A Direct and Efficient Stereoconservative Procedure for the Selective Oxidation of N-Protected β-Amino Alcohols

Marta Ocejo, Jose L. Vicario, Dolores Badía,* Luisa Carrillo, Efraim Reyes

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco-Euskal Herriko Unibertsitatea, P.O. Box 644, 48080 Bilbao, Spain
Fax +34(94)6012748; E-mail: qopbaurm@lg.ehu.es

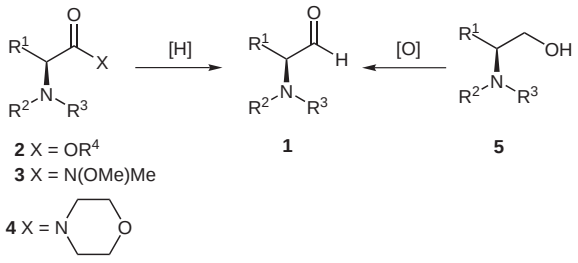
Received 6 May 2005

Abstract: An efficient, very simple and eco-friendly procedure has been developed for the synthesis of highly enantioenriched α-amino aldehydes by IBX-mediated oxidation of the corresponding β-amino alcohols. The procedure has been applied to a wide range of substrates with different side chains and protecting groups showing that the final aldehydes can be obtained in very high yields and with no racemization at the stereogenic center present in the starting compounds.

Key words: amino aldehydes, amino alcohols, oxidations, iodine, green chemistry

Enantiomerically pure α-amino aldehydes **1** are particularly important chiral intermediates in asymmetric synthesis. These compounds are extremely versatile reagents due to the presence of both the formyl group and a suitably protected amino functionality. Furthermore, they are readily available in both enantiomeric forms from the corresponding α-amino acids. In particular, α-amino aldehydes are excellent candidates to undergo diastereoselective C–C bond forming processes such as Grignard-type reactions, aldol additions or hetero-Diels–Alder cycloadditions, in which the stereochemistry of the newly created stereogenic center(s) results efficiently controlled by the chirality of the starting material, provided that the appropriate reaction conditions are chosen.

In general, α-amino aldehydes **1** are typically prepared by reduction of the corresponding α-amino esters **2**,[1a,2] Weinreb amides **3**,[1a,3] morpholine amides **4**[4] or related activated forms of carboxylic acid derivatives.[1a,5] An alternative approach consists of the selective oxidation of the respective β-amino alcohols **5** (Scheme 1).[1]



Scheme 1 The most commonly used approaches to the synthesis of enantioenriched α-amino aldehydes

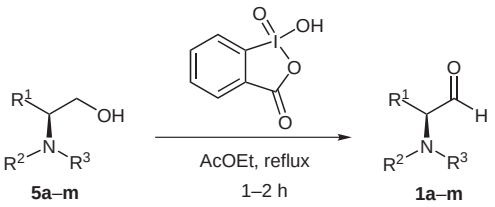
The main problem encountered in most of the reductive methods reported is the overreduction to the corresponding alcohols and/or racemization. Alternatively, a wide variety of methods have been applied to the selective oxidation of β-amino alcohols of type **5**, in which the main drawback that has to be overcome is the racemization of the final product during the reaction or isolation. Among the oxidation methods employed, one of the most widely used so far has been the Swern oxidation,[1,6] which has to be performed under strict adherence to the documented reaction conditions in order to avoid racemization side processes. Alternatively, other groups have reported the use of TEMPO[7] and Dess–Martin periodinane (DMP)[8] for the selective oxidation of N-protected β-amino alcohols.

