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Synthesis of *C*-Protected α-Amino Aldehydes of High Enantiomeric Excess from Highly Epimerizable *N*-Protected α-Amino Aldehydes

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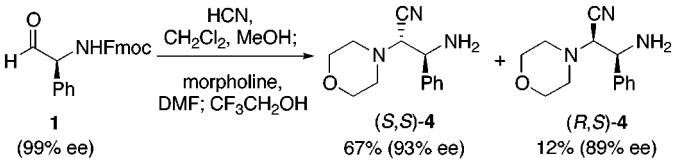
ABSTRACT



A new procedure for the preparation of *C*-protected α-amino aldehydes of high enantiomeric excess is illustrated using five differently substituted α-(*N*-Fmoc)amino aldehydes as starting materials. Highly epimerization-prone substrates were converted to the corresponding morpholino nitrile-protected α-amino aldehydes with minimal racemization (products ≥ 89% ee). Morpholino nitrile derivatives of phenylglycinal were crystallized and subjected to X-ray structural analysis, allowing for definitive determination of the stereochemistry of amino nitrile formation. A rationale for the stereoselectivity of amino nitrile formation is presented.

We recently described the preparation of a series of protected α-amino aldehydes in which the aldehyde carbon was masked as an amino nitrile function (see, e.g., structures **4**).[1] These "*C*-protected" α-amino aldehydes were prepared from the corresponding α-(*N*-Fmoc)amino aldehydes in a three-step sequence (two operations, vide infra), typically in ≥ 92% ee.[1,2] Subsequent efforts to extend this methodology revealed that racemization was a serious problem when highly epimerizable α-(*N*-Fmoc)amino aldehydes were used as substrates. A modified procedure was developed that likely involves the intermediacy of free α-amino aldehydes.[3,4] As detailed herein, the new method promises to be generally applicable; highly enantiomerically enriched amino nitrile-masked α-amino aldehydes have been prepared from all α-(*N*-Fmoc)amino aldehydes examined, including those that are readily epimerized. We have also determined the stereochemistry of amino nitrile formation and have elucidated conformational features of these products using X-ray crystallography and solution ^{1}H NMR data. A rationale for the stereochemistry of amino nitrile formation is presented.

The original procedure for the preparation of amino nitrile-masked α-amino aldehydes began with cyanohydrin formation from the corresponding α-(*N*-Fmoc)amino aldehydes and hydrogen cyanide in dichloromethane−methanol (Figure 1).

(1) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401−8402.

(2) For leading references to prior work describing the preparation of acetal-, thioacetal-, and aminal-protected α-amino aldehydes, see: (a) Bringmann, G.; Geisler, J.-P. *Synthesis* **1989**, 608−610. (b) Thiam, M.; Chastrette, F. *Tetrahedron Lett.* **1990**, *31*, 1429−1432. (c) Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 418−421. (d) Denmark, S. E.; Nicaise, O. *Synlett* **1993**, 359−361. (e) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489−7492. (f) Alexakis, A.; Lensen, N.; Tranchier, J.-P.; Mangeney, P.; Feneau-Dupont, J.; Declercq, J. P. *Synthesis* **1995**, 1038−1049.

(3) Myers, A. G.; Kung, D. W.; Zhong, B. *J. Am. Chem. Soc.* **2000**, *122*, 3236−3237.

(4) For other approaches to minimize racemization of α-amino aldehydes, see: (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236−239. (b) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141−1143.

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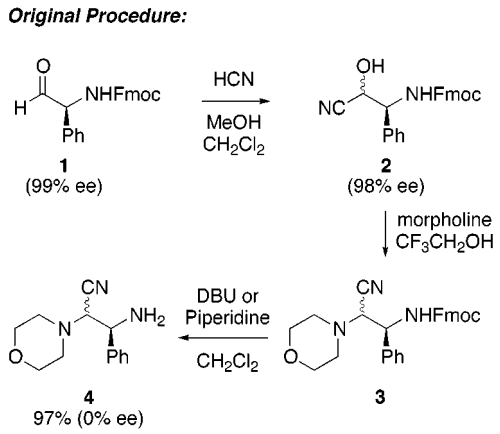


Figure 1. The original procedure for α-amino morpholino nitrile synthesis, leading to racemic products **4** in the case of *N*-Fmoc phenylglycine (**1**).

