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Amino Acid-Derived Iodobenzene Dicarboxylates: Reagents for Oxidative Conversion of Alkenes to Amino Acid Esters

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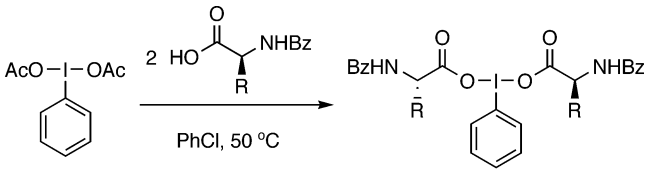
ABSTRACT



R = CH_3, CH_2Ph, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$

New amino acid-derived iodobenzene dicarboxylates were prepared by the reaction of (diacetoxyiodo)benzene with N-protected natural amino acids. These compounds in the presence of iodide anion can be used as reagents for *β*-iodocarboxylation of alkenes leading to the respective amino acid esters.

Iodobenzene dicarboxylates are the most important, well investigated, and practically useful organic derivatives of hypervalent iodine.[1] The best known representative of this class of compounds is (diacetoxyiodo)benzene (DIB, **1**), which has found broad practical application as a commercially available, versatile oxidizing reagent for organic synthesis. In particular, DIB was found to be useful for the oxidative functionalization of alkenes and other unsaturated substrates to various acetoxy derivatives.[1,2] Recent examples of these transformations include iodoacetoxylation,[2a] bromoacetoxylation,[2b] and phenylselenoacetoxylation[2c] of alkenes with DIB in the presence of iodide or bromide anions, or diphenyldiselenide, respectively. Despite the widespread interest in practical application of iodobenzene dicarboxylates, few examples of these compounds other than the acetate and the trifluoroacetate are known.[1,3,4] Among these examples, the preparation of the chiral iodobenzene dicarboxylate by the reaction of DIB with dibenzoyl-L-tartaric acid is particularly interesting, since this compound is potentially useful as an oxidizer in asymmetric synthesis.[4] However, synthetic utility of the chiral iodine(III) tartrate is restricted due to its polymeric nature.[4] In 1975, Merkushev and co-workers reported a general procedure for the preparation of iodobenzene dicarboxylates by heating DIB with various carboxylic acids.[3b] Among iodobenzene dicarboxylates reported in this paper, several derivatives of N-protected amino acids such as glycine, racemic alanine, and leucine were listed with minimal characterization data.[3b]

Considering the potential importance of derivatives of natural L-amino acids in organic chemistry and biochemistry,

(1) (a) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997. (b) Togo, H.; Katohgi, M. *Synlett* **2001**, 565. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.

(2) (a) Kirschning, A.; Plumeier, C.; Rose, L. *J. Chem. Soc., Chem. Commun.* **1998**, 33. (b) Hashem, A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* **1998**, 195. (c) Tingoli, M.; Tiecco, M.; Testaferri, L.; Temperini, A. *Synth. Commun.* **1998**, *28*, 1769.

(3) (a) Merkushev, E. B. *Russ. Chem. Rev.* **1987**, *56*, 826. (b) Merkushev, E. B.; Novikov, A. N.; Makarchenko, S. S.; Moskal'chuk, A. S.; Glushkova, V. V.; Kogai, T. I.; Polyakova, L. G. *J. Org. Chem. USSR (Engl. Trans.)* **1975**, *11*, 1246. (c) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272. (d) Imamoto, T.; Koto, H. *Chem. Lett.* **1986**, 967. (e) Hatzigrigoriou, E.; Varvoglis, A.; Bakola-Christianopoulou, M. *J. Org. Chem.* **1990**, *55*, 315. (f) Ray, D. G., III; Koser, G. F. *J. Am. Chem. Soc.* **1990**, *112*, 5672. (g) Ochiai, M.; Takaoka, Y.; Masaki, Y.; Nagao, Y.; Shiro, M. *J. Am. Chem. Soc.* **1990**, *112*, 5677.

