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The versatile conversion of acyclic amides to α-alkylated amines

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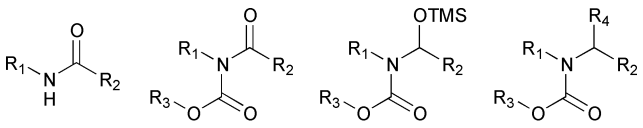
A general and efficient method for the versatile functionalization of acyclic amide *via* *N,O*-acetal TMS ether, an excellent precursor for the *N*-acyliminium ion, has been developed.

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.[1] 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.

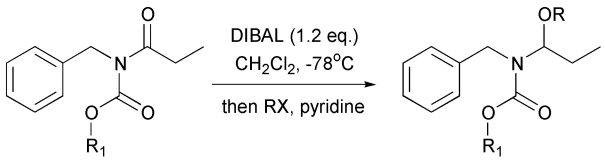
The use of α-alkoxy carbamates and amides as precursors for *N*-acyliminium ions is well reviewed,[1] and these versatile systems arise from the partial reduction of cyclic imides,[2] addition of amides or carbamates to aldehydes,[3] or oxidation of the hydrocarbon under electrochemical or transition metal-mediated conditions.[4] Among them, partial reduction of the carbonyl in imides or acylamides has been considered as the best procedure in terms of the reaction efficiency and the substrate diversity. However, this method has a limitation that it can be applicable only to cyclic systems, and few are reported for acyclic ones.[5]

We have been continuously interested in the functionalization of cyclic and acyclic amide carbonyls 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 (**2a**–**2c**) 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 acyclic 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 CH_2Cl_2 at −78 °C for 1 h, followed by sequential addition of pyridine and TMSOTf, afforded the *N,O*-acetal TMS ether in excellent yield. TMS *N,O*-acetal 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

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



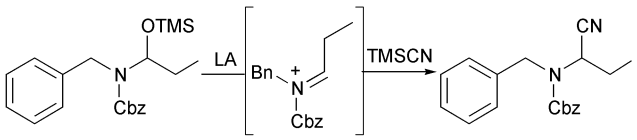
Substrate (**2**)	RX	Product (**3**) (% yield)[a]
2a (R_1 = Benzyl)	Ac_2O	—
	MeOTf	—
	TMSOTf	**3a** (92) (R = TMS)
2b (R_1 = *tert*-Butyl)	TMSOTf	**3b** (89) (R = TMS)
2c (R_1 = Methyl)	TMSOTf	**3c** (83) (R = TMS)

[a] Isolated yields.

yield. Other trapping reagents such as Ac_2O–pyridine and MeOTf–pyridine gave no desired alkoxy carbamates.

To study the reaction details of *N,O*-acetal TMS ether as an *N*-acyliminium precursor, we examined various conditions for the amidoalkylation 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 $TiCl_4$, known as a strong Lewis

Table 2 Effect of Lewis acids and solvents[a]



Lewis acid (eq.)	Solvent	Time	Yield of **3** (%)
$BF_3.OEt_2$ (0.2)	CH_2Cl_2	20 min	98
$BF_3.OEt_2$ (1.0)	CH_2Cl_2	20 min	99
TMSOTf (0.2)	CH_2Cl_2	10 min	99
$TiCl_4$ (1.0)	CH_2Cl_2	2 h	20[b]
$SnCl_4$ (0.2)	CH_2Cl_2	20 min	98
TfOH (0.2)	CH_2Cl_2	15 min	98
$BF_3.OEt_2$ (0.2)	CH_3CN	30 min	99
$BF_3.OEt_2$ (0.2)	THF	30 min	98
$BF_3.OEt_2$ (0.2)	$PhCH_3$	1 h	92

[a] 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. [b] Stirred at 0 °C

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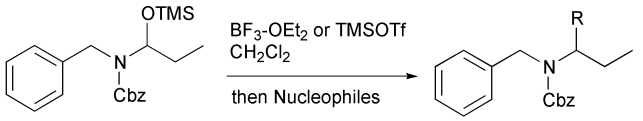
acid, the yield was unexpectedly very low. Variation of solvents gave little difference in yields.

With BF_3.OEt or TMSOTf as the catalyst, reactions of **3a** with various nucleophiles were also investigated (Table 3). Allyltrimethylsilane, allyltributyltin, silyl enol ether and propargyltrimethylsilane nucleophiles underwent facile alkylation to afford the desired adducts in excellent yields. In the case of allylation, the allyltin reagent provided higher yields than allylsilane.