With these precedents in mind, we decided to explore an alternative methodology for the preparation of enantiopure α-amino aldehydes in a more simple way than the others reported. In this context, hypervalent iodine reagents have recently found wide applications in organic synthesis[9] and especially as highly chemoselective oxidation reagents for the conversion of alcohols into aldehydes (Dess–Martin periodinane itself has already been successfully employed in the oxidation of β-amino alcohols).[8] Among various iodine(V) reagents, IBX (*o*-iodoxybenzoic acid) has also found wide applications in this context because of its high efficiency, easy availability, stability against moisture or air and its environmentally benign properties.[10]

We therefore subjected to several commercially available, N-protected, enantiomerically pure β-amino alcohols **5a**–**m** to reaction with 3.0 equivalents of IBX in refluxing ethyl acetate (Scheme 2),[11] observing that starting material was consumed in 1–2 hours. The reaction proceeded smoothly, affording the wanted α-amino aldehydes as the only detectable product by TLC, which were isolated as almost pure products by ^{1}H NMR after simple filtration of the crude reaction mixture and evaporation of the solvent.[12] Nevertheless, the final α-amino aldehydes were further purified by column chromatography for characterization purposes. The ee in which these compounds were obtained was calculated by chiral HPLC analysis of the corresponding β-amino alcohols, obtained by reduction of samples of pure **1a**–**m** with $NaBH_4$ in methanol.

As can be seen in Table 1, several β-amino alcohols with a broad spectrum of different substitution patterns were tested under these reaction conditions observing that in all

SYNLETT 2005, No. 13, pp 2110–2112
Advanced online publication: 12.07.2005
DOI: 10.1055/s-2005-871947; Art ID: G12505ST



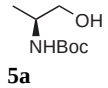
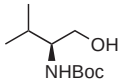
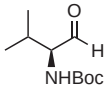
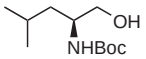
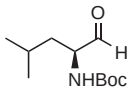
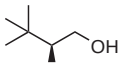
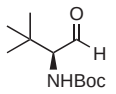
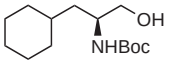
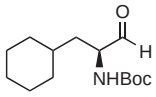
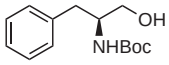
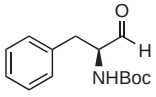
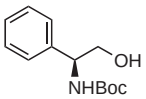
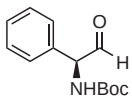
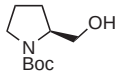
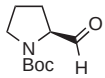
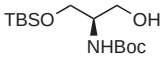
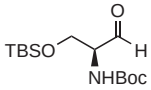
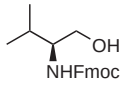
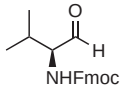
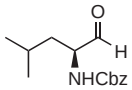
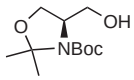
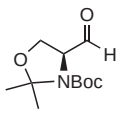
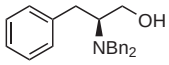
Scheme 2

cases the yields were consistently high and that almost no racemization was observed in the final products. Remarkably, *N*-Boc-phenylglycinol (**5g**) yielded cleanly *N*-Boc-phenylglycinal (**1g**), which is known to be one of the most racemization-prone α-amino aldehydes. In our case it could be obtained in 80% yield and >99% ee (entry 7) even after flash column chromatography purification.[13]

Concerning the protective group tolerance, all the carbamate-type N-protecting groups tested (Boc, Cbz and Fmoc) showed to be stable under the oxidation conditions. Also the silyloxy group found in β-amino alcohol **5i** and the *N*,*O*-acetal present in amino alcohol **5l** were compatible with these reaction conditions (entries 9 and 12, respectively). On the other hand, the *N*,*N*-dibenzylamino derivative **5m** afforded only a complicated mixture of products (entry 13), which indicates that the benzyl moieties are not suitable protecting groups to be employed in this reaction. The case of aldehyde **1l** (also known as Garner's aldehyde, entry 12), which is a widely employed chiral intermediate in total synthesis,[14] is a remarkable example of the synthetic applicability of this methodology.

