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Synthesis of 9-fluorenylmethoxycarbonyl-protected amino aldehydes

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Abstract

9-Fluorenylmethoxycarbonyl-protected amino aldehydes could be efficiently prepared in good yields by using two methods: (i) $NaBH_4$ reduction of Fmoc-protected mixed anhydrides, followed by the Swern oxidation of the alcohols; and (ii) $LiAlH_4$ reduction of Fmoc-protected amino acid Weinreb amides. Both methods afforded comparable overall synthetic yields (70–80%). © 1998 Elsevier Science Ltd. All rights reserved.

The reduced peptide bond, $\psi[CH_2NH]$, is widely used for the synthesis of pseudopeptide-based enzymatic inhibitors and antagonists.[1] Among the features provided by this amide bond isostere are: (1) increased flexibility; (2) resistance to enzymatic degradation; and (3) introduction of a protonation site under physiological conditions.[2] Traditionally, the incorporation of the $\psi[CH_2NH]$ isostere into a peptide sequence was achieved by performing a resin bound reductive amination on the resin bound protonated amine and a *tert*-butoxycarbonyl-protected amino aldehyde in the presence of $NaBH_3CN$.[3] This approach is convenient and facile, however it is incompatible with solid supports incorporating acidic labile linkages, such as Wang[4] and Rink resins.[5] In order to overcome this incompatiblity between the protecting group and linkages, a non-acid labile protecting group (Fmoc, allyl, etc.) for the amino aldehydes is needed. Herein, we report our recent studies on the synthesis of 9-fluorenylmethoxycarbonyl-protected amino aldehydes.

We envisioned that 9-fluorenylmethoxycarbonyl-protected amino aldehydes could be potentially synthesized by two approaches: (i) reduction of the acids to alcohols, followed by oxidation to the corresponding aldehydes; and/or (ii) transformation of the acids to Weinreb amides, followed by reduction of the corresponding amides (Scheme 1).

To investigate the feasibility of both approaches, we first focused our attention on the reduction of Fmoc-protected amino acids. Initially, we used a borane–tetrahydrofuran complex (BH_3–THF)[6] as the reducing reagent for this purpose. For all acids tested, the reduction proceeded smoothly at 0°C and afforded the desired alcohols in 56%–80% yields (Table 1), along with a hydrophobic side product

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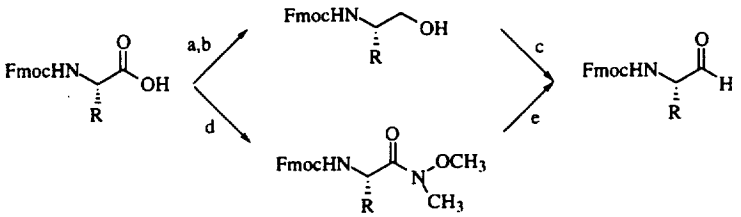

Scheme 1. Reagents and conditions: (a) iBuOCOCl, NMM, DME, −10°C; (b) $NaBH_4$, H_2O, 0°C; (c) $(COCl)_2$/DMSO/DIEA, CH_2Cl_2, −60°C to r.t.; (d) N,O-dimethylhydroxylamine hydrochloride/HBTU/DIEA; (e) $LiAlH_4$

(10%–20%) identified as the Fmoc-cleavage product, 9-fluorenylmethylene.[7] In an effort to minimize cleavage of the Fmoc-group during the reduction, we carried out the reduction at −78°C. We found that cleavage of the Fmoc-group still occurred under lower temperature conditions, however to a smaller degree, and at the cost of slowing down overall reduction kinetics as well as decreasing the synthetic yield. Thus it became clear that in order to minimize the cleavage of the Fmoc-group and improve the reduction yield significantly, an alternative approach was needed. Subsequently, we found that the reduction of Fmoc-protected mixed anhydrides with $NaBH_4$, as proposed by Martinez et al.[8] provides an excellent approach for preparing Fmoc-protected alcohols with remarkably high yields (83–98%). The reduction yields from both reduction approaches are listed in Table 1.

Table 1

Entry	Alcohol	Yield (%)	
		BH_3/THF reduction	$NaBH_4$ reduction
1	Fmoc-Leu-ol	73	85
2	Fmoc-Phe-ol	82	88
3	Fmoc-Val-ol	76	83
4	Fmoc-Met-ol	62	97
5	Fmoc-Ser(But)-ol	56	98
6	Fmoc-Glu(But)-ol	71	90

Our next endeavor was to investigate the oxidation of Fmoc-protected amino alcohols using well established oxidants. To identify optimal oxidation conditions for this purpose, we used the Fmoc–Phe-ol as a model substrate, and oxidized it with various oxidants including pyridinium chlorochromate (PCC),[9] pyridinium dichromate (PDC),[10] SO_3/pyridine/DMSO,[11] and the Swern oxidation (DMSO/$(COCl)_2$/DIEA).[12] It was found that: (i) PCC and PDC provided easy and convenient approaches for oxidizing Fmoc–Phe-ol, but suffered from slow oxidation kinetics and moderate synthetic yields (40–50%). This resulted primarily from the incomplete oxidation of the alcohol and partial cleavage of the Fmoc-group during the oxidation. (ii) Sulfur trioxide oxidation of Fmoc–Phe-ol afforded Fmoc–Phe-al in a moderate yield (50%). The Fmoc-group was also partially cleaved during the oxidation. (iii) Swern oxidation worked effectively for the oxidation of Fmoc–Phe-ol to Fmoc–Phe-al, with a good 79% synthetic yield, even though the Fmoc-group was partially cleaved. Based on these results, we concluded that Swern oxidation is the best choice for oxidizing Fmoc-protected amino alcohols to Fmoc-protected amino aldehydes. For most of the alcohols used in this study, the oxidation yields ranged from 72% to 85% (Table 2).[13] Under optimal $NaBH_4$ reduction and Swern

