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Addition of Carbon-Based Nucleophiles to Fmoc-Protected Acyl Iminium Ions†

Alison E. Hartman, Cheryl L. Brophy, Julia A. Cupp, Daniel K. Hodge, and Timothy J. Peelen*

Department of Chemistry, Lebanon Valley College, Annville, Pennsylvania 17003

peelen@lvc.edu

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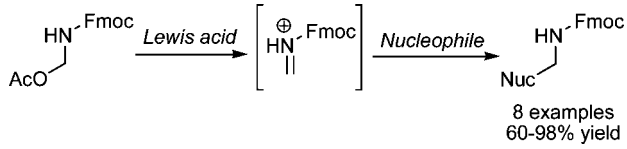


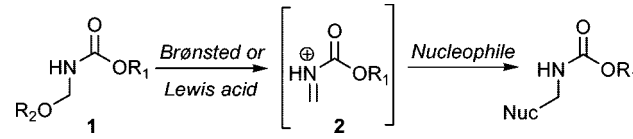
Weakly basic carbon nucleophiles add efficiently to a Fmoc-protected *N*,*O*-acetal compound. The new reactions highlight the compatibility of the Fmoc protecting group with moderately basic reaction conditions and should serve as a model for the development of more efficient syntheses of Fmoc-protected amino acids.

The base-labile *N*-fluoren-9-ylmethoxycarbonyl (Fmoc) amine protecting group plays a central role in solid phase peptide synthesis.[1] The prominence of Fmoc-protected amines is underscored by a recent literature search: over 37 000 different Fmoc-protected amines have been synthesized, of which 2261 are commercially available.[2]

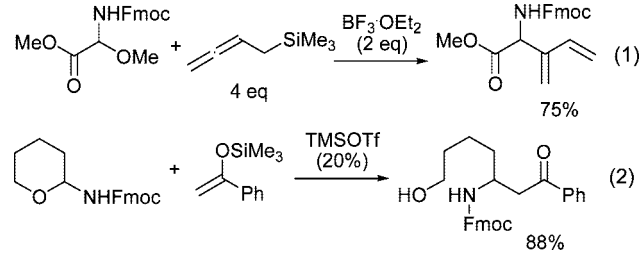
Despite their importance, the methods for preparing Fmoc-protected amines and amino acids are limited. The base sensitivity of the Fmoc group often precludes its use early in synthetic sequences. Thus, Fmoc-protected amines are almost exclusively prepared by a final protection of a free amine with the Fmoc group. The need for late stage incorporation of the Fmoc protecting group typically leads to an inefficient "protecting group shuffle", in which deprotection and protection steps end the synthesis.

The inefficiency of current methods for the synthesis of Fmoc-protected amines makes more efficient methods desirable. A common strategy for the synthesis of carbamate-protected amines involves the reaction of an acyl iminium ion intermediate.[3] Nucleophilic additions to acyl iminium ions **2**, generated in situ from an *N*,*O*-acetal **1** or a similar adduct, provide a direct and convergent approach for the assembly of complex carbamate-protected amines (Scheme 1).

SCHEME 1. General Reaction Scheme of Acyl Iminium Ions Derived from *N*,*O*-Acetals



Despite the wealth of literature pertaining to acyl iminium ions, there are few examples of reactions of Fmoc-protected acyl iminium ions. We are aware of only two C−C bond-forming reactions using Fmoc-protected acyl iminium ions: Hiemstra performed additions using an allenyl silane (eq 1) while Kobayashi added a silyl enol ether to cyclic acyl imines (eq 2).[4,5]



The base lability of the Fmoc protecting group precludes its use with strongly basic nucleophiles that would result in competitive deprotection (Figure 1). Nevertheless, we suspect that there exists a set of weakly basic nucleophiles that are compatible with the Fmoc group. Exploration of these nucleophiles should provide an attractive, efficient route to precursors of unnatural amino acids. Herein, we describe a study of weakly basic carbon nucleophiles with a model *N*,*O*-acetal.

We have prepared *N*,*O*-acetal **3** through a simple condensation reaction (Scheme 2).[6] The condensation reaction produces a crystalline, bench stable *N*,*O*-acetal in a single step from inexpensive, commercially available starting materials. More complex *N*,*O*-acetals have been prepared by others using a variety of oxidative methods, including electrochemical oxidation of *N*-alkyl carbamates[7] and electrochemical[8] or chemical[9] oxidative fragmentation of carbamate-protected amino acids or amino alcohols.

Our study shows that a variety of nucleophiles add efficiently to *N*,*O*-acetal **3** in C−C bond-forming reactions (Table 1). Selection of an appropriate Lewis acid is essential for obtaining

† Dedicated to the memory of H. Anthony Neidig, 1924−2008.

(1) (a) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 401–407. (b) Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 506−507.

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(7) (a) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264–4268. (b) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, *63*, 206–213.

