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A Direct and Stereoretentive Synthesis of Amides from Cyclic Alcohols

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Abstract

Chlorosulfites prepared in situ using thionyl chloride react with nitrile complexes of titanium (IV) fluoride to give a one-pot conversion of alcohols into amides. For the first time, amides are obtained from cyclic alcohols with stereoretention. Critical to the design of these new Ti(IV) reactions has been the use of little explored Ti(IV) nitrile complexes which are thought to chelate chlorosulfites in the transition state to create a carbocation that is rapidly captured by the nitrile nucleophile via a front-side attack mechanism.

Keywords

stereoretentive amidation; one-pot amidation; chlorosulfite leaving group; hyperconjugomers

Introduction

Amides are among the most abundant functional groups in nature and, understandably, decades of creative research have been devoted towards their efficient synthesis with the majority of these studies centering on the dehydrative coupling of amines with carboxylic acids.^[1] For the past few years, we have been engaged in the development of methods to directly transform chiral secondary alcohols into new compound classes with retention of configuration especially since non-racemic alcohols have become increasingly more available thanks to the development of recent powerful catalytic methods.^[2] Recently, a metal-free procedure for the transformation of phenols into amides has been described using a radical cascade reaction.^[3] Primary alcohols have also been converted to amides *via* hemiaminal intermediates under catalytic dehydrogenation conditions.^[4] As a tool for the direct conversion of alcohols to amides, the Ritter reaction has received substantial attention over the years. Excluding anchimeric assistance^[5] or diastereomeric control,^[6] this reaction is well-known to proceed by a non-stereospecific carbocation mechanism and is often limited to alcohols where such intermediates are stabilized. However, two examples describing unexpectedly stereospecific Ritter amidations have been reported.^[7] Nevertheless

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Supporting Information (see footnote on the first page of this article): Characterization data for compounds **1a-e**, **1g**, **3-7** and **5** - cholestan-3 -chloride; copies of ¹H and ¹³C NMR for compounds **1**, **3-7**, and **8**, **10**, and **11**; NMR spectra of product mixtures for variously substituted cyclohexanols.

most stereoselective approaches to amides from chiral alcohols require multistep procedures.^[8]

As a complementary technique, we have previously reported a stereoretentive reaction using a nucleophile assisting leaving group (NALG) to position a Ti(IV) azidation reagent for a front-face attack.^[9] Using a designed chelating leaving group,^[10] we fortuitously discovered a more direct stereospecific Ritter-type amidation reaction for cyclic alcohols. This initial observation involved the reaction of an 8-quinoline sulfonate (quisylate, QsO) with titanium(IV) fluoride in the presence of alkyl or aryl nitriles (scheme 1). We next thought to extend the concept of chelating leaving groups to chlorosulfites which can be generated *in situ*. To our knowledge, chlorosulfites have not been exploited as leaving groups being primarily relegated to use as intermediates in the classic SOCl₂ chlorination reaction. In this communication, we report our success in utilizing chlorosulfites for one-pot, two-step reactions of cyclic alcohols to yield amide products with predominant retention of configuration (scheme 1). Importantly, these findings appear to be the first experimental verification of secondary hyperconjomers,^[11] a theory of non-planar carbocations developed by Sorensen and Schleyer.^{[12],[13]}

Results and Discussion

The initial inclination to use titanium(IV) fluoride in reactions with chelating leaving groups was based on our desire to develop a stereoretentive fluorination reaction as a follow-up to our success with chlorinations^[14] and brominations^[9] using the corresponding Ti(IV) halogen reagents. Although currently under study by various groups for use in dental varnishes,^[15] titanium(IV) fluoride has received only modest attention from the organic synthesis community^[16] probably due to its moderate complexing ability,^[17] propensity for oligomer complex formation, and sparing solubility in typical reaction solvents. Following up on a report indicating that TiF₄ can be solubilized as nitrile complexes,^[18] we hypothesized that a fluorination reaction might still be possible with added nitrile. To our surprise, the subsequent reaction of this solubilized reagent with the chlorosulfite ester of *L*-menthol failed to give the expected fluoride but instead afforded amide product **1a** after aqueous workup with complete retention of configuration (table 1). The major side product in this reaction is chloride **2**. Interestingly, the chlorosulfite of menthol failed to yield product **2** at the reaction temperature of 0 °C except in the presence of the Ti(IV) reagent. Indeed, our subsequent studies revealed that a number of Ti(IV) species can be used to catalyze halosulfite reactions leading to alkyl halides in excellent yields under mild conditions with nearly exclusive retention of configuration.^[19] Based on previous studies,^[18] we suspected that multiple equivalents^[20] of TiF₄ and nitrile would be necessary for our amidation reaction. Indeed, the optimal ratio of benzonitrile to TiF₄ appears to be 4:1. Using ten equivalents of TiF₄ (2.5 M) led to an 84% yield of amide **1a**.^[21] Further studies with the *L*-menthol substrate revealed that the stereoretentive amidation reaction is successful with both aromatic and aliphatic nitriles (table 2). The primary limitation appears to be with strongly electron deficient nitriles such as trichloroacetonitrile (entry 5) presumably due to their poor liganding ability. We note that acetamide product **1g** was produced in an excellent yield of 92% (entry 6).