(4) Ray, D. G.; Koser, G. F. *J. Org. Chem.* **1992**, *57*, 1607.

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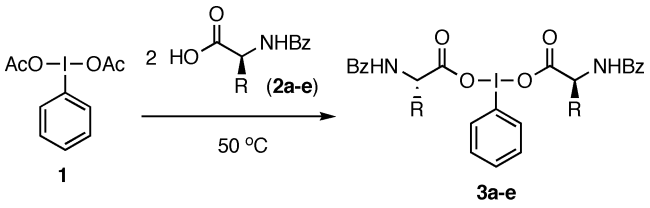
we decided to synthesize several new amino acid-derived iodobenzene dicarboxylates and investigate their reactions with unsaturated organic substrates in the presence of tetraphenylphosphonium iodide under conditions previously described for the reactions of DIB.[2a]

Amino acid-derived iodobenzene carboxylates **3** were conveniently prepared by the exchange reaction of DIB **1** with the readily available *N*-protected amino acids **2**[5] (Scheme 1).

Scheme 1. Preparation of Dicarboxylates **3**



a: R = Me, **b:** R = CH_2Ph, **c:** R = $CH(CH_3)_2$, **d:** R = $CH_2CH(CH_3)_2$, **e:** R = $CH(CH_3)CH_2CH_3$

Products **3** were isolated in good yields (Table 1) in the form of stable, white, microcrystalline solids and were characterized by spectroscopic data, elemental analysis, and high-resolution mass spectrometry.[6] In particular, the ^{1}H NMR spectra contain the typical signals of the iodobenzene moiety as well as the respective signals of the amino acid fragment and the benzoyl protective group. In the ^{13}C NMR spectra, the most characteristic are the signals from the carboxylic group. The ESI-HRMS spectra of compounds **3b** and **3d** demonstrated strong $[M + K]^+$ peaks.

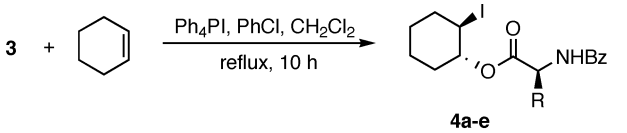
Table 1. Preparation of Dicarboxylates **3**[a]

product	yield (%)
3a	79
3b	89[b]
3c	85
3d	80
3e	68

[a] For typical reaction conditions, see ref 6. [b] Prepared by reflux in acetonitrile.

We have investigated the reactivity of compounds **3** in the reaction of iodocarboxylation of cyclohexene and dihydropyran under conditions reported by Kirschning[2a] for DIB. First of all, we have found that the reactivity of carboxylates **3** with alkenes is lower than the reactivity of DIB **1**; only a trace amount of the expected β-iodocarboxylate **4** was observed after reacting reagent **3** with cyclohexene and tetraphenylphosphonium iodide in methylene chloride under reflux for several hours. Raising the temperature of the reaction mixture by adding chlorobenzene (bp 132 °C) resulted in a significant improvement of the product **4** yield (Scheme 2).[7]

Scheme 2. Reaction of Dicarboxylates **3** with Cyclohexene



(1:1 mixture of two diastereomers)

a: R = Me, **b:** R = CH_2Ph, **c:** R = $CH(CH_3)_2$, **d:** R = $CH_2CH(CH_3)_2$, **e:** R = $CH(CH_3)CH_2CH_3$

The optimized yields of β-iodocarboxylates **4** formed in the reactions of compounds **3** with cyclohexene and dihydropyran are listed in the Table 2. All products **4** were isolated after column chromatography as a mixture of nonseparable diastereomers.

