



## Chiral *N*-Protected $\beta$ -Iodoamines from $\alpha$ -Aminoacids: a General Synthesis

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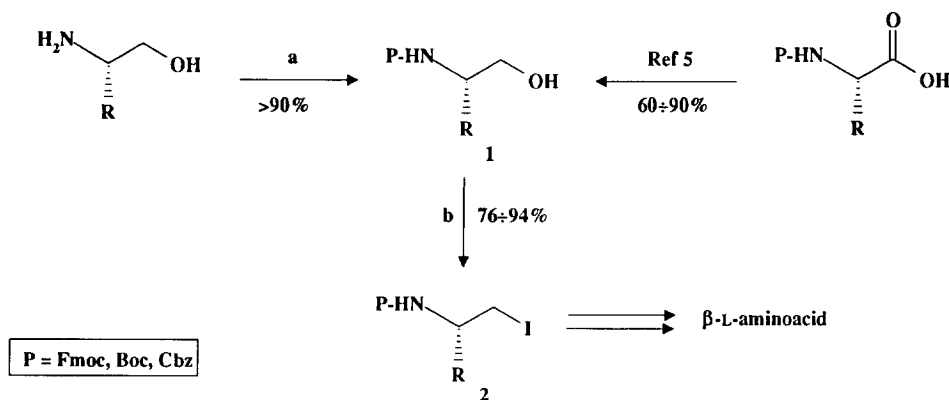
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**Abstract:** *N*-Protected D- or L- $\beta$ -iodoamines (as **2**), which are useful intermediates for the preparation of chiral  $\beta$ -aminoacids, are obtained smoothly from  $\beta$ -aminols (as **1**) in two steps and high yields.

The preparation of enantiomerically pure  $\beta$ -aminoacids has emerged only in the last decade as an important and challenging synthetic endeavour, and excellent reviews in this area have recently appeared<sup>1</sup>. A prompt approach to the synthesis of enantiopure  $\beta$ -aminoacids should consist of the homologation of their (D or L)  $\alpha$ -analogues. This was previously achieved either by the troublesome and "large-scale unsuitable" Arndt-Eistert reaction<sup>1</sup> or, in a general sense, by converting the preexisting  $\alpha$ -carboxyl group into a  $\text{CH}_2\text{-X}$  function where X is a good leaving group (e.g., a tosylate<sup>1</sup>). In this view, *N*-protected iodoamines (like **2**) represent appealing intermediates in the homologation of  $\alpha$ -aminoacids. The weak point does reside in the preparation itself of species like **2** that hitherto are obtained mainly by conversion of their corresponding aminols into tosyl<sup>2</sup> (or mesyl<sup>3</sup>) esters and treatment of the latter with sodium iodide. Unfortunately iodoamines, as a consequence of their high electrophilic reactivity, have also a somewhat low stability and are in fact photolabile and scarcely resistant to the common separation and purification procedures.

Following our current interest<sup>4</sup> in synthetic application of triarylphosphine-iodine complexes, we report now a general synthesis of chiral *N*-protected  $\beta$ -iodoamines (as **2**), having either D- or L-configuration, by treatment of their corresponding *N*-protected  $\beta$ -aminols (**1**) (ready available from commercial  $\beta$ -aminols or *N*-protected  $\alpha$ -aminoacids<sup>5</sup>: see Scheme) with polystyryl diphenyl phosphine-iodine complex (PDPI), in high yields, quickly, under mild conditions, and without detectable racemization of the chiral center. The choice of polystyryl diphenyl phosphine implies that phosphine oxide, which is formed as the sole by-product of the reaction, is linked to a polymeric matrix and thus can be finally separated by simple filtration.

Scheme



a) FmocOSu, or (Boc)<sub>2</sub>O, or CbzOSu (1.0 eq) / TEA (1.0 eq), THF, r.t., 1h; b) PDPI (2.2 eq), imidazole (2.5 eq), CH<sub>2</sub>Cl<sub>2</sub>, reflux, 1h

Table. *N*-Protected Chiral  $\beta$ -Iodoamines.

