Stereoselective N-Acylation Reactions of α-Alkoxy Carbamates

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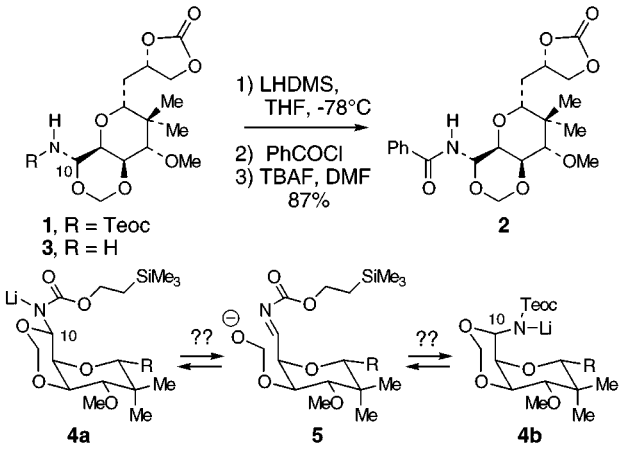
In connection with studies on the synthesis of mycalamides A and B,[2,3] we reported that the base-promoted N-acylation of carbamate **1** (Teoc = $CO_2CH_2CH_2SiMe_3$) with benzoyl chloride followed by deprotection of the Teoc unit provided amide **2** with complete control of the C(10) stereocenter.[4] The excellent stereocontrol realized in this reaction is striking, especially in view of Kishi's report that the corresponding amine, **3**, is configurationally unstable under acidic, neutral, and weakly basic conditions and that acylations of **3** with a pederic acid derivative provided a mixture of C(10)-epimers.[5] Although N-acylations and N-alkylations of amides and carbamates are well-established transformations,[6−8] relatively few examples of these reactions with α-alkoxy amides or carbamates are known,[9−16] and the vast majority of these shed no light on the stereoselectivity of the base-promoted acylations of α-alkoxy carbamates such as **1**.



The chemistry of the intermediate α-alkoxy carbamate anion **4a** is central to the origin of stereoselectivity of this process. If anions such as **4a** are configurationally stable, then the acylations should proceed with complete preservation of the C(10) stereochemistry of the starting material. On the other hand, if the carbamate anion is not stable with respect to reversible elimination of the α-alkoxy substituent (via the highly electrophilic *N*-carbamoylimine intermediate **5**),[17] then the C(10) stereochemistry in the reaction product will be determined by the relative stabilities of the epimeric α-alkoxy carbamate anions **4a** and **4b** and/or the rates of their acylation and equilibration. Under these circumstances, one would anticipate generating comparable product mixtures starting from either α-alkoxy carbamate diastereomer. We report herein the results of several experiments designed to address these issues, as well as define more broadly the scope of these reactions.

α-Methoxy carbamate **8** was prepared by O-methylation of diol **6**,[18] ester hydrolysis, and then Curtius reaction of **7** in the presence of 2-(trimethylsilyl)ethanol.[19] Treatment of a THF solution of **8** with lithium hexamethyldisilazide (LHMDS, 1.15 equiv) at −78 °C for 30 min followed by addition of benzoyl chloride (1.5 equiv) provided imide **9a** as a single diastereomer in 84% yield. When the carbamate anion solution was allowed to warm to 0 °C before addition of benzoyl chloride, imide **9a** was again obtained as a single diastereomer, albeit in lower yield (48%). Similarly, acylation of **8** by using in situ generated[20] $C_6H_{11}COCl$ or the mixed anhydride **11a** in the presence of DMAP (1 equiv) provided imide **9b** in 75−78% yield. However, when mixed anhydride **11b** was utilized, substantial quantities of **12** were obtained (20−37%) in addition to **9b** (43−47%).

Deprotection of **9a** or **9b** by treatment with *n*-Bu_4NF in THF or DMF at 0 °C provided amides **10a** and **10b** in 90−92% yield. In each case, the product was a single diastereomer according to ^1H NMR analysis. The stereochemistry of **10a** was verified by a single-crystal X-ray analysis,[21] which established that this two-step acylation-deprotection sequence proceeded with retention of stereochemistry of the α-methoxy carbamate center.