The main advantage of this methodology over the others reported, especially the Swern oxidation, lies in the fact of the simplicity of the methodology. The experimental protocol is simple, does not require special equipment, nor strictly controlled reaction conditions, it can be performed under open atmosphere, requiring short reaction times and the isolation of the final product is performed by simple filtration of the crude reaction mixture followed by evaporation of the solvent. Besides, it has to be pointed out that the methodology is eco-friendly, due to the 'green' character of the oxidation reagent. This is an additional advantage of this methodology if compared with the Swern oxidation protocol, in which the production of malodorous waste compounds precludes in most cases its utilization on high scale. A good example of this can be found in the preparation of Garner's aldehyde **1l**, which has been prepared by Swern[15] and TEMPO[7b] oxidation of **5l** in comparable yield and enantiomeric excess than those reported herein, but using much more complicated experimental protocols.

Table 1 Synthesis of α-Amino Aldehydes **1a–m**

Entry	Amino alcohol **5**	Product **1**	Yield (%)[a]	ee (%)[b]
1	 **5a**	 **1a**	89	92
2	 **5b**	 **1b**	82	92
3	 **5c**	 **1c**	95	97
4	 **5d**	 **1d**	73	98
5	 **5e**	 **1e**	74	96
6	 **5f**	 **1f**	97	>99
7	 **5g**	 **1g**	80	>99
8	 **5h**	 **1h**	74	99
9	 **5i**	 **1i**	97	98
10	 **5j**	 **1j**	82	96
11	 **5k**	 **1k**	95	>99
12	 **5l**	 **1l**	95	>99
13	 **5m**	Decomp.	–	–

[a] Yield of pure product after flash column chromatography purification.

[b] Calculated by chiral HPLC of the corresponding β-amino alcohols **5a–l** obtained by $NaBH_4$ reduction of crude aldehydes (chiralcel OD column, UV detector, hexanes–*i*-PrOH 9:1, flow rate 1.00 mL/min.).

In conclusion, we have presented a very simple new methodology for the preparation of highly enantioenriched N-protected α-amino aldehydes using the IBX oxidation of the corresponding β-amino alcohols. This methodology affords excellent yields and, remarkably, proceeds with almost no racemization in the stereogenic center present at the starting material, which is a problem commonly found in other methodologies reported for the synthesis of α-amino aldehydes. In view of the wide number of compounds amenable to be prepared in this way due to the broad substrate tolerance shown by the reaction, it can be anticipated that this methodology will be of broad interest to the chemical community.

Acknowledgment

The authors thank the University of the Basque Country (Subvención General a Grupos de Investigación, and a fellowship to M.O. and E.R.) and the Spanish Ministerio de Ciencia y Tecnología (Project BQU2002-00488) for financial support.

References

(1) For some reviews see: (a) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514. (b) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226. (c) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136. (d) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. (e) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(2) (a) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Pazos, R.; Odriozola, J. M.; Bañuelos, P.; Tello, M.; Linden, A. *J. Org. Chem.* **2004**, *69*, 4126. (b) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Taddei, M. *J. Org. Chem.* **1999**, *64*, 8962. (c) Dondoni, A.; Perrone, D.; Semola, T. *Synthesis* **1995**, 181. (d) Zlatoidsky, P. *Helv. Chim. Acta* **1994**, *77*, 150. (e) Ho, T. P.; Ngu, K. *J. Org. Chem.* **1993**, *58*, 2313. (f) Maeda, H.; Maki, T.; Ohmori, H. *Tetrahedron Lett.* **1992**, *33*, 1347.

(3) (a) Wen, J. J.; Crews, C. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1855. (b) Paris, M.; Pothion, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **1998**, *39*, 1341. (c) Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676.

(4) Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37.

(5) Zlatoidsky, P. *Tetrahedron Lett.* **1995**, *36*, 7281.

(6) (a) Drag, M.; Latajka, R.; Gumienna-Kontecka, E.; Kozlowski, H.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1837. (b) De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, *66*, 7907. (c) Lee, K.-Y.; Kim, Y.-H.; Park, M.-S.; Oh, C.-Y.; Ham, W.-H. *J. Org. Chem.* **1999**, *64*, 9450. (d) Veeresa, G.; Datta, A. *Tetrahedron Lett.* **1998**, *39*, 3069. (e) Jayashinge, L.-R.; Datta, A.; Ali, S. M.; Zygmunt, J.; VanderVelde, D. G.; Georg, G. I. *J. Med. Chem.* **1994**, *37*, 2981. (f) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939.