2	P	R	Yield% <sup>a</sup>	m.p. (°C)	<sup>25</sup> <sub>D</sub> <sup>b</sup> [ $\alpha$ ] <sub>D</sub>
a	Fmoc	CH <sub>3</sub>	92	127-128	-11.3 (c=1.02)
b	Fmoc	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	94	111-113	-21.3 (c=1.20)
c	Fmoc	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	94	148-149	+2.7 (c=1.36)
d <sup>c</sup>	Fmoc	CH <sub>2</sub> COO <i>t</i> Bu	90	145-146	-9.4 (c=0.98)
e	Boc	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	92	110-111	+1.3 (c=1.20)
f	Boc	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	90	55-57	-29.9 (c=1.54)
g	Boc	CH <sub>3</sub>	90	58-59	-18.6 (c=0.99)
h	Boc	CH(CH <sub>3</sub> ) <sub>2</sub>	76	48-51	-18.7 (c=2.10)
i	Boc	CH <sub>2</sub> COOBn	82	42-43	+6.6 (c=1.08)
l <sup>c</sup>	Boc	C <sub>6</sub> H <sub>5</sub>	95	97-98	-51.6 (c=0.88)
m	Boc	CH <sub>2</sub> CH <sub>3</sub>	94	51-52	-36.7 (c=0.49)
n	Cbz	CH <sub>3</sub>	89	76-77	-11.2 (c=2.86) <sup>d</sup>
o	Cbz	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	90	90-91	+8.2 (c=0.88)

<sup>a</sup> Yield of pure crystallized (CH<sub>2</sub>Cl<sub>2</sub>-hex.) product; <sup>1</sup>H NMR spectra (Bruker WH270) consistent with expected structures; satisfactory microanalyses obtained for all new products. <sup>b</sup> Rotations (Perkin Elmer 141) measured on CHCl<sub>3</sub> solutions (1.0 dm cell).

<sup>c</sup> From *N*-protected  $\beta$ -D-aminol. <sup>d</sup> Measured on CH<sub>2</sub>Cl<sub>2</sub> solution: reported<sup>6</sup> for the enantiomer +11.0 (c=3.00).

In a typical procedure, the chiral *N*-protected  $\beta$ -aminol (as **1**) (1.0 mmol) in anhydrous dichloromethane is refluxed 1h with freshly prepared<sup>7</sup> PDPI (2.2 mmol) and imidazole (2.5 mmol) under an inert atmosphere (Ar or N<sub>2</sub>). After filtering, the dichloromethane solution is washed (sodium thiosulfate and water until neutral), dried, and evaporated to afford the *N*-protected  $\beta$ -iodoamine (as **2**) which is directly crystallized from dichloromethane-hexane (1:9).

This conversion is apparently effective (see Table) for  $\beta$ -aminols carrying three of the commonly used *N*-protecting groups (Fmoc, Boc, Cbz) (**1a-o**). Chiral column (Chiralcel OD<sup>TM</sup>, hexane-*i*PrOH) HPLC analysis of *N*-protected  $\beta$ -iodoamines **2a-o** showed no traces of their enantiomeric products.

The ready availability of chiral *N*-protected  $\beta$ -iodoamines represents a significant tool towards the synthesis of enantiomerically pure  $\beta$ -aminoacids by simple homologation of their  $\alpha$ -analogues; successful work in this area is already in progress in our lab and full experimental details will be reported in due course.

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## REFERENCES

1. a) Cole, D.C. *Tetrahedron* **1994**, *50*, 9517-9582. b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3-11.
2. El Marino, A.; Roumestant, M.L.; Razafindramboa, D.; Bonato, M.; Follet, M. *Synthesis* **1992**, 1104-1108.
3. McKillop, A.; Taylor, R.J.K.; Watson, R.J.; Lewis, N. *Synthesis* **1994**, 31-33.
4. Caputo, R.; Cassano, E.; Longobardo, L.; Mastroianni, D.; Palumbo, G. *Synthesis* **1994**, in press.
5. a) Kokotos, G. *Synthesis* **1990**, 299-301. b) Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923-926.
6. Schlessinger, R. H.; Iwanowicz E. J. *Tetrahedron Lett.* **1987**, *28*, 2083-2086.
7. Caputo, R.; Ferreri, C.; Noviello, S.; Palumbo, G. *Synthesis* **1986**, 499-501.

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