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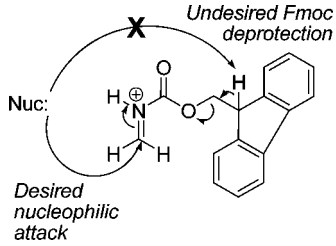


FIGURE 1. Reaction pathways available to Fmoc-protected iminium ions.

SCHEME 2. Preparation of Model *N*,*O*-Acetal

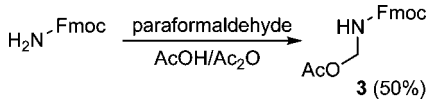
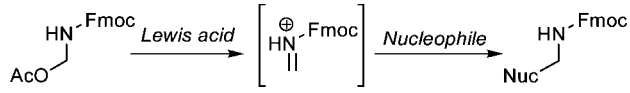
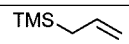
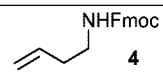
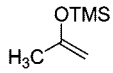
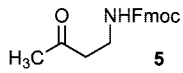
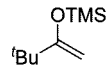
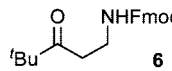
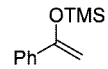
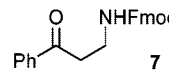
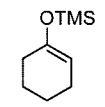
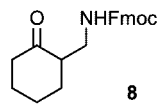
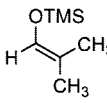
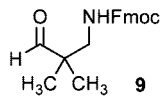
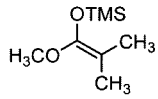
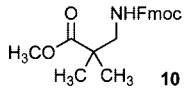
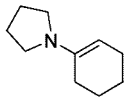
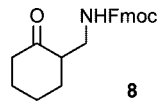


TABLE 1. Addition of Weakly Basic Nucleophiles to Fmoc-Protected *N*,*O*-Acetals



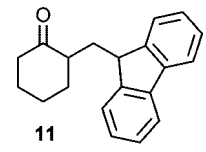
entry	Nucleophile	Lewis Acid	product	Yield (%)
1		BF_3	 **4**	60
2		$ZnCl_2$	 **5**	87
3		$ZnCl_2$	 **6**	93
4		$ZnCl_2$	 **7**	98
5		$ZnCl_2$	 **8**	90
6		$ZnCl_2$	 **9**	80
7		$ZnCl_2$	 **10**	78
8		none	 **8**	64

good yields. As an initial test reaction, we examined addition of allyl silane; BF_3 effectively catalyzed this reaction as observed previously (entry 1).[4,10]

A variety of silyl enol ether (entries 2−6) and silyl ketene acetal (entry 7) nucleophiles react with *N*,*O*-acetal **3**.[5,11] Unlike the reactions with allyl silane, BF_3 does not afford a high yield of product. Screening of other Lewis acids identified $ZnCl_2$ as the optimal Lewis acid for reactions involving silyl enol ethers and silyl ketene acetals.[12] The need to match Lewis acid with nucleophile suggests that the Lewis acid not only is involved in the formation of the acyl iminium ion, but also has a role in the nucleophilic addition step. Entries 6 and 7 are notable as they produce products that can be readily converted to Fmoc-protected β-amino acids, either through oxidation of the aldehyde or hydrolysis of the ester.[13,14]

The $ZnCl_2$-catalyzed additions of silyl enol ethers and silyl ketene acetals to Fmoc-protected *N*,*O*-acetal **3** are operationally simple and tolerant of a wide variety of reaction conditions. The silyl enol ethers and silyl ketene additions proceed equally well in toluene, acetonitrile, and methylene chloride solvent. The reactions can be performed under ambient conditions with no prior purification of the solvent. The reaction also proceeds in chloroform, though ethanol-stabilized chloroform must be distilled prior to use, or else the ethanol-derived Fmoc-protected *N*,*O*-acetal is also obtained. Silyl enol ethers and silyl ketene acetal additions are typically complete (using 10 mol % of $ZnCl_2$) over several hours, though the Fmoc-protected products are stable to the reaction conditions and no diminution of product is observed over extended reaction times. The $ZnCl_2$-catalyzed additions afford complete conversion to product by using as low as 10 mol % of catalyst loadings, though higher catalyst loadings and even stoichiometric Lewis acid are also effective.

Ketone-derived enamines also react with *N*,*O*-acetal **3** to afford β-amino ketones (entry 8). The moderate yield for this reaction is due primarily to competing side reactions. These side reactions include Fmoc deprotection, indicating that we are approaching the limits of nucleophile basicity that can be tolerated with Fmoc-protected compounds. The reaction also proceeds with the morpholine-derived enamine, though much more slowly and with a lower yield. The enamine addition proceeds best in the absence of Brønsted or Lewis acid additives, which is unusual given that acids are typically required to form the acyl iminium ion intermediate. Addition of Lewis acids such as $ZnCl_2$ or BF_3 results in rapid consumption of starting material to a complex mixture of byproducts with negligible product formation. One of the side products that we have isolated is **11**, which can form either through nucleophilic displacement of the Lewis acid-activated carbamate by the enamine or, alternatively, by reaction of the enamine with dibenzofulvene formed in Fmoc deprotection.[15] In the enamine addition, the reaction time must be monitored carefully to avoid decomposition of the product under the basic reaction conditions; we have obtained optimal yields after 4 h.



