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Activation of Fmoc-Protected *N,O*-Acetals Using Trimethylsilyl Halides: Mechanistic and Synthetic Studies

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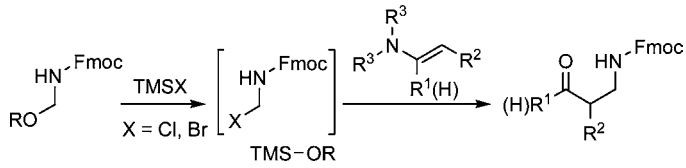
ABSTRACT



Trimethylsilyl halide activation of Fmoc-protected *N,O*-acetals yields reactive intermediates capable of efficiently adding to a variety of enamines. NMR studies have provided evidence that a stable halomethyl carbamate intermediate forms in solution. Good yields are obtained over a broad range of enamine nucleophiles encompassing both cyclic and acyclic ketone-derived and aldehyde-derived enamines. Preliminary studies suggest that the enamine additions occur through a concerted, S_N2-type mechanism.

N-Fluoren-9-ylmethoxycarbonyl (Fmoc)-protected amines and amino acids are valuable building blocks for synthesis, particularly for the solid-phase synthesis of peptides.[1,2] Despite their importance, the methods for the preparation of unnatural Fmoc-protected amines and amino acids are limited. Due to the base lability of the Fmoc-protecting group, Fmoc protection is typically reserved for the final step of synthetic sequences. Often, these syntheses require different protecting groups early in the synthesis, resulting in inefficient procedures requiring multiple protection and deprotection steps.

We envisioned efficient routes to Fmoc-protected amines through C−C bond-forming reactions involving Fmoc-protected acyl iminium ion precursors. While acyl iminium ion chemistry is well established,[3] there were only two reported carbon−carbon bond-forming reactions using Fmoc-protected *N,O*-acetals prior to our studies.[4] Recently, we reported a model study of additions of weakly basic nucleophiles to an Fmoc-protected *N,O*-acetal.[5] Catalyzed by Lewis acids (10 mol %), allylsilane, silyl enol ether/silyl ketene acetal, and ketone enamine nucleophiles were found to be compatible with the Fmoc-protecting group in these reactions.

The addition of the ketone enamine, which was the most basic of our nucleophiles, to the Fmoc-protected *N,O*-acetal required careful control of reaction conditions. Surprisingly, no Lewis acid was required for the enamine addition. Furthermore, competing reaction pathways, mostly involving Fmoc-deprotection, severely limited the scope and yields of enamine additions. Examination of the prior literature

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

(2) For an overview of solid-phase peptide synthesis, see: Amblard, M.; Fehrentz, J.-A.; Martinez, J.; Subra, G. *Mol. Biotechnol.* **2006**, *33*, 239–254.

(3) For recent reviews, see: (a) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856. (c) Hiemstra, H.; Speckamp, W. N. *Comprehensive Organic Synthesis*, 1st ed.; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 2, pp 1047−1082.

(4) (a) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510–12517. (b) Mentink, G.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2002**, *4*, 3497–3500.

(5) Hartman, A. E.; Brophy, C. L.; Cupp, J. A.; Hodge, D. K.; Peelen, T. J. *J. Org. Chem.* **2009**, *74*, 3952–3954.

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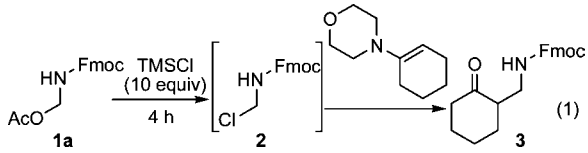
revealed that there were few examples of enamine additions to *N*,*O*-acetals or acyl iminium ions.[6]

To expand the scope of enamine additions to Fmoc-protected *N*,*O*-acetals, we were interested in identifying alternative strategies for activating Fmoc-protected *N*,*O*-acetals. We felt that the ability to exchange the oxygen leaving group in the *N*,*O*-acetal for a more reactive halide, as had recently been done using TMSCl, held great promise for expanding the scope of *N*,*O*-acetal chemistry.[7,8] Herein, we report a mechanistic and synthetic study of the activation of Fmoc-protected *N*,*O*-acetals using trimethylsilyl halides and subsequent addition of enamines.