Table 3 Reactions of **3a** with various nucleophiles[a]



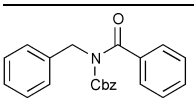
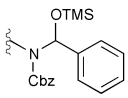
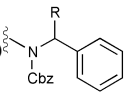
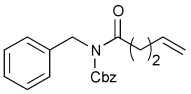
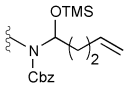
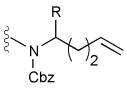
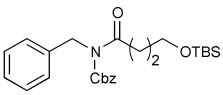
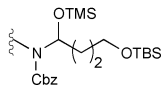
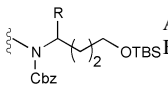
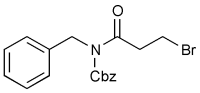
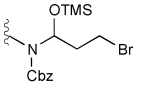
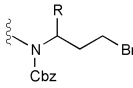
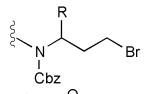
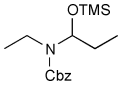
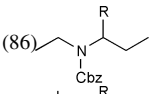
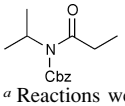
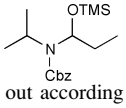
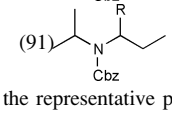
3a **4**

Nucleophile	Lewis acid	R (**4**)	Yield (%)[b]
CH_2=$CHCH_2SiMe_3$	BF_3.OEt_2	-CH_2CH=CH_2 (**4b**)	83
	TMSOTf		77
CH_2=$CHCH_2SnBu_3$	BF_3.OEt_2		89
	TMSOTf		84
CH_2=C(OTBS)Ph	BF_3.OEt_2	-CH_2C(O)Ph (**4c**)	93
	TMSOTf		81
CH≡CCH_2TMS	BF_3.OEt_2	-CH=C=CH_2 (**4d**)	85

[a] All reactions were carried out with **3a** (0.2 mmol), a nucleophile (1.5 eq.), and Lewis acids (0.2 eq.) in DCM at −78 °C, and warmed to −20 °C. [b] Isolated yields.

Table 4 shows extended examples for various other acyclic amides. The selected acylamides possessing the common functionalities were conveniently prepared from the corresponding amides simply by protective reactions (CbzCl, *n*-BuLi or LHMDS, THF, 0 °C). The acylamides possessing phenyl, alkene, silyl ethers, or bromoalkyl substituents afforded the *N,O*-acetal TMS ether and the alkylated products in high yields.[8] The amides derived from simple ethylamine and sterically hindered isopropylamine also gave such good results as other amides. It is noticeable that the various functional groups are tolerant under the conditions for our two step procedure.

Table 4 Extended examples for various acyclic amides; generation of *N,O*-acetal TMS ethers[a] and their reactions with TMSCN and allyltributyltin[b]

Amide	TMS *N,O*-acetal (% yield)	Product (A: R = CN, B: R = allyl)	
		(91) 	A: 98 B: 91
		(87) 	A: 99 B: 83
		(90) 	A: 98 B: 79
		(93) 	A: 97 B: 80
		(86) 	A: 96 B: 84
		(91) 	A: 98 B: 82

[a] Reactions were carried out according to the representative procedure in footnote †. [b] Reactions were carried out with TMSCN and allyltributyltin according to the general procedure.

In summary, this communication discloses a novel and general method for the efficient functionalization of acyclic amide carbonyl *via* a stable *N,O*-acetal TMS ether intermediate. Particularly, the reactive *N,O*-acetal TMS ether could be conveniently prepared in an excellent yield from the acyl protected amides by sequential partial reduction of amide carbonyl with DIBAL-H followed by TMSOTf trapping of resulting hemiaminal. The *N,O*-acetal TMS ethers proved to be excellent precursors for *in situ* generation of *N*-acyliminium ions in overall reaction conditions. The representative functionalities are tolerant during the two step process for the generation of *N,O*-acetal TMS ethers and their facile substitutions with a variety of carbon nucleophiles. Future studies will involve studies on asymmetric versions and its application to the synthesis of macrolactam alkaloids.

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Notes and references

† **Representative procedure for the preparation of *N,O*-acetal TMS ether**: to a solution of the amide **2a** (820 mg, 2.76 mmol) in CH_2Cl_2 (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 Et_2O (40 mL). The resultant mixture was warmed to rt and stirred vigorously until two layers were completely separated. The mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc–hexanes) to afford 942 mg (92%) of *N,O*-acetal TMS ether **3a** as a colorless oil.

‡ **Spectral data for 3a**; FT-IR (neat) 1703 cm^{-1} (C = O); ^{1}H-NMR ($CDCl_3$, 500 MHz) rotamers δ 7.42–7.18 (m, 10H), 5.77 and 5.61 (br s, 1H total), 5.24 and 5.16 (s, 2H 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); ^{13}C-NMR ($CDCl_3$, 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, 126.5, 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).

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