Additional studies of the α-alkoxy carbamate acylation protocol were performed by using the *N*-glycosyl carbamates **14** and **15**, which were prepared by acylation of glucosylamine **13**[22] with Teoc-Cl.[23] This sequence provided a 4:1 mixture of **14** and **15**, which were separated chromatographically. Acylation of the anion of **14** in THF at −78 °C with several freshly distilled acid chlorides (e.g., C_6H_5COCl,

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(20) Mixed anhydrides **11a**, **11b**, and $C_6H_{11}COCl$ were generated in situ by treatment of $C_6H_{11}CO_2H$ (1 equiv) with *n*-BuLi (1.1 equiv) in THF at −78 °C in the presence of activated 4 Å molecular sieves (20 mg/mL of THF). This solution was warmed to 0 °C and then was treated with 1.0 equiv of Ph_2POCl, $C_6H_2Cl_3COCl$, or $(COCl)_2$ for 1 h at 23 °C. DMAP (1 equiv) was added, and then this solution was transferred by syringe to the −78 °C solution of the carbamate anion.
(21) Details of the X-ray strcture analysis of **10a** are provided in Report No. 96197 of the Indiana University Molecular Structure Center. Final residuals are $R(F) = 0.0296$ and $R_w(F) = 0.0307$. We thank Dr. Kirsten Folting for performing this analysis.
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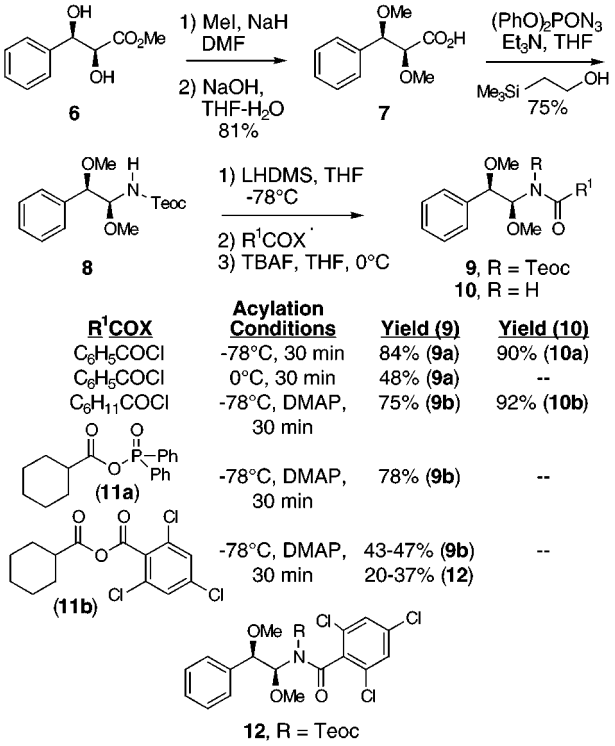
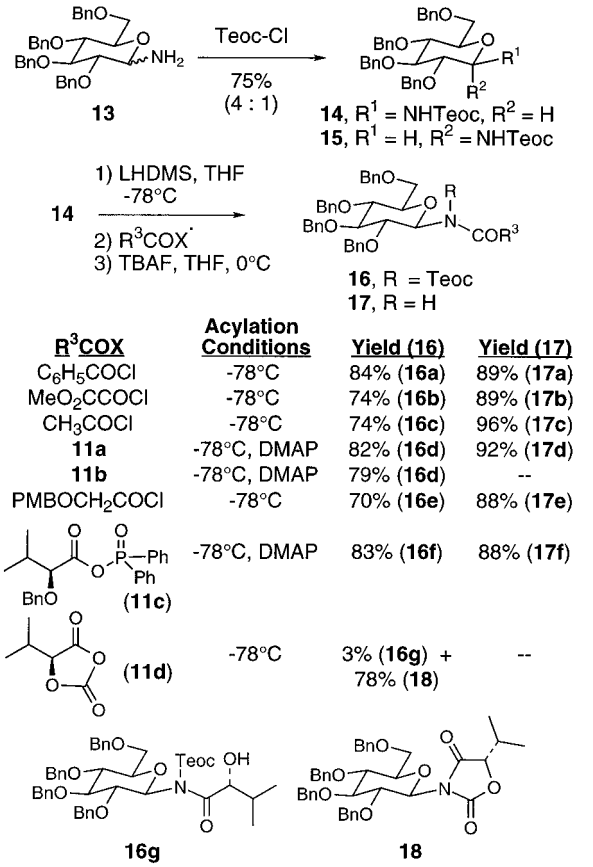