The resulting cyanohydrins were then coupled to an amine such as morpholine (5.0 equiv) in 2,2,2-trifluoroethanol (TFE) at 23 °C, followed by cleavage of the *N*-Fmoc protective group with DBU or piperidine in dichloromethane.[1] Although this procedure was highly effective with the range of α-(*N*-Fmoc)amino aldehydes originally examined, when *N*-Fmoc phenylglycinal (**1**) was later investigated as a substrate, racemic products were obtained. Efforts to develop an alternative procedure therefore focused on the epimerization-free transformation of this substrate. We began by identifying those steps in the sequence that were responsible for racemization. The substrate (**1**) was prepared by the oxidation of *N*-Fmoc phenylglycinol (>99% ee) with the Dess−Martin periodinane, a reagent found to be optimal for this purpose in terms of the chemical yield and enantiopurity of the product (>95% yield, unpurified, 99% ee).[5] The crude product, a white solid, was used directly in cyanohydrin formation, for it decomposed upon attempted chromatography on silica gel. Treatment of a freshly prepared solution of *N*-Fmoc phenylglycinal (**1**) of 99% ee in dichloromethane with methanolic hydrogen cyanide (prepared in situ by combination of acetic acid and potassium cyanide, 2.7 and 2.5 equiv, respectively) at 0 °C for 2 h afforded the corresponding cyanohydrins **2** in 99% yield after extractive isolation. Reduction of the latter products with sodium borohydride in methanol afforded *N*-Fmoc phenylglycinol in 99% yield and 98% ee (chiral HPLC analysis), establishing that the transformation of **1** to **2** had proceeded with <1% epimerization. Racemization in the synthesis of the α-amino morpholino nitrile derivatives **4** must therefore have occurred after cyanohydrin formation, during morpholino nitrile formation (**2** → **3**) or later, upon cleavage of the *N*-Fmoc group (**3** → **4**). Given the stability of the morpholino nitrile group under basic reaction conditions, the latter possibility seemed unlikely; racemization was thus presumed to have occurred during formation of the amino nitrile (**2** → **3**).

Among possible solutions to the problem of racemization during amino nitrile formation, we were led to consider changing the order of the last two steps, that is, conducting cleavage of the *N*-Fmoc group prior to amino nitrile formation (Figure 2). The proposed alternative sequence was not viewed optimistically initially because it invoked the intermediacy of a free α-amino aldehyde. Several lines of evidence suggested that the idea was not without merit, however, and we were eventually led to explore the preparation of α-amino aldehydes without protective groups. We found that "free" α-amino aldehydes were indefinitely stable, configurationally as well as constitutionally, in mildly acidic, protic media, where they were shown to exist as their ammonium salt carbonyl solvates (hydrate or methanol adduct).[3] Further studies showed that these species could be intercepted by nucleophilic addition under basic conditions, for example, with sodium borohydride in methanol, and that this addition proceeded without detectable epimerization.[3]

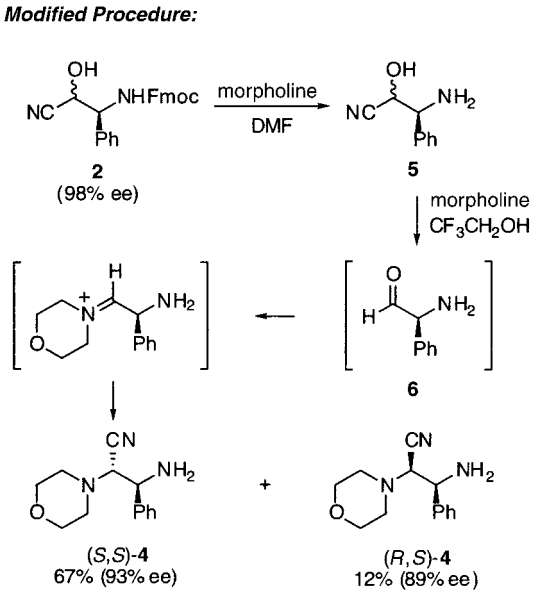


Figure 2. Modified procedure for α-amino morpholino nitrile synthesis, involving "free" α-amino aldehyde **6** as an intermediate.