Preliminary experiments using *N*,*O*-acetal **1a** with TMSCl followed by addition of morpholinocyclohexene cleanly afford the desired Fmoc-protected amino ketone **3** (eq 1). Reaction optimization indicated that using an excess of TMSCl was beneficial and that the reaction worked best if the TMSCl was premixed with the *N*,*O*-acetal compound prior to addition of the enamine. Simultaneous addition of TMSCl and the enamine resulted in little or no product formation.



^{1}H NMR experiments clarified the operative reaction pathway (Figure 1). Reaction of *N*,*O*-acetal **1a** with TMSCl

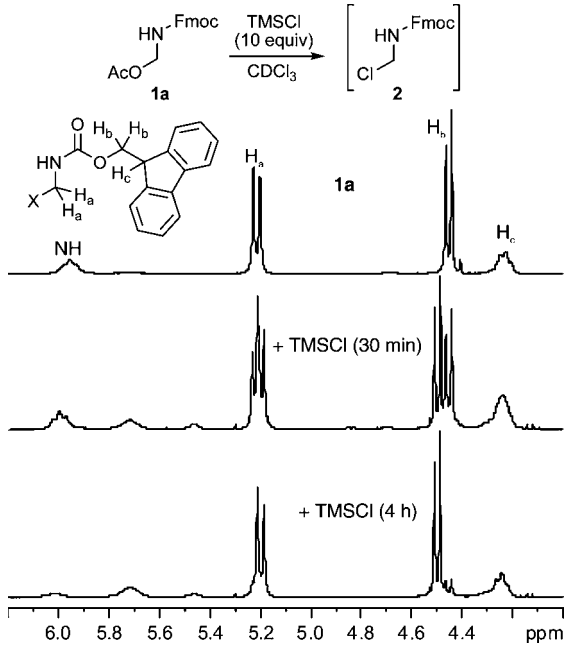
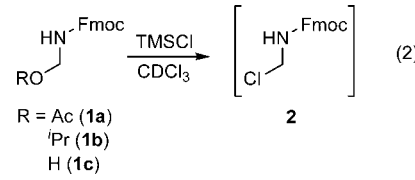


Figure 1. Activation of *N*,*O*-acetal **1a** with TMSCl over 4 h.

in $CDCl_3$ afforded slow conversion to a new intermediate. The conversion is roughly complete at room temperature after 4 h using a 10-fold excess of TMSCl; the intermediate appears to be relatively stable under the reaction conditions. Following addition of morpholinocyclohexene, the intermediate is completely consumed before an NMR spectrum can be acquired (not shown).[9] Workup affords the expected Fmoc-protected amino ketone **3**.

We assign the intermediate in the reaction as the chloromethyl carbamate **2**. The observed ^{1}H NMR chemical shift for the chloromethyl group agrees well with the chemical shifts observed for stable chloromethyl carbamates and amides reported previously.[10,11] Further evidence for the chloromethyl carbamate was obtained by examining intermediates formed from the addition of TMSCl to Fmoc-protected *N*,*O*-acetals **1a**−**c** (Figure 2). When starting with either the hydroxy, acetoxy, or isopropoxy *N*,*O*-acetal, the reactions converge to a common intermediate (eq 2).[9] This result is consistent with replacement of the oxygen group resulting in the formation of a chloromethyl carbamate.



