Pergamon

Tetrahedron Letters 41 (2000) 1359–1362

TETRAHEDRON LETTERS

Synthesis of highly epimerizable *N*-protected α-amino aldehydes of high enantiomeric excess

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Received 16 November 1999; accepted 29 November 1999

Abstract

The Dess–Martin periodinane was found to be a superior oxidant for the efficient, epimerization-free synthesis of optically active *N*-protected α-amino aldehydes from the corresponding *N*-protected β-amino alcohols. Highly racemization-prone products, including *N*-Fmoc phenylglycinal and *N*-trifluoroacetyl α-amino aldehydes, were prepared in ≥95% yield with ≤1% epimerization. © 2000 Elsevier Science Ltd. All rights reserved.

Optically active *N*-protected α-amino aldehydes are widely used synthetic intermediates of importance in the pharmaceutical and fine chemical industries.[1] The facility with which they undergo epimerization has been noted and strategies have been devised to minimize this propensity, such as Rapoport's 9-(9-phenylfluorenyl) substitution of the α-amino group[2] and Reetz' *N,N*-dibenzyl derivatization.[3] In the course of studies directed toward the synthesis of saframycin A and related alkaloids with antitumor activity, we were led to prepare a series of chiral α-amino aldehydes with simple, base-labile *N*-protective groups such as fluorenylmethoxycarbonyl (Fmoc) and trifluoroacetyl (TFA). Several of these aldehydes proved to be exceedingly susceptible to base-induced epimerization. In surveying methods for the preparation of these compounds with maximal enantiomeric enrichment we have consistently found that oxidation of the corresponding *N*-protected β-amino alcohols with the Dess–Martin periodinane[4] provides exceptional results, furnishing the desired aldehydes with ≤1% epimerization of the α-stereocenter, including highly epimerizable products such as *N*-Fmoc phenylglycinal. Because of the broad utility of these compounds as intermediates in chemical synthesis, we describe the details of our findings herein.

A large number of optically active *N*-protected α-amino aldehydes have been described in the literature.[1] These are typically among the less racemization-prone α-amino aldehydes, however, with α-side-chains such as benzyl, isobutyl, and the like, and can often be prepared in high optical purity by Swern oxidation of the corresponding *N*-protected β-amino alcohols.[1] There are far fewer references to α-amino aldehydes with epimerization-enhancing features such as an α-aryl group or a strongly electron-withdrawing *N*-protective group. From consideration of literature reports concerning *N*-protected derivatives of phenylglycinal, it is evident that such compounds can be difficult to prepare and handle.

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PII: S0040-4039(99)02293-5

Greene et al. noted that addition of vinyl magnesium bromide to *N*-benzoyl and *N*-*tert*-butoxycarbonyl phenylglycinal, prepared by Swern oxidation of the corresponding alcohols using diisopropylethylamine as base, afforded racemic products (adducts of high ee were obtained by an inverse addition protocol).[5] Dondoni et al. reported obtaining poor yields upon attempted synthesis of *N*-benzoyl phenylglycinal using the same Swern protocol, and instead turned to a semireduction method to produce the aldehyde. They described the product, *N*-benzoyl phenylglycinal, as a material which decomposed upon standing and upon attempted purification by chromatography.[6,7]

We chose the oxidation of *N*-Fmoc phenylglycinol (99% ee, determined by direct HPLC analysis using a Chiralcel OD column) as a focal point for our studies. Attempted Swern oxidation of *N*-Fmoc phenylglycinol using triethylamine as base failed to provide any of the desired *N*-Fmoc phenylglycinal (**1**). Thin-layer chromatographic analysis of the reaction mixture showed that dibenzofulvene had been formed as a product. This was somewhat surprising, for the *N*-Fmoc group is generally found to be compatible with Swern oxidation conditions (vide infra). Its instability in this particular instance may be indicative of enolization of the product aldehyde, promoting internal cleavage of the Fmoc group. Use of diisopropylethylamine as base in the Swern procedure did provide some of the desired aldehyde (ca. 37% yield, 50±5% ee), but the reaction was prohibitively slow and was in no sense a viable protocol. In accord with findings from the Abbott process group, TEMPO-catalyzed oxidation (using bleach as the stoichiometric oxidant) was found to be an effective method,[8] affording the desired aldehyde (**1**) in 87% yield after aqueous work-up. Consistent with the observations of Dondoni et al.,[6] attempted chromatographic purification of **1** on silica gel led to its decomposition. To determine the enantiomeric excess of the product, the crude material was reduced with sodium borohydride in ethanol at 23°C. The resulting *N*-Fmoc phenylglycinol, isolated in 97% yield, was found by direct HPLC analysis to be of 95% ee.[9] This value was initially considered to be a lower limit, given the possibility that racemization might have occurred in the reduction step of the ee determination; however, subsequent results established that the degree of epimerization in the reduction was at most 1%, and, thus, the erosion in optical purity must be ascribed to racemization during the oxidation or upon work-up. With further experimentation we found that optimal results in the oxidation were obtained using the Dess–Martin periodinane (2 equiv.)[10] in wet dichloromethane[11] at 23°C (25 min). Aqueous work-up afforded the crude aldehyde in >95% yield. Reduction with sodium borohydride, as described above, provided *N*-Fmoc phenylglycinol of 99% ee. This finding established both the superiority of the Dess–Martin oxidation protocol and the validity of the borohydride reduction procedure as a method for determining the ee of the product. *N*-Fmoc phenylglycinal prepared in this manner was obtained as a white solid and was shown to be of >90% purity by ^{1}H and ^{13}C NMR spectroscopy. The efficiency of the conversion was confirmed by subsequent transformations of the aldehyde to purified products, such as reduction to the alcohol (with sodium borohydride or diisobutylaluminum hydride) or cyanohydrin formation, affording yields of >90% for each two-step procedure. Further examination of the Dess–Martin protocol for the epimerization-free preparation of *N*-protected α-amino aldehydes leads us to speculate that the procedure may be of general value.[12]