Using benzonitrile as a convenient coupling partner, a variety of substrate alcohols were examined using our optimized amidation conditions (table 3). Very similar to the previously mentioned menthol example, we observed that a number of cyclic chiral alcohols were converted to amide products with complete retention of configuration (entries 1 – 4). In some cases, significant inversion product (~25%) was observed under these reaction conditions (entry 5). In particular, the reaction outcome of cholestanol (a saturated derivative of **5**) led to a mixture of retention to inversion products (not shown). This

attracted our attention since others have commented that this substrate should proceed by a different mechanism in our system due to the absence of a nearby double bond.^[22] We have recently achieved a high yielding chlorination of cholesterol using a closely related Ti(IV) reaction with exclusive retention of configuration.^{[19],[23]} Nevertheless, this less stereospecific result with the present amidation reaction prompted us to further examine our mechanistic hypotheses for these titanium(IV) reactions as discussed below.

In general, this amidation reaction gives high yielding results with cycloalkanols of varying ring sizes under mild conditions (entries 6 – 9). However, with the exception of 1-adamantanol (entry 10), our conditions failed to yield amides with tertiary alcohol substrates giving the chloride products instead. Given the preference of our reaction for secondary substrates, we deem this reactivity profile complementary to the classic Ritter reaction which is generally only useful in easily ionized systems such as tertiary alcohols. In light of our emerging mechanistic conception for this reaction (discussed below), we were not surprised to observe that the stereospecificity of the present amidation reaction does not extend to acyclic systems. We conducted a study of acyclic alcohols using (S)-2-octanol and (S)-1-phenyl ethanol.^[22] In a reaction of the non-racemic phenyl ethanol with benzonitrile and TiF₄, amide **13** was obtained entirely as the racemate (scheme 2). It should be noted that the chlorosulfite of phenyl ethanol readily converts to the chloride product at 0 °C. Accordingly, the chlorosulfite was prepared at –78 °C and then added to a Ti(IV) solution. The amidation reaction with 2-octanol produced a mixture of direct substitution product **14** and hydride shifted product **15** (2.9:1). Polarimetry measurements of purified hydride shifted product **15** indicated that it was essentially racemic. However, direct substitution product **14** gave an enantiomeric excess of 28% favoring inversion (scheme 2).^[24] Finally, primary alcohols (table 3, entry 11) reacted very slowly, consistent with our previous work with titanium(IV) mediated reactions.^[9]

In our previous communications involving titanium (IV) reagents, we suggested that stereoretentive products are likely achieved via an S_Ni mechanism.^{[9],[14]} However, the recent work of Braddock (Imperial College London) and Burton (Oxford) provide convincing evidence that an S_N1-type mechanism may also be operative in NALG/Ti(IV) reactions.^[22] Specifically, the British researchers argue that these Ti(IV)-mediated reactions proceed via carbocation intermediates whose nucleophilic capture is under diastereomeric control. They further point out that, in some cases carbocations are not completely dissociated from the leaving group leading to tight ion-pair formation and thus attack is favored from the less hindered backside.

To help distinguish between the various mechanistic possibilities in the present amidation reaction, we closely examined *trans*- and *cis*-3-methyl cyclohexanol. If the reactions of these isomeric alcohols proceed through a classical S_N1 mechanism they should form the same carbocation intermediate. Attack of this intermediate should then lead to the same product outcome. This was not the case. Instead, we observed a clear preference for retention products in these amidation reactions (scheme 3). Thus *cis*-3-methyl cyclohexanol (**16**) led primarily to *cis*-product **18** (4:1) and the *trans*-substrate (**17**) led to mainly *trans*-product **19** (3:1). Though no hydride shift product was observed for *cis*-3-methyl cyclohexanol substrate, the chlorosulfite of *trans*-3-methyl-cyclohexanol (**17**) gave hydride shift product **20** with the amide group exclusively as the *trans*