Additional evidence for formation of a halomethyl carbamate intermediate was obtained by treating *N*,*O*-acetals with different trimethyl silyl halide reagents. Reaction of Fmoc-protected *N*,*O*-acetal **1a** in $CDCl_3$ with TMSBr afforded an insoluble white precipitate, presumably the corresponding bromide, that could not be characterized using NMR. Addition of enamine to the intermediate results in rapid consumption of the solid and smooth conversion to the corresponding Fmoc-protected amino ketone. Spectroscopic evidence of soluble halide-containing intermediates

(6) (a) Statkova-Abeghe, S.; Angelov, P. A.; Ivanov, I.; Nikolova, S.; Kochovska, E. *Tetrahedron Lett.* **2007**, *48*, 6674–6676. (b) Attrill, R.; Tye, H.; Cox, L. R. *Tetrahedron: Asymmetry* **2004**, *15*, 1681–1684.

(7) For the first report of a TMSCl activation approach to Pictet−Spengler reactions, see: Cheung, G. K.; Earle, M. J.; Fairhurst, R. A.; Heaney, H.; Shuhaibar, K. F.; Eyley, S. C.; Ince, F. *Synlett* **1991**, 721–723. For a related opening of a cyclic acetal using dialkylboron bromide, see: Guindon, Y.; Ogilvie, W. W.; Bordeleau, J.; Cui, W. L.; Durkin, K.; Gorys, V.; Juteau, H.; Lemieux, R.; Liotta, D.; Simoneau, B.; Yoakim, C. *J. Am. Chem. Soc.* **2003**, *125*, 428–436.

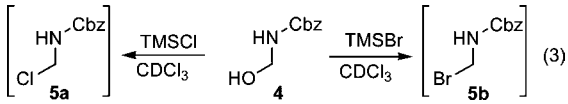
(8) (a) Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328–6331. (b) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577–1580. (c) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405.

(9) See the supporting information.

(10) (a) Hartung, R.; Golz, G.; Schlaf, S.; Silvennoinen, G.; Polborn, K.; Mayer, P.; Pfaendler, H. R. *Synthesis* **2009**, 495–501. (b) Aciro, C.; Davies, S. G.; Garner, A. C.; Ishii, Y.; Key, M.-S.; Ling, K. B.; Prasad, R. S.; Roberts, P. M.; Rodriguez-Solla, H.; O'Leary-Steele, C.; Russell, A. J.; Sanganee, H. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2008**, *64*, 9320–9344. (c) Majumdar, S.; Sloan, K. B. *Synth. Commun.* **2006**, *36*, 3537–3548. (d) Williams, G. D.; Wade, C. E.; Clarkson, G. J.; Wills, M. *Tetrahedron: Asymmetry* **2007**, *18*, 664–670. (e) Böhme, H.; Raude, E. *Chem. Ber.* **1981**, *114*, 3421–3429. (f) Smith, M. B.; Dembofsky, B. T.; Son, Y. C. *J. Org. Chem.* **1994**, *59*, 1719–1725. (g) Ortiz, J.; Guijarro, A.; Yus, M. *Tetrahedron* **1999**, *55*, 4831–4842.

(11) halomethylcarbamates **2**, and the other halomethylcarbamates described herein, can be isolated, though they are very sensitive to moisture and are less pure upon isolation than they were in situ. Thus, we prefer to avoid handling the halomethylcarbamate compounds directly.

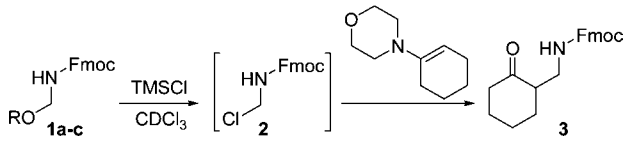
was obtained using Cbz-protected hydroxy *N*,*O*-acetal **4** (eq 3). Activation of **4** with TMSCl or TMSBr led to intermediates with distinct ^{1}H and ^{13}C NMR spectra, consistent with formation of different halide-containing intermediates **5a** and **5b**.[9] Intermediates **5a** and **5b** were both competent electrophiles in subsequent reactions with enamines.