Although the *N*-Fmoc phenylalaninal derivative **2** must clearly be categorized among the less racemization-prone α-amino aldehydes (it could be prepared without epimerization by Swern oxidation of the corresponding alcohol using triethylamine as base, see Fig. 1), efforts to prepare the corresponding *N*-trifluoroacetyl derivative **3** quickly established that this product exhibited an equal or perhaps even greater propensity to undergo base-induced epimerization than *N*-Fmoc phenylglycinal (**1**). Attempted preparation of **3** from the corresponding *N*-trifluoroacetyl β-amino alcohol (92% ee) by Swern oxidation using triethylamine as base (–40°C, >95% yield, unpurified) afforded nearly racemic product (6% ee, determined by reduction, Mosher ester formation, then ^{1}H NMR analysis). Using diisopropylethylamine as base in the Swern oxidation, the rate of reaction was found to be prohibitively slow, and that product

which had formed was shown to be only 45±5% ee. By contrast, Dess–Martin oxidation afforded a product of 90% ee (1% epimerization) and 95% yield (unpurified). That **3** should exhibit a comparable or greater propensity to undergo base-induced epimerization relative to **1** must clearly be attributed to the strongly electron-withdrawing nature of the *N*-trifluoroacetyl protective group. Correlations such as this have been previously noted, e.g., in the case of enolization of *N*-protected α-amino ketones,[13] as well as in the propensities of *N*-protected α-amino acids to epimerize.[14] It is reasonable to propose that the rate of deprotonation of the α-stereocenter slows as the electron density on the α-amino group increases.

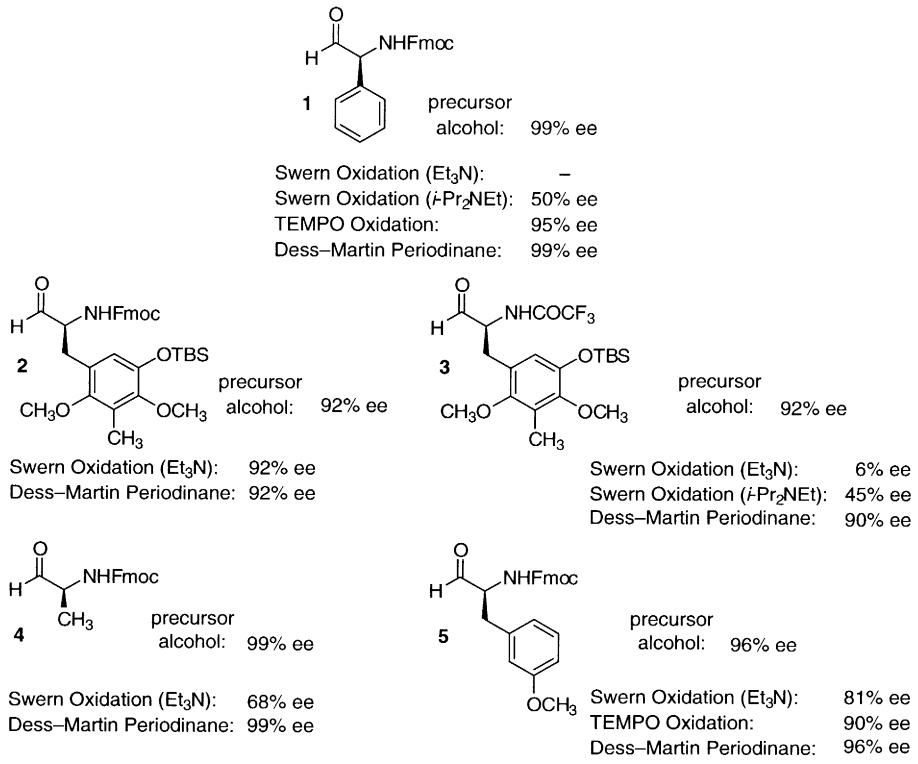

Fig. 1. Preparation of *N*-protected α-amino aldehydes by oxidation of the corresponding alcohols

As summarized in Fig. 1, further studies directed toward the preparation of *N*-Fmoc alaninal (**4**)[15] and *N*-Fmoc (*m*-methoxyphenyl)alaninal (**5**) are in keeping with the findings above and suggest the following generalizations for the preparation of *N*-protected α-amino aldehydes by oxidation of the corresponding *N*-protected β-amino alcohols. Swern oxidation using triethylamine as base is effective only with the most robust *N*-protected α-amino aldehydes and leads to a high degree of racemization with epimerization-prone substrates. Use of diisopropylethylamine as base in the Swern oxidation produces less racemization, but the rate of oxidation can be unacceptably slow and in epimerization-prone cases products of high ee are not obtained. The TEMPO-catalyzed oxidation is a practical and efficient method to produce optically active aldehydes, but does lead to a small degree of racemization (4–6%) with the most demanding cases that we have explored, whereas the Dess–Martin procedure is highly efficient for all substrates that we examined, proceeding with minimal epimerization of the α-stereocenter.[16]

Acknowledgements

Financial support from the National Institutes of Health is gratefully acknowledged. M.M. is supported by a Roche predoctoral fellowship. D.W.K. and B.A.L. acknowledge predoctoral fellowships from the National Science Foundation.

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