The versatile conversion of acyclic amides to α-alkylated amines

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A general and efficient method for the versatile functionalization of acyclic amide via N,O-acetal TMS ether, an excellent precursor for the N-acyliminium ion, has been developed.

The reaction of an N-acyliminium ion with a variety of nucleophiles is one of the most powerful methods to introduce various substituents at the α-carbon of an amine. Particularly, this type of inter and intramolecular C–C bond formation can be effectively applied to the synthesis of the bioactive natural or unnatural compounds as well as many bioactive peptidomimetics. Accordingly, much attention has been devoted to the practical and efficient methods for the generation of acyliminium ion precursors though there are many important aspects in the reaction involving N-acyliminium ions.

The use of α-alkoxy carbamates and amides as precursors for N-acyliminium ions is well reviewed,1 and these versatile systems arise from the partial reduction of cyclic imides,2 for acyclic ones.5 In the case of TiCl4, known as a strong Lewis acid, it is able to undergo facile substitution reactions with a variety of nucleophiles. In the case of TiCl4, known as a strong Lewis acid, it is able to undergo facile substitution reactions with a variety of nucleophiles.

We have been continuously interested in the functionalization of cyclic and acyclic amide carbamoyl derivatives with regard to syntheses of natural alkaloids. Herein we report a novel and general method for the preparation of stable N,O-acetal TMS ethers,3,6 excellent precursors of linear acyliminium ions, and we also describe their reactivities and reaction scopes.

Our initial concern was searching for suitable reducing agents for partial reduction of the acyl-protected amides to hemiaminals and their trapping reagents. The acylamide substrates (2–4) could be readily prepared by a protective reaction of amides with the corresponding reagents using n-butyllithium or other bases in THF as reported.7 Unlike the cyclic imides of which many reducing agents have been used for the partial reductions, only DIBAL–H was effective for the acyl amide. DIBAL–H of 1.2 eq. was sufficient for the completion of the carbonyl reduction. Surveying the trapping reagents commonly used, we found the TMSOTf–pyridine system, to give the most satisfactory results as shown in Table 1. Thus, treatment of acylamide with 1.2 eq. of DIBAL–H in CH2Cl2 at −78 °C for 1 h, followed by sequential addition of pyridine and TMSOTf, afforded the N,O-acetal TMS ether in excellent yield. TMSN(O)CH2–TMS ether, a very stable intermediate neat as well as in a variety of solvents, could be easily purified by flash column chromatography and stored for months. Benzyl and tert-butyl carbamates were superior to the methyl carbamate in terms of yield. Other trapping reagents such as Ac2O–pyridine and MeOTf–pyridine gave no desired alkylamine carboxamides.

To study the reaction details of N,O-acetal TMS ether as an N-acyliminium precursor, we examined various conditions for the amidalkylation reaction. Generally, the reaction was initiated in the presence of suitable Lewis acids to form N-acyliminium intermediates, which were then reacted with a nucleophile, to afford α-substituted amines. With the N,O-acetal TMS ether 3a as a substrate and TMSCN as a good nucleophile, various aprotic or protic Lewis acids and solvents were investigated. As illustrated in Table 2, 3a presented excellent reactivities to the most aprotic or protic Lewis acids commonly used, to afford the adduct 4a in nearly quantitative yields. This result implies that N,O-acetal TMS ethers are able to undergo facile substitution reactions with a variety of nucleophiles. In the case of TiCl4, known as a strong Lewis acid, the use of TiCl4 as a Lewis acid, it is able to undergo facile substitution reactions with a variety of nucleophiles.

Table 1 Optimization of trapping conditions and the effect of an N-protective group.

<table>
<thead>
<tr>
<th>Substrate (2)</th>
<th>RX</th>
<th>Product (3) (% yield)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a (R1 = Benzyl)</td>
<td>Ac2O</td>
<td>—</td>
</tr>
<tr>
<td>2b (R1 = tert-Butyl)</td>
<td>TMSOTf</td>
<td>3a (92) (R = TMS)</td>
</tr>
<tr>
<td>2c (R1 = Methyl)</td>
<td>TMSOTf</td>
<td>3b (89) (R = TMS)</td>
</tr>
</tbody>
</table>

* Isolated yields.