For the present purpose it was necessary to generate the "free" phenylglycinal intermediate (**6**) under carefully defined conditions in order to trap it by Strecker reaction (amino nitrile formation with morpholine and cyanide) without epimerization. This entailed the development of a protocol for cleavage of the *N*-Fmoc group of **2** under conditions that did not promote premature breakdown of the cyanohydrin-masked aldehyde. Morpholine was a particularly attractive candidate in this regard because of its mild basicity and, more importantly, because it was incorporated into the product in the following step, potentially allowing the sequence to be streamlined. Empirically, the course of reaction of α-(*N*-Fmoc)amino cyanohydrins such as **2** with morpholine is

(5) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359−1362.

found to be exceedingly sensitive to the reaction solvent. In polar, protic media such as TFE, Strecker reaction of the cyanohydrin group occurs preferentially, leading to the formation of the α-(*N*-Fmoc)amino morpholino nitriles, which were racemic in the case of products **3**, as discussed above. By contrast, in aprotic media cleavage of the *N*-Fmoc group is observed to occur preferentially. Thus, treatment of α-(*N*-Fmoc)amino cyanohydrins **2** with a 50% solution of morpholine in dichloromethane led to complete *N*-Fmoc cleavage within 2 h at 23 °C, leaving intact the cyanohydrin group. Reduction of the resulting α-amino cyanohydrins (**5**)-with sodium borohydride in methanol afforded phenylglycinol of 72% ee. That partial racemization had occurred was interpreted as evidence for reversible breakdown of the cyanohydrin intermediate during cleavage of the *N*-Fmoc group, providing an avenue for α-epimerization via the aldehyde intermediate. What was not clear was whether epimerization had occurred prior to *N*-Fmoc cleavage or subsequently, via the free α-amino aldehyde. This question was largely resolved when extended exposure of the products **5** to morpholine−dichloromethane (20 h for complete reaction, 23 °C) was shown to provide the diastereomeric α-amino morpholino nitriles **4** with little additional epimerization (46 and 11% yields, 63 and 66% ee, respectively), despite the 10-fold increase in reaction time. That the majority of racemization had occurred during cleavage of the *N*-Fmoc group, and not during the subsequent amino nitrile synthesis, showed that the α-(*N*-Fmoc)amino aldehyde was much more prone to epimerization than the corresponding α-amino aldehyde, validating the hypothesis that led to the proposed inverted reaction sequence. However, further enhancement of the enantiomeric purity of the products was viewed as necessary for the development of a useful process. This was achieved by conducting the cleavage reaction in the dipolar aprotic solvent *N*,*N*-dimethylformamide (DMF).[6] *N*-Fmoc cleavage was found to be much faster in DMF than in dichloromethane,[4] whereas further transformation of the α-amino cyanohydrin products to the corresponding α-amino morpholino nitriles was negligibly slow in this solvent, consistent with the idea that the cyanohydrin group was stabilized against breakdown. By adding the protic solvent TFE (and additional morpholine), amino nitrile formation occurred smoothly at ambient temperature (23 °C, 10 h), and with little racemization. After isolation by flash column chromatography, the diastereomeric morpholino nitriles were obtained in 67% and 12% yields (93 and 89% ee, respectively). Recrystallization of each diastereomer afforded crystals suitable for X-ray analysis; the structures are shown in Figure 3. The major diastereomer was thus shown to have the (*S*,*S*)-configuration (anti) and, correspondingly, the minor diastereomer the (*R*,*S*)-configuration (syn). In the solid state, both diastereomeric products adopt the one staggered conformation that avoids any syn-pentane like interactions between the morpholine ring and the non-hydrogen substituents of the α-carbon while maintaining an antiperiplanar

