Facile and Selective *O*-Alkyl Transesterification of Primary Carbamates with Titanium(IV) Alkoxides†

Gideon Shapiro* and Martin Marzi

Preclinical Research, Novartis Pharma Ltd,
CH-4002, Basel Switzerland

Received August 13, 1997

Transesterification reactions mediated by titanium(IV) alkoxides now constitute a powerful method in organic synthesis. This is largely due to the work of Seebach who brought the use of titanium(IV) alkoxides as catalysts for the transesterification of carboxylic acid esters to the attention of academic organic chemists some 15 years ago (Figure 1).[1] A broad range of alcohols are effective under mild, essentially neutral, transesterification conditions compatible with a wide range of functionality in the substrate.

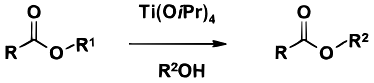


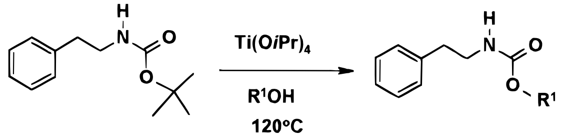
Figure 1.

Since then, asymmetric esterifications have been achieved with homochiral titanium(IV) alkoxide complexes[2] and the scope of titanium(IV) alkoxide-mediated transesterification reactions has been broadened to include sultams[3] and phosphite esters.[4] Herein, we wish to report a new application for titanium(IV) alkoxides, namely, the facile *O*-alkyl transesterification of primary carbamates.[5−7]

In the course of a drug derivatization program we needed to perform the transesterification of a methyl ester to the corresponding benzyl ester in a substrate molecule bearing an array of additional sensitive functionality. Heating the substrate with Ti(O*i*Pr)$_4$ in benzyl alcohol at 120 °C smoothly effected the desired benzyl carboxylate formation; however, we also observed the conversion of a substrate primary *tert*-butoxycarbonyl amine (R-NHBoc) function to the corresponding benzyloxycarbonyl group (R-NHCbz). This was an unexpected result in light of work from Steglich.[8] He had reported that terminal N-Boc-dipeptide methyl esters were smoothly transesterified without racemization to the corresponding isopropyl or benzyl esters with no detectable reaction at the carbamate function.

Intrigued by this result, we decided to determine the scope of this titanium(IV) alkoxide mediated carbamate transesterification reaction. When the simple model substrate, (*tert*-butoxycarbonyl)phenylethylamine (**1**), was treated with 10 mol % Ti(O*i*Pr)$_4$ in benzyl alcohol at 120 °C, conversion to the corresponding benzyloxycarbonyl derivative, PhCH$_2$CH$_2$NHCbz (**2**), was insignificant.

For an acceptable rate of conversion it was necessary to increase the amount of Ti(O*i*Pr)$_4$. After reaction of **1** with 1 equiv of Ti(O*i*Pr)$_4$ in benzyl alcohol at 120 °C for 18 h some starting material still remained. However, using 2 equiv of Ti(O*i*Pr)$_4$, **1** was completely consumed after 18 h. Reaction workup was performed by concentrating the mixture in vacuo, dissolving the residue in methanol, and adding 5% water.[9] Filtering and concentration yielded a product which, aside from containing benzyl alcohol, was quite pure by ^{1}H NMR. After chromatography, the *O*-alkyl carbamate transesterification product **2**, was isolated in 82% yield (Figure 2). Having confirmed the initial result, we expanded the study to a range of *t*-Boc-amines (see Table 1).



1

2 R^1 = CH$_2$Ph
3 R^1 = CH$_2$CH=CH$_2$
4 R^1 = CH$_2$CH$_2$OSi(CH$_3$)$_3$
5 R^1 = CH(CH$_3$)$_2$

Figure 2.