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(10) Meester, W. J. N.; van Dijk, R.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2909–2911.

(11) For selected recent examples, see:(a) Liautard, V.; Desvergnes, V.; Itoh, K.; Liu, H.-w.; Martin, O. R. *J. Org. Chem.* **2008**, *73*, 3103–3115. (b) Attrill, R.; Tye, H.; Cox, L. R. *Tetrahedron: Asymmetry* **2004**, *15*, 1681–1684. (c) Sugiura, M.; Hagio, H.; Kobayashi, S. *Helv. Chim. Acta* **2002**, *85*, 3678–3691. (d) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477–480.

(12) Several different Lewis and Brønsted acids were screened. $ZnCl_2$ was clearly the best catalyst; BF_3 was moderately effective (~80% conversion) while no product was observed with $AlCl_3$, $TiCl_4$, or trifluroacetic acid.

(13) For an example of an oxidation of a Fmoc-protected amino aldehyde, see: Spino, C.; Gobdout, C. *J. Am. Chem. Soc.* **2003**, *125*, 12106–12107.

(14) For a recent example of an ester hydrolysis of a Fmoc-protected amino ester, see: Triola, G.; Brunsveld, L.; Waldmann, H. *J. Org. Chem.* **2008**, *73*, 3646–3649.

(15) For an addition of a silyl enol ether to dibenzofulvene, see: Cho, B. P. *Tetrahedron Lett.* **1995**, *36*, 2403–2406.

In summary, we describe Lewis acid-catalyzed additions of carbon-based nucleophiles to Fmoc-protected *N*,*O*-acetals. Expanding reactions of acyl iminium ions to include Fmoc-protected versions is important in light of the central role that Fmoc-protected amino acids play in automated peptide synthesis. The base-lability of the Fmoc-protecting group presents unique synthetic challenges that can be managed effectively by using appropriate combinations of weakly basic nucleophiles and Lewis acids.

Experimental Section

General Procedure for the Addition of Silyl Enol Ethers and Silyl Ketene Acetals to Fmoc-Protected *N*,*O*-Acetals. To **3** in $CHCl_3$ in a 1 dram vial equipped with a stir bar was added the silyl enol ether or silyl ketene acetal (1.5−2 equiv) and $ZnCl_2$ (0.5 M in THF, 0.1 equiv). After the indicated time, the reaction was quenched with 1 M HCl and extracted into CH_2Cl_2 (3×). The combined organic extracts were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude products were purified by liquid chromatography (hexane and ethyl acetate, using a gradient elution) to afford the desired Fmoc-protected amine product.

Procedure for the Addition of Enamine to Fmoc-Protected *N*,*O*-Acetals. To *N*,*O*-acetal **3** (62.2 mg, 0.200 mmol) in toluene (2 mL) in a 1 dram vial equipped with a stir bar was added 1-pyrrolidinocyclohexene (45 μL, 0.28 mmol, 1.4 equiv). After 4 h, the reaction was quenched with 2 mL of 3 M HCl and stirred vigorously for 5 min. The product was extracted into CH_2Cl_2 (3 × 2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by liquid chromatography (hexane and ethyl acetate, using a gradient elution) to afford 44.6 mg (0.128 mmol, 64%) of Fmoc-protected amino ketone **8** as a white solid: IR (KBr) ν 3350, 2937, 2852, 1688, 1538, 1447, 1272, 1007 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 5.27−5.43 (br s, 1H), 4.30−4.42 (m, 2H), 4.20 (t, J = 7.0 Hz, 1H), 3.35 (ddd, J = 13.9, 7.6, 3.8 Hz, 1H), 3.24 (ddd, J = 14.0, 7.7, 5.7 Hz, 1H), 2.47−2.63 (m, 1H), 2.23−2.47 (m, 2H), 2.04−2.18 (m, 2H), 1.82−1.96 (m, 1H), 1.52−1.78 (m, 2H), 1.40 (qd, J = 12.7, 3.4 Hz, 1H). A minor set of resonances (∼10%), which we attribute to rotamers about the carbamate C−N bond, is observed. The minor resonances begin to coalesce with the main resonances upon heating the NMR sample. These observed resonances for the minor rotamer appear at δ 4.85−4.99 (br s, 1H), 4.50−4.63 (br s, 2H), 2.86−3.14 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 213.6, 156.7, 144.2, 141.5, 127.8, 127.2, 125.3, 120.2, 66.8, 51.3, 47.5, 42.5, 41.1, 31.7, 28.0, 25.0; HRMS (ESI, *m*/*z*) calcd for $C_{22}H_{23}NO_3Na$ $[M + Na]^+$ 372.1570, found 372.1564.

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Supporting Information Available: General experimental methods, additional experimental procedures, compound characterization data, and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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