(7) (a) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (b) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. (c) Leanna, M. R.; Sowin, T. J.; Morton, H. E. *Tetrahedron Lett.* **1992**, *33*, 5029.

(8) (a) Wroblewski, A. E.; Piotrowska, D. G. *Tetrahedron: Asymmetry* **2002**, *13*, 2509. (b) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359.

(9) Reviews: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Nicolaou, K. C.; Baran, P. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2678. (c) Wirth, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 2812.

(10) See: (a) Moore, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001. See also: (b) Moorthy, J. N.; Singhal, N.; Venkatakrishnan, P. *Tetrahedron Lett.* **2004**, *45*, 5419. (c) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Tetrahedron* **2004**, *60*, 2131. (d) Liu, Z.; Chen, Z.-C.; Zheng, Q.-G. *Org. Lett.* **2003**, *5*, 3321. (e) Surenda, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058. (f) Karthikeyan, G.; Perumal, P. T. *Synlett* **2003**, 2249. (g) Bose, D. S.; Gurjar, S. M. K. *Tetrahedron Lett.* **1997**, *38*, 5839. (h) de Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272. (i) A polymer-supported IBX-derived reagent has also been applied in the oxidation of alcohols: Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4395. (j) For an overview of the use of IBX in other oxidative transformations see: Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192; and references therein.

(11) IBX can explode on impact or heating at high temperatures: Plumb, J. B.; Harper, D. J. *Chem. Eng. News* **1990**, *68 (29)*, 3; in our hands, using IBX at temperatures between 20 °C and 90 °C, no hazards have been experienced.

(12) **Representative Experimental Procedure.** IBX (2.40 g, 8.57 mmol) was added to a solution of the β-amino alcohol **5a** (0.50 g, 2.86 mmol) in EtOAc (40 mL) and the mixture was refluxed for 2 h opened to the atmosphere. The mixture was cooled to r.t., filtered and the solvent was removed under reduced pressure to afford α-amino aldehyde **1a** pure as its ^{1}H NMR spectrum indicated. For correct characterization purposes, the crude mixture was purified by short path flash column chromatography (hexanes–EtOAc, 8:2) affording pure product as a white solid (0.44 g, 2.54 mmol, 89% yield). All spectral data of compounds **1a–l** were in agreement with those previously reported.[16]

(13) *N*-Boc-phenylglycinal is known to racemize under basic conditions (see ref. 8a) and during flash chromatography purification on SiO_2 (ref. 1e) but in our hands we have not observed racemization at all.

(14) For a review see: Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136.

(15) (a) Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64. (b) Meffre, P.; Durand, P.; Branquet, E.; Le Goffic, F. *Synth. Commun.* **1994**, *24*, 2147.

(16) Aldehydes **1a–c** and **1f**: see ref. 3c. (a) For aldehydes **1d** and **1g** see: Morita, T.; Nagasawa, Y.; Yahiro, S.; Matsunaga, H.; Kunieda, T. *Org. Lett.* **2001**, *3*, 897. (b) Aldehyde **1e**: Dondoni, A.; Merchan, F. L.; Merino, P.; Rojo, I.; Tejero, T. *Synthesis* **1996**, 641. (c) Aldehyde **1h**: Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, *64*, 6434. (d) Aldehyde **1i**: Kang, M.; Park, J.; Konradi, A. W.; Pedersen, S. F. *J. Org. Chem.* **1996**, *61*, 5528. (e) Aldehyde **1j**:Wen, J. J.; Crews, C. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1855. (f) Aldehyde **1k**: Ito, A.; Takahashi, R.; Baba, Y. *Chem. Pharm. Bull.* **1975**, *23*, 3081. (g) Aldehyde **1l**: Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64.