Activation of Fmoc-protected *N*,*O*-acetal **1a** with even more strongly electrophilic silyl reagents TMSI and TMSOTf did not afford activated intermediates. Instead, treatment of a variety of *N*,*O*-acetals with both TMSI and TMSOTf resulted in decomposition of the *N*,*O*-acetal and formation of $FmocNH_2$. TMSOTf[12] and TIPSOTf[13] have previously been used as promoters of *N*,*O*-acetals in reactions proposed to involve acyl iminium ion intermediates. Our inability to identify a stable triflate-containing intermediate may suggest that these reactions proceed through acyl iminium ion intermediates without significant participation of stable triflate-containing intermediates.

Next, we examined the synthetic scope of enamine additions to TMSCl-activated *N*,*O*-acetals. The TMSCl activation of Fmoc-protected *N*,*O*-acetals **1a**−**c** containing different oxygen leaving groups was explored (Table 1). The

Table 1. Effect of Oxygen Leaving Group



entry	−OR	TMSCl (equiv)	activation time (h)	yield (%)
1	−OAc (**1a**)	10	2	60
2	−O^{i}Pr (**1b**)	10	16	46
3	−OH (**1c**)	2	1	71

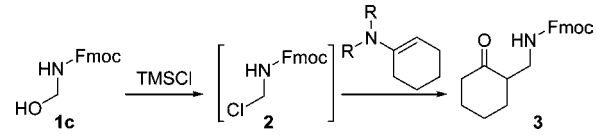
amount of TMSCl, the activation time required, and the extent of activation all vary on the basis of the oxygen leaving group. TMSCl activation of *N*,*O*-acetals **1a** and **1c** typically occurs in >90% conversion (based upon ^{1}H NMR integrations), and subsequent enamine addition affords good yields of ketone product. Hydroxy-substituted *N*,*O*-acetal **1c** activates the most rapidly and cleanly and also affords the highest yield of enamine addition products and, thus, was used in further synthetic studies.

(12) For selected recent examples, see: (a) Mancey, N. C.; Butlin, R. J.; Harrity, J. P. A. *Synlett* **2008**, 2647–2650. (b) Xiao, Q.; Floreancig, P. E. *Org. Lett.* **2008**, *10*, 1139–1142. (c) Liu, G.; Meng, J.; Feng, C.-G.; Huang, P.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 1297–1303. (d) Romero, A.; Woerpel, K. A. *Org. Lett.* **2006**, *8*, 2127–2130. (e) Shirakawa, S.; Lombardi, P. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 9974–9975.

(13) Othman, R. B.; Bousquet, T.; Fousse, A.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825–2828.

The effect of enamine *N*-substitution was also investigated (Table 2). Morpholino-, piperidino-, and pyrrolidinocyclo-

Table 2. Effect of Enamine Nitrogen Substitution[a]



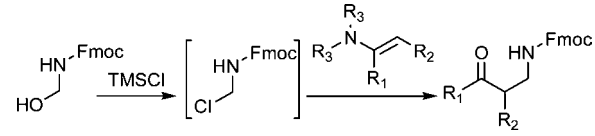
entry	-NR$_2$	yield (%)
1		71
2		85
3		91[b]

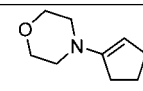
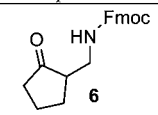
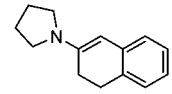
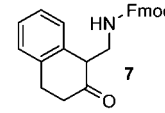
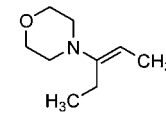
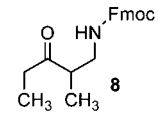
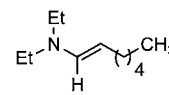
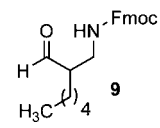
[a] TMSCl (2 equiv), $CDCl_3$, 60 min; then enamine (3 equiv), 10 min. [b] CH_2Cl_2 was used as the solvent.