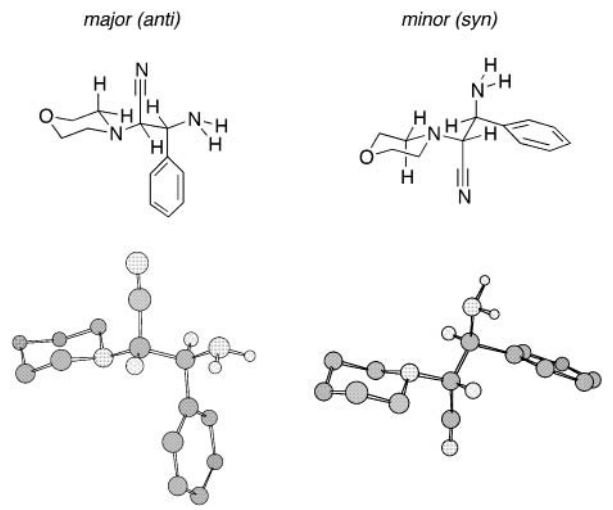


Figure 3. Solid-state structures of anti and syn morpholino nitrile derivatives of phenylglycinal.

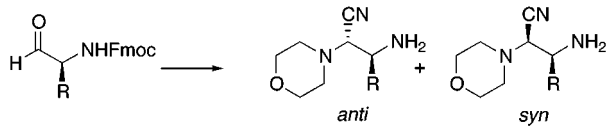
orientation of the morpholine nitrogen lone pair and the cyano group. This would appear to be energetically more important than any preference for the vicinal amines or the bulky phenyl and morpholino groups to adopt trans orientations. The solid-state structures show no evidence of intramolecular hydrogen-bonding interactions. Both diastereomers are believed to adopt solution conformations that are quite similar to the solid-state conformations on the basis of ^{1}H NMR evidence. For example, the ^{1}H−^{1}H coupling constants between the α-protons and the vicinal protons of the amino nitrile groups in solution are large (8−10 Hz) and nearly identical for the two diastereomers (precluding stereochemical determination on this basis), consistent with the solid-state structures in which these protons are antiperiplanar in both cases.

As shown in Table 1, the modifed procedure has provided superior results in the formation of optically active morpholino nitrile products. Substrates whose amino acid counterparts were known to be problematic with regard to racemization in peptide couplings were chosen specifically for study. Thus, α-(*N*-Fmoc)amino aldehyde derivatives of alanine and methionine were transformed into the corresponding morpholino nitrile derivatives, in both cases with high enantiomeric excesses (entries 7 and 8, Table 1). Parenthetically, the preparation of *C*-protected methioninal required a reliable route to methioninal of high enantiomeric purity. Oxidation of the corresponding *N*-Fmoc amino alcohol with the Dess−Martin periodinane in moist dichloromethane proved to be optimal for this purpose, as it was for the synthesis of optically active *N*-Fmoc phenylglycinal. The compatibility of the thioether group of methioninal to the conditions of the oxidation is especially noteworthy.[7] As in the case of *N*-Fmoc phenylglycinal, *N*-Fmoc methioninal

(6) Atherton, E.; Sheppard, R. C. In *The Peptides*; Undenfriend, S., Meienhofer, J., Eds.; Academic Press: San Diego, 1987; Vol. 9, Chapter 1, pp 16−20.

(7) Swern oxidation is complicated by the oxidation of the thioether group, see: Wen, J. J.; Crews, C. M. *Tetrahedron: Asymmetry* **1998**, *9*, 1855−1858.

Table 1. Synthesis of α-Amino Morpholino Nitriles[a]



entry	R	anti yield[a]	(ee)	syn yield[a]	(ee)	dr
original procedure						
1	Ph	67	(0)	30	(0)	2.2
2	$CH_2CH_2SCH_3$	34	(84)	45	(87)	0.8
3	CH_3	20[b]	(88)	17[b]	(82)	1.2
4	*m*-$CH_2C_6H_4OCH_3$	51	(82)	43	(80)	1.2
5	$CH_2(CH_2)_2OTBDPS$	43	(92)	40	(94)	1.1
modified procedure						
6	Ph	67	(93)	12	(89)	5.6
7	$CH_2CH_2SCH_3$	53	(98)	14	(98)	3.8
8	CH_3	52	(95)	15	(97)	3.5
9[c]	*m*-$CH_2C_6H_4OCH_3$	59	(95)	15	(96)	3.9
10	$CH_2(CH_2)_2OTBDPS$	59	(96)	22	(97)	2.7