The *O*-alkyl carbamate transesterification reaction proceeded in analogous fashion for PhCH$_2$NHBoc (**6**) to give **7**. Using 4 equiv of Ti(O*i*Pr)$_4$, the more challenging bifunctional substrate BocNH(CH$_2$)$_5$NHBoc (**8**) was also smoothly converted to the corresponding bis-Cbz derivative **9**. Interestingly, Boc-Gly-OBn (**10**) was also transesterified to Cbz-Gly-OBn in benzyl alcohol at 120 °C. Treatment of **10** with Ti(O*i*Pr)$_4$ in benzene at reflux resulted in only exchange of the ester function to give Boc-Gly-O*i*Pr (**12**). However, performing the same reaction in refluxing toluene resulted in smooth carbamate ester exchange along with concomitant carboxylic acid transesterification, to give (*i*PrOCO)-Gly-O*i*Pr, (**13**). Thus, by controlling the reaction temperature, it is conveniently possible to selectively transesterify the ester function of an amino acid or peptide ester in the presence of N-terminal carbamate groups even when using excess titanium alkoxide.[10] The secondary substrates N-Boc-pyrrolidine (**14**) and N-Boc-piperidine (**15**) were stable to the standard reaction conditions.[11] This had dramatic implications since: *a general selective removal of a primary amine protecting group would be a novel transformation in organic synthesis.* We have demonstrated that this can now be readily achieved taking bis-Boc substrate **16** as an example (Figure 3). Treatment of (**16**) with 4 equiv of a Ti(O*i*Pr)$_4$ in benzyl alcohol at 120 °C for 18 h resulted in smooth conversion of the primary *t*-Boc function to give **17** with the secondary *t*-Boc group unaffected.

---

† Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

(1) (a) Seebach, D.; Hungerbuehler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zueger, M. *Synthesis* **1982**, 138. (b) Seebach, D.; Weidmann, B.; Widler, L. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Verlag Sauerlaender: Aarau, 1983; p 217.

(2) (a) Ramon, D.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1986**, *79*, 875. (b) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539.

(3) Oppolzer, W.; Lienard, P. *Helv. Chim. Acta* **1992**, *75*, 2572.

(4) Froneman, M.; Modro, T. A. *Synthesis* **1991**, 201.

(5) (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870. (b) Sakaitani, M.; Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1986**, 3753. (c) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1985**, 5543.

(6) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1990**, *55*, 5170.

(7) Roos, E. C.; Bernabe, P.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1995**, *60*, 1733.

(8) Steglich, W.; Rehwinkel, H. *Synthesis* **1982**, 826.

(9) Ti(OMe)$_4$ is a highly insoluble species. When absolute methanol was used, the titanium salt precipitate formed slowly, but addition of 5% water accelerated the process dramatically.

(10) This is consistent with the selectivity for carboxylic acid esters observed by Steglich using 0.25−0.5 equiv of titanium alkoxide in refluxing THF.

(11) At higher temperatures the starting material began to disappear with the desired transesterification remaining undetected.

S0022-3263(97)01498-9 CCC: $14.00

Table 1

reactant	temp, °C	$Ti(OiPr)_4$, equiv	solvent	product	yield, %
$PhCH_2CH_2NHBoc$ (**10**)	120	2	$PhCH_2OH$	$PhCH_2CH_2NHCbz$ (**2**)	82
$PhCH_2NHBoc$ (**6**)	120	2	$PhCH_2OH$	$PhCH_2NHCbz$ (**7**)	73
$BocNH(CH_2)_5NHBoc$ (**8**)	120	4	$PhCH_2OH$	$CbzNH(CH_2)_5NHCbz$ (**9**)	65
Boc-Gly-OBn (**10**)	120	4	$PhCH_2OH$	Cbz-Gly-OBn (**11**)	60
10	80	4	PhH	Boc-Gly-OiPr (**12**)	65
10	120	2	$PhCH_3$	(*i*PrOCO)-Gly-OiPr (**13**)	58
$(CH_2)_5NBoc$ (**14**)	120	2	$PhCH_2OH$	no reaction	
$(CH_2)_6NBoc$ (**15**)	120	2	$PhCH_2OH$	no reaction	
16	120	4	$PhCH_2OH$	**17**	85
1	120	2	$PhCH_3/CH_2{=}CHCH_2OH$[12]	$PhCH_2CH_2NHAlloc$ (**3**)	85
1	120	2	$(CH_3)_3SiCH_2CH_2OH$	$PhCH_2CH_2NHTeoc$ (**4**)	82
1	120	2	$PhCH_3$	$PhCH_2CH_2NHCOO\mathit{i}Pr$ (**5**)	75
$PhCH_2CH_2NHCO_2Et$ (**18**)	120	2	$PhCH_3/CH_2{=}CHCH_2OH$[12]	**3**	78
18	120	2	$PhCH_3/(CH_3)_3SiCH_2CH_2OH$[12]	**4**	83
18	120	2	$PhCH_3$	**5**	85
$PhCH_2CH_2NHCbz$ (**2**)	120	2	$PhCH_3$	**5**	82

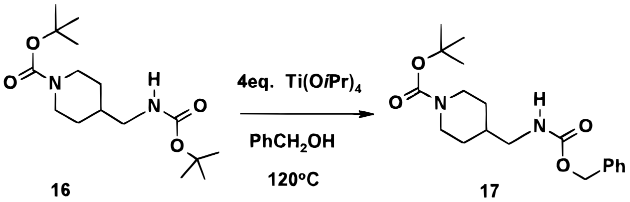


Figure 3.

