urea adducts.[2] If this method is used to generate isocyanates of peptides, then efficient stirring is necessary to prevent epimerization of the peptide isocyanates.[3], [4]

Amino acid ester isocyanates are useful synthetic building blocks, precursors to peptides and azapeptides,[7,8] chiral derivatizing agents,[9,10] and reagents for the preparation of chiral chromatographic media.[11,12] (S)-2-Isocyanato-3-phenylpropanoate (phenylalanine methyl ester isocyanate) has been used as a building block for 1,2,4-triazine azapeptides,[8] and inhibitors of thermolysin[13] and human leukocyte elastase (HLE).[14]

References and Notes

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

Methyl (S)-2-isocyanato-3-phenylpropanoate:
Benzenepropanoic acid, α-isocyanato-, methyl ester, (S)- (9); (40203-94-9)

L-Phenylalanine methyl ester hydrochloride:
L-Phenylalanine methyl ester, hydrochloride (9); (7524-50-7)

Triphosgene:
Carbonic acid, bis(trichloromethyl) ester (8,9); (32315-10-9)