hexene all afford addition products in good yields. The enamine scope contrasts with our previous studies of enamine additions to unactivated *N*,*O*-acetal **1a**, where only the most nucleophilic pyrrolidinocyclohexene added with an acceptable yield.[5]

The TMSCl activation strategy has broadened the scope of additions of enamines to *N*,*O*-acetals (Table 3). A wide

Table 3. Addition of Enamines to TMSCl-Activated Fmoc-Protected *N*,*O*-Acetals[a]



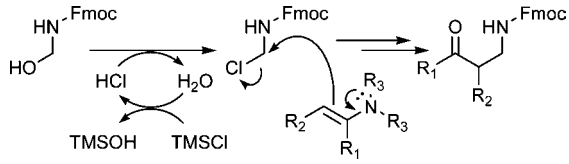
entry	enamine	product	yield (%)
1			87
2			83
3			54[b]
4			57[c]

[a] TMSCl (2 equiv), CH_2Cl_2, 60 min; then enamine (3 equiv), 10 min. [b] 10 equiv of TMSCl was used. [c] $CDCl_3$ was used as the solvent.

variety of enamines react smoothly with *N*,*O*-acetal **1c** following TMSCl activation. Good yields are observed with enamines derived from cyclic (entries 1 and 2) and acyclic ketones (entry 3). Notable is the reactivity observed with the aldehyde-derived enamine (entry 4), which has been shown to be difficult in the past.[14]

Two features of the likely reaction mechanism are notable (Scheme 1). First, since the reaction is conducted using

Scheme 1. Proposed Mechanism



undistilled solvents, the formation of the chloromethylcarbamate intermediate likely proceeds through the action of HCl generated in situ by hydrolysis of the TMSCl.[8a,c] Second, the subsequent enamine addition to the chloromethylcarbamate intermediate appears to proceed through a concerted, S_N2 displacement of the chloride. While prior studies using related chloroalkyl carbamate[15] and chlorolactam[8a,c] intermediates (albeit with weaker nucleophiles) have implicated a S_N1 mechanism, enamine alkylation reactions are generally believed to proceed through S_N2 mechanisms.[16] Preliminary kinetic studies of the enamine addition display a dependence on the concentration of the enamine nucleophile, consistent with a second-order reaction pathway.[9,17]

An S_N2 mechanism is also consistent with our previous studies of an enamine addition to *N*,*O*-acetal **1a** (without TMSCl activation).[5] This enamine addition to acetate **1a** proceeded in the absence of Lewis or Brønsted acids, which are typically required for acyl iminium ion formation. Nucleophile strength proved to be critical when comparing enamine additions to *N*,*O*-acetal **1a** with chloromethylcarbamate **2**. Only the most nucleophilic pyrrolidine enamine reacts with acetate **1a**, while chloride **2** reacts with a variety of enamines.[18]

In summary, TMSCl activation has been investigated in enamine addition reactions to Fmoc-protected *N*,*O*-acetals. Activation results in formation of a halomethyl carbamate intermediate, which undergoes S_N2 addition with a variety of enamine nucleophiles. The TMSCl activation strategy yields reaction pathways that are complementary to acyl iminium ions.

Acknowledgment. This research was supported by an award from Research Corporation.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Hodgson, D. M.; Bray, C. D.; Kindon, N. D.; Reynolds, N. J.; Coote, S. J.; Um, J. M.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 1019–1028.

(15) Barnes, D. M.; Barkalow, J.; Plata, D. J. *Org. Lett.* **2009**, *11*, 273–275.

(16) (a) Fu, A.; List, B.; Thiel, W. *J. Org. Chem.* **2006**, *71*, 320–326. (b) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

(17) The dependence on the concentration of enamine is also consistent with rate-limiting addition of the enamine to an acyliminium ion, which cannot be discounted but seems unlikely.

(18) For a study of enamine nucleophilicity, see: Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem.—Eur. J.* **2003**, *9*, 2209–2218.