Table 2 Effect of Lewis acids and solvents

<table>
<thead>
<tr>
<th>Lewis acid (eq.)</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield of 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF3.OEt2 (0.2)</td>
<td>CH3CN</td>
<td>20 min</td>
<td>98</td>
</tr>
<tr>
<td>BF3.OEt2 (1.0)</td>
<td>CH3CN</td>
<td>20 min</td>
<td>99</td>
</tr>
<tr>
<td>TMSOTf (0.2)</td>
<td>CH3CN</td>
<td>10 min</td>
<td>99</td>
</tr>
<tr>
<td>TiCl4 (1.0)</td>
<td>CH3CN</td>
<td>2 h</td>
<td>20</td>
</tr>
<tr>
<td>SnCl4 (0.2)</td>
<td>CH3CN</td>
<td>20 min</td>
<td>98</td>
</tr>
<tr>
<td>TIOH (0.2)</td>
<td>CH3CN</td>
<td>15 min</td>
<td>98</td>
</tr>
<tr>
<td>BF3.OEt2 (0.2)</td>
<td>CH2CN</td>
<td>30 min</td>
<td>99</td>
</tr>
<tr>
<td>BF3.OEt2 (0.2)</td>
<td>THF</td>
<td>30 min</td>
<td>98</td>
</tr>
<tr>
<td>BF3.OEt2 (0.2)</td>
<td>PhCH3</td>
<td>1 h</td>
<td>92</td>
</tr>
</tbody>
</table>

* Reactions were carried out with 3a (0.2-0.3 mmol) and TMSCN (1.3 eq.) at −78 °C and warmed to −30 °C unless otherwise noted. * Stirred at 0 °C.
and Lewis acids (0.2 eq.) in DCM at 0 °C according to the general procedure. Allylmethylsilane, allyltributyltin, silyl enol ether and propargytrimethylsilane nucleophiles underwent facile alkylation to afford the desired adducts in excellent yields. In the case of allylation, the allylthine reagent provided higher yields than allylsilane.

Table 3 Reactions of 3a with various nucleophiles

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Lewis acid</th>
<th>R (4)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH2=C(CH3)2SiMe3</td>
<td>BF3·OEt2</td>
<td>-CH2CH=CH-2</td>
<td>83</td>
</tr>
<tr>
<td>CH2=C(CH3)2SnBu4</td>
<td>TMSOTf</td>
<td>-CH2CH=CH-2</td>
<td>77</td>
</tr>
<tr>
<td>CH2=CH(O)TBSPh</td>
<td>BF3·OEt2</td>
<td>-CH2CH(O)Ph</td>
<td>93</td>
</tr>
<tr>
<td>CH2=C·CCH2TMS</td>
<td>BF3·OEt2</td>
<td>-CH2C(OTBS)Ph</td>
<td>84</td>
</tr>
<tr>
<td>CH2=C·CCH2TMS</td>
<td>BF3·OEt2</td>
<td>-CH2C(C6H4)2N=O</td>
<td>81</td>
</tr>
</tbody>
</table>

* A: TMSOTf, CH2Cl2, -20 °C, 20 h; B: BF3·OEt2, CH2Cl2, 0 °C, 20 h.

Table 4 shows extended examples for various other acyclic amides. The selected acylamides possessing the common amides are tolerant during the two step process for the generation of N,O-acetamidochromones. Future studies will involve studies on asymmetric versions and its application to the synthesis of macrolactam alkaloids.

Notes and references

† Representative procedure for the preparation of N,O-acetyl TMS ether: to a solution of the amide 2a (820 mg, 2.76 mmol) in CH2Cl2 (12 mL) was added DIBAL-H (1.0 M solution in toluene, 3.4 mL, 3.4 mmol) dropwise at −78 °C. After 1 h, the reaction mixture was treated with pyridine (0.67 mL, 8.32 mmol) and then TMSOTf (1.25 mL, 6.91 mmol). The mixture was stirred at −78 °C for 10 min, quenched with 15% aqueous sodium potassium tartrate (10 mL), and diluted with Et2O (40 mL). The resultant mixture was warmed to rt and stirred vigorously until two layers were completely separated. The mixture was extracted with Et2O and the combined organic layers were washed with brine, dried over anhydrous MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography (10% EtOAc–hexanes) to afford 942 mg (92%) of N,O-acetyl TMS ether 3a as a colorless oil.

† Spectral data for 3a: FT-IR (neat) 1703 cm−1 (C = O); 1H-NMR (CDCl3, 500 MHz) rtotanmer δ 7.42–7.18 (m, 10H); 5.77 and 5.61 (br s, 1H total), 4.53 and 4.48 (ABq, J = 16.2 Hz, 2H total), 1.58 (m, 2H), 0.86 and 0.78 (t, J = 7.1 Hz, 3H total), 0.13 and 0.03 (s, 9H total); 13C-NMR (CDCl3, 75 MHz) δ 156.0, 139.6, 136.6, 136.4, 129.0, 128.6, 128.4, 128.2, 128.1, 127.9, 127.5, 127.1, 126.9, 125.1, 116.8, 114.3, 105.7, 81.6, 67.4, 67.1, 44.5, 44.3, 29.7, 29.4, 9.81, 1.3; LRMS (EI) 372 (M+ + H+).

8. Satisfactory spectral and analytical data were obtained for all new compounds.