Table 2

Entry	Aldehyde	Yield (%)		$[\alpha]_D$ *	FABMS $[M+H]^+$*		mp (°C)*
		Swern oxidation	Weinreb amide reduction	(c, MeOH)	Calc.	Found	
7	Fmoc-Leu-al	80	73	-19.1 (0.23)	338.4	338.1	71-73
8	Fmoc-Phe-al	79	92	-48.7 (0.23)	372.4	372.1	106-108
9	Fmoc-Val-al	85	80	-10.9 (0.22)	324.4	324.1	oil
10	Fmoc-Met-al	25	89	-23.8 (0.20)	356.5	356.1	55-57
11	Fmoc-Ser(But)-al	72	85	+1.3 (0.23)	368.4	368.2	oil
12	Fmoc-Glu(But)-al	83	82	-19.0 (0.26)	410.5	410.2	72-74

* The aldehydes prepared from Weinreb amide reduction were used for measurements.

oxidation conditions, the overall synthetic yields for making Fmoc-protected amino aldehydes from the Fmoc-protected amino acids could be between 70% to 80%.

The reduction of *tert*-butoxycarbonyl-protected Weinreb amides to the corresponding aldehydes was first reported by Castro.[14] The reduction was effected using $LiAlH_4$ at 0°C and afforded the desired aldehydes in high yields. By the same measure, we envisioned that the Fmoc-protected amino aldehydes could also potentially be prepared by this reduction method. However, since $LiAlH_4$ is a very strong reducing reagent,[15] a low reduction temperature appears to be necessary for minimizing the cleavage of the Fmoc-group during the reduction process. Subsequently, we synthesized a series of Fmoc-protected Weinreb amides (>90% yields) and subjected them to $LiAlH_4$ reduction at −78°C under nitrogen. As expected, the reduction proceeded smoothly and was usually complete within one hour. Under these reduction conditions, only a small amount of the Fmoc-group was cleaved (5%–10%). The desired Fmoc-protected amino aldehydes could be synthesized in 73–92% yields (Table 2). The following procedures are illustrative.

1. Swern oxidation of Fmoc–Phe-ol

A solution of 26 μl oxalyl chloride (0.3 mmol) in 0.5 ml CH_2Cl_2 was stirred at −60°C under nitrogen. To the solution was added 43 μl DMSO (0.6 mmol), then the solution was stirred vigorously. After 10 min, 75 mg Fmoc–Phe-ol in 1 ml CH_2Cl_2 was added dropwise to the solution using a syringe. The reaction mixture was stirred at −60°C under nitrogen for 15 min, followed by the addition of 209 μl DIEA (1.2 mmol). The cooling bath was removed after 5 min, and the reaction mixture was allowed to warm to room temperature. Water (5 ml) was then added to the reaction mixture. The mixture was stirred at rt for an additional 10 min, and extracted twice with CH_2Cl_2 (60 ml). The organic layer was washed with 1 N HCl solution, saturated NaCl solution, dried over anhydrous $MgSO_4$, and evaporated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 15%–30% EtOAc:hexane). Yield: 79%; mp: 106–108°C; $[\alpha]_D$=−48.7 (c 0.21, MeOH); ^{1}H-NMR ($CDCl_3$): δ 3.17 (d, 2H, J=6.4 Hz); 4.22 (t, 2H, J=6.8 Hz); 4.42 (m, 1H); 4.52 (m, 1H); 7.13–7.79 (m, 13H); 9.56 (s, 1H). FAB MS: calcd for [$C_{24}H_{21}NO_3$, $M+H^+$] 372.4, found 372.1.

2. $LiAlH_4$ reduction of Fmoc–Phe–$CON(CH_3)OCH_3$

A solution of 53 mg $LiAlH_4$ (1.4 mmol) in 4 ml THF was stirred at −78°C under nitrogen. To the solution was added dropwise 300 mg Weinreb amide (0.7 mmol) in 2 ml THF. The reaction was quenched after 60 min by adding cold water to the solution. The solution was evaporated *in vacuo* and the residue was extracted twice with ethyl acetate (40 ml) and 1 N HCl solution (5 ml). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated to afford 240 mg of a white solid product. Yield: 92%; mp: 106–108°C; $[\alpha]_D$=−48.7 (c 0.23, MeOH); ^{1}H-NMR and FAB MS data are identical to those described above.

In conclusion, we have demonstrated that the 9-fluorenylmethoxycarbonyl-protected amino aldehydes could be successfully synthesized by either reducing the Fmoc-protected mixed anhydrides with $NaBH_4$, followed by a Swern oxidation of the alcohols, or converting the Fmoc-protected amino acids to the corresponding Weinreb amides, followed by a reduction of the amides with $LiAlH_4$. Overall, both approaches afforded comparable synthetic yields.

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