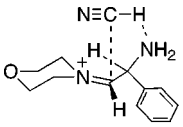
[a] Original procedure: HCN, CH_2Cl_2−MeOH; morpholine, TFE; DBU, CH_2Cl_2. Modified procedure: HCN, CH_2Cl_2−MeOH; morpholine, DMF; morpholine, TFE. Yields are determined using α-(*N*-Fmoc)amino alcohols as starting materials and include oxidation to the α-(*N*-Fmoc)amino aldehyde with the Dess−Martin periodinane.[3] [b] Lower yield due to multiple chromatographic purifications in this experiment. [c] Cleavage of *N*-Fmoc group conducted in morpholine−CH_2Cl_2 (1:1).

did not survive chromatography on silica gel and was therefore used in crude form.

Entries 9 and 10 of Table 1 provide two examples of morpholino nitrile derivatives of nonnatural α-amino aldehydes that we have employed as key intermediates in complex synthetic problems; in both cases improved enantioselectivities were obtained using the modified procedure elaborated herein. Although the combined yield of morpholino nitrile diastereomers may be slightly lower in the modified procedure relative to the original protocol, the enhanced optical purity of the products makes it by far the superior method.

The stereochemistry of amino nitrile formation is interesting and merits comment. In the five cases examined the diastereoselectivity of morpholino nitrile formation was substantially higher in the modified procedure than in the earlier procedure proceeding via α-(*N*-Fmoc)amino aldehyde intermediates. The major stereoisomer is proposed to be the (*S*,*S*)-diastereomer in all cases. Although only the products derived from phenylglycinal have been rigorously determined, careful analysis of the ^{13}C spectra ($CDCl_3$) of the 10 products of Table 1 has shown small, but consistent, variations in the chemical shifts of a morpholine N−CH_2 resonance (δ 50.7−51.0, major, δ 50.2−50.4, minor) and the nitrile carbon resonance (δ 116.1−116.3 major, δ 114.7−115.6, minor) as a function of stereochemistry.[8] In addition, in every case the major diastereomer produced in the modified procedure is found to be the less polar compound (higher R_f value, SiO_2, MeOH−CH_2Cl_2). While no one of these features is compelling in and of itself, taken together, the evidence suggests that each reaction follows a similar stereochemical course.

The stereoselectivity of amino nitrile formation is clearly kinetically determined.[9] This was established conclusively in the case of the products derived from phenylglycine, where each diastereomer was recovered unchanged when resubjected to the conditions of its formation. The selectivity of amino nitrile formation can be rationalized by invoking addition of cyanide to a rotamer of the morpholinium ion intermediate in which the α-CH bond is coplanar, or nearly so, with the iminium ion. In such a model, the major diastereomer results from addition of cyanide to the iminium ion along a trajectory close to the vector defined by the adjacent α-CN bond, perhaps directed by hydrogen bonding between hydrogen cyanide and the amino group (possibly mediated by a bridging solvent molecule).



The method elaborated herein provides a simple and, it is proposed, general route to a useful class of *C*-protected α-amino aldehyde intermediates for chemical synthesis. These have been shown to be fundamental components of more complex structures, assembled by a variety of basic condensation reactions.[10]

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

Supporting Information Available: Spectroscopic and analytical data for morpholino nitrile-protected α-amino aldehydes as well as experimental procedures for **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Vicinal $^1H-^1H$ coupling constants between the methine hydrogens are not reliable indicators of syn or anti stereochemistry. As noted in the discussion above, the preferred conformations of both diastereomers place the α-CH and the amino nitrile CH bonds antiperiplanar. The corresponding coupling constants are thus quite similar and cannot be used to differentiate the diastereomers.

(9) (a) Ogata, Y.; Kawasaki, A. *J. Chem. Soc. B* **1971**, *2*, 325−329. (b) Taillades, J.; Commeyras, A. *Tetrahedron* **1974**, *30*, 2493−2501. (c) Stout, D. M.; Black, L. A.; Matier, W. L. *J. Org. Chem.* **1983**, *48*, 5369−5373. (d) Chakraborty, T. K.; Hussain, K. A.; Reddy, G. V. *Tetrahedron* **1995**, *51*, 9179−9190.

(10) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828−10829.