R^1COX	Acylation Conditions	Yield (9)	Yield (10)
C_6H_5COCl	-78°C, 30 min	84% (**9a**)	90% (**10a**)
C_6H_5COCl	0°C, 30 min	48% (**9a**)	--
$C_6H_{11}COCl$	-78°C, DMAP, 30 min	75% (**9b**)	92% (**10b**)
(**11a**)	-78°C, DMAP, 30 min	78% (**9b**)	--
(**11b**)	-78°C, DMAP, 30 min	43-47% (**9b**) 20-37% (**12**)	--

MeO_2CCOCl, MeCOCl, and $PMBOCH_2COCl$) provided the corresponding imides **16a**−**c** and **16e** in 70−84% yields *as single diastereomers*. However, when $PMBOCH_2COCl$ was generated in situ (by treatment of the corresponding carboxylic acid with 1.1 equiv of BuLi in THF followed by $(COCl)_2$), the yield of **16f** was only 37%. On the other hand, in situ generated[20] mixed anhydrides **11a**−**c** reacted smoothly with the lithium anion of **14**, providing imides **16d** and **16f** in 79−83% yield. The reaction of dioxalanedione **11d**[24] with the lithium anion of **14** provided the cyclic imide **18** as the major product (78%). Decarbamoylation of imides **16a**−**f** proceeded in excellent yield (88−96%), giving a single diastereomer of **17** (the β-anomer) in all cases.

Acylations of the α-*N*-glucosyl carbamate **15** were much less efficient, owing to the very hindered nature of the axial carbamate anion. For example, acylation of the lithium anion of **15** with benzoyl chloride required a reaction temperature of 0 °C for product formation to occur. Under these conditions, carbamate **19** was obtained in 61% yield, along with recovered **15** (38%). Moreover, the deprotection of **19** was very sluggish in THF and, therefore, was performed with TBAF in DMF. This provided the α-*N*-glucosylbenzamide **20** in 87% yield, along with 3% of the corresponding β-anomer **17a**. *This is the only case where we observed any epimerization of the α-alkoxy carbamate stereocenter.* Finally, attempted acylation of the lithium anion of **15** with active ester derivatives of aliphatic aldehydes gave extremely poor yields (e.g., 3% with **11a**), suggesting that the hindered anion functions in these cases as a base rather than as a nucleophile.



R^3COX	Acylation Conditions	Yield (16)	Yield (17)
C_6H_5COCl	-78°C	84% (**16a**)	89% (**17a**)
MeO_2CCOCl	-78°C	74% (**16b**)	89% (**17b**)
CH_3COCl	-78°C	74% (**16c**)	96% (**17c**)
11a	-78°C, DMAP	82% (**16d**)	92% (**17d**)
11b	-78°C, DMAP	79% (**16d**)	--
$PMBOCH_2COCl$	-78°C	70% (**16e**)	88% (**17e**)
(**11c**)	-78°C, DMAP	83% (**16f**)	88% (**17f**)
(**11d**)	-78°C	3% (**16g**) + 78% (**18**)	--

In summary, these studies establish that α-alkoxy carbamate anions (e.g., **4a**) are configurationally stable (=97%) under the conditions of these acylation reactions, unlike the corresponding α-alkoxy amines. We anticipate that this methodology will prove useful in the stereocontrolled synthesis of the mycalamides as well as N-linked glycopeptides.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds (20 pages).

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