At this point we then turned to the investigation of different alcohols in the reaction, with particular attention to those leading to synthetically useful carbamate protecting groups (Table 1). Taking **1** as the model substrate, reaction with $Ti(OCH_2CH{=}CH_2)_4$ in toluene[12] at reflux was found to proceed smoothly to give $PhCH_2CH_2NHAlloc$ (**3**) in 85% yield. The reaction in trimethylsilyl ethanol was somewhat slower requiring 2 days for complete conversion to the trimethylsilyloxycarbonyl (Teoc) derivative $PhCH_2CH_2NHCOOCH_2CH_2SiMe_3$ (**4**). Simply treating **1** with 2 equiv of $Ti(O\mathit{i}Pr)_4$ in toluene at reflux also resulted in clean formation of the corresponding isopropyl carbamate $PhCH_2CH_2NHCOOCH(CH_3)_2$ (**5**). These studies demonstrate that the desired transesterification proceeds with a range of alcohols leading to synthetically useful protecting groups: Cbz, Alloc, and Teoc. Furthermore, for low boiling alcohols or cases in which use of the given alcohol as solvent is undesirable, it has been demonstrated that the reaction proceeds smoothly in toluene solvent with the corresponding titanium(IV) alkoxides.[13]

Finally, it remained to study the reactivity of the carbamate ester functionality. To this end we investigated the reaction of **2** and the ethoxycarbonyl derivative **18** of the model phenethylamine substrate with 2 equiv of $Ti(\mathit{i}OPr)_4$ in refluxing toluene. In both cases, **5** was formed in good yield. Furthermore, **18** was also readily converted into the Alloc and Teoc derivatives **3** and **4** using the corresponding titanium alkoxides in refluxing toluene.

The details of the reaction mechanism remain to be studied experimentally. We speculate that the first step involves the formation of an imino-carbonate species which is only accessible to primary carbamates having an active hydrogen. We propose that this species dissociates reversibly to a formal isocyanate−titanate complex with transfer of the incoming alkoxide ligand from the titanium coordination-sphere leading to transesterification product.

In summary, few carbamate ester exchange methods have been reported heretofore.[5−7] These methods are specific for particular carbamate ester functionalities. We describe an efficient reaction which is specific for primary carbamates but is general for the *O*-alkyl group to be exchanged. This specificity on one hand, but generality on the other, is of great utility. One may now readily employ a carbamate function which tolerates a gamut of synthetic conditions (e.g. ethoxycarbonyl) and then transform it to one which is easily removed as needed. Finally, preliminary experiments indicate that this reaction can be extended to the preparation of ureas from primary carbamates using titanium(IV) amides.

JO971498Z

---

(12) $Ti(OCH_2CH{=}CH_2)_4$ was preformed by treating $Ti(\mathit{i}OPr)_4$ in refluxing toluene twice with an excess, 3−4 equiv, of allyl alcohol with azeotropic removal of 2-propanol. For higher boiling alcohols such as benzyl alcohol, a slight excess of the alcohol is used with a single azeotropic removal of 2-propanol.

(13) Qualitatively, the reaction with preformed titanium alkoxides in toluene appears to be faster. Clearly, this is the method of choice in case the alcohol is a precious material. In addition, reaction workup is also more facile for alcohols which are tedious to remove (eg. $PhCH_2OH$) when used as solvent. **Example Procedure**: A mixture of titanium tetraisopropoxide (1.14 g., 4.0 mmol) in 25 mL of toluene containing (20 mmol, 2.1 mL) of benzyl alcohol was distilled to a volume of ca. 15 mL. Compound **16** (314 mg., 1.0 mmol) was added, and the resulting mixture was heated under reflux for 18 h. The reaction mixture was concentrated, the residue was dissolved in methanol, and 5% water was added. The resulting suspension was filtered and concentrated to a residue which was taken up in ether. This solution was filtered, concentrated, and chromatographed over silica gel (1:1, ether:hexane) to give 310 mg (89%) of white crystalline **17**. This reaction was readily repeated on a 10 mmol scale. ^1H NMR and MS characterization was performed for all compounds which were also independently prepared by standard procedures using the corresponding amine and an appropriate carbamoylating agent.