Amino acid esters **4a**−**e** were characterized by spectroscopic data and elemental analysis, and the structure of ester **4c** was unambiguously established by single-crystal X-ray analysis.[8] In particular, the ^{1}H NMR spectra of **4** contain the typical signals of trans disubstituted cyclohexane as well as the respective signals of the amino acid fragment and the benzoyl protective group. The LC analysis of the mixture

(5) No reaction was observed between unprotected amino acids and DIB due to the insolubility of amino acids in organic solvents. Protected amino acids **2** are commercially available or can be prepared by known methods; see: Zhdankin, V. V.; Smart, J. T.; Zhao, P.; Kiprof, P. *Tetrahedron Lett.* **2000**, *41*, 5299.

(6) **Representative Procedure.** A mixture of DIB **1** (0.322 g, 1 mmol) and *N*-benzoyl-L-leucine **2d** (0.47 g, 2 mmol) was dissolved in chlorobenzene (40 mL). The flask was placed on a rotary evaporator, and the reaction mixture was heated to 50 °C at aspirator vacuum. After complete evaporation of solvent, the residue was recrystallized from ethyl acetate/hexanes and dried in a vacuum to afford 0.538 g (80%) of analytically pure product **3d**. Mp: 124−126 °C. ^{1}H NMR ($CDCl_3$): δ 8.08 (dd, J_1 = 8.7 Hz, J_2 = 1.2 Hz, 2H), 7.75 (d, J = 6.9 Hz, 4H), 7.61 (t, J = 7.8 Hz, 1H), 7.5−7.40 (m, 8H), 6.58 (d, J = 8.1 Hz, 2H), 4.82 (m, 2H), 1.61 (m, 6H), 0.90 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 177.4, 167.0, 134.8, 134.1, 132.1, 131.6, 131.1, 128.5, 127.0, 122.0, 51.0, 42.2, 25.0, 22.7, 22.2. Anal. Calcd for $C_{32}H_{37}IN_2O_6$: C, 57.15; H, 5.55; I, 18.87; N, 4.17. Found: C, 57.15; H, 5.65; I, 18.65; N, 4.10. ESI MS: *m/z* (%) 711.13 (100), $[M + K]^+$.

(7) **Representative Procedure.** A mixture of reagent **3a** (0.588 g, 1 mmol) and tetraphenylphosphonium iodide (0.466 g, 1 mmol) in methylene chloride (20 mL) was stirred for 15 min at room temperature until the solution turned dark red. Then, chlorobenzene (20 mL) and cyclohexene (0.027 g, 0.33 mmol) were added and the resulting mixture was refluxed. The reaction was monitored by TLC. When the starting materials were consumed (approximately 10 h), the resulting solution was washed twice with aqueous $NaHSO_3$ (30 mL of saturated solution) and dried, and then the solvent was removed under reduced pressure. Crude product was purified by column chromatography (hexanes/ethyl acetate 2:1) and recrystallized from a hexanes/ethyl acetate mixture to afford 0.105 g (79%) of analytically pure product **4a** (isolated as a mixture of nonseparable diastereomers). Mp: 135−137 °C. ^{1}H NMR ($CDCl_3$): δ 7.82 (d, J = 7.2 Hz, 2H), 7.48 (m, 3H), 6.81 (br.s, 1H), 4.97 (m, 1H), 4.83 (m, 1H), 4.11 (m, 1H), 2.48 (m, 1H), 2.14 (m, 1H), 2.04 (m, 1H), 1.84 (m, 1H), 1.63 (d, J = 7.2, 3H), 1.58−1.33 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 172.1 (171.8), 166.7, 133.9, 131.7, 128.6, 127.0, 78.1 (77.8), 48.7, 38.2, 31.8, 30.9 (30.8), 27.2, 23.6 (23.4), 19.0 (18.6). Anal. Calcd for $C_{16}H_{20}INO_3$: C, 47.89; H, 5.02; I, 31.63; N, 3.49. Found: C, 47.84; H, 4.97; I, 31.47; N, 3.37. EI MS: *m/z* (%) 402 (10), $[M + H]^+$.

(8) Compound **4c** ($C_{18}H_{24}INO_3$; formula weight 429.28), monoclinic, space group $P2_1$ with a = 9.6884(11) Å, b = 17.902(2) Å, c = 11.1630(13) Å; β = 93.511(2)°, V = 1932.5(4) Å^3, Z = 4; R = 0.0513 for 8751 independent observed reflections ($I > 2\sigma(I)$); wR_2 = 0.1418 (F^2, all data). Full details on the crystal structure of **4c** are available in Supporting Information.

Table 2. Preparation of Iodocarboxylates **4**−**6**[a]

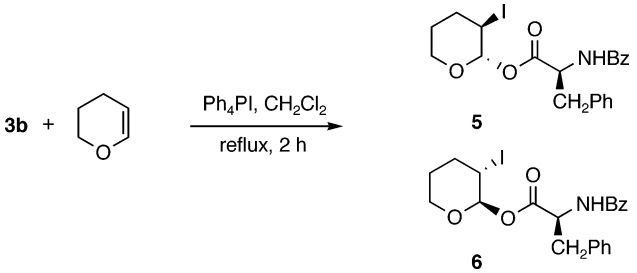
product[b]	yield (%)
4a	79[c]
4b	70[c]
4c	73[c]
4d	33[d]
4e	54[d]
5 + **6**	86[e]

[a] For typical reaction conditions of cyclohexene with reagents **3**, see ref 7. [b] All products **4** were isolated as an unseparable mixture of two diastereomers (approximately 1:1 ratio according to ^{1}H NMR). [c] Yield after chromatography, before recrystallization. [d] Isolated yield for recrystallized analytically pure compound. [e] Yield after chromatography; products **5** and **6** were isolated as individual diastereomers by fractional crystallization from hexane/ethyl acetate.

shows a single peak of the product; however, in the ^{13}C NMR spectra, two very close sets of signals are displayed due to the presence of two diastereomers with similar properties. In the X-ray, both diastereomers are present in the unit cell. The X-ray analysis and the previous work by Kirschning[2a] confirms the anti-stereoselectivity of the iodocarboxylation reaction.

The reaction of tetrahydropyran with reagent **3b** was complete after 2 h of reflux in methylene chloride and afforded a 1:1 mixture of diastereomers **5** and **6** (Scheme 3). We were able to separate this mixture by fractional crystallization from hexane/ethyl acetate.

Scheme 3. Reaction of Reagent **3b** with Dihydropyran



Individual diastereomers **5** and **6** were characterized by spectroscopic data and elemental analysis. The facile separation of the diastereomeric β-iodocarboxylated **5** and **6** is especially noteworthy, since it provides a straightforward approach to the enantiomerically pure *trans*- or *cis*-glycols via Woodward−Prevost reaction and its modern modifications.[9] The stereoselective conversion of *trans*-iodocarboxylates to *cis*- or *trans*-glycols is a well-established experimental procedure providing an entry into a plethora of important chiral building blocks.[9]

In conclusion, we have reported the preparation and reactions of new, chiral iodobenzene carboxylates derived from natural L-amino acids. Dicarboxylates **3** have reactivity similar to that of (diacetoxyiodo)benzene toward alkenes and, in the presence of iodide anion, can be used as reagents for the anti-stereoselective β-iodocarboxylation of alkenes leading to the respective amino acid esters.

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Supporting Information Available: Synthetic and characterization data for all new compounds (PDF) and X-ray crystallographic details for compound **4c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Prevost, C. *Compt. Rend.* **1933**, *196*, 1129. (b) Woodward, R. B.; Brutcher, F. V. *J. Am. Chem. Soc.* **1958**, *80*, 209. (c) Brimble, M. A.; Nairn, M. R. *J. Org. Chem.* **1996**, *61*, 4801. (d) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 6403. (e) Kim, J. H.; Long, M. J. C.; Kim, J. Y.; Park, K. H. *Org. Lett.* **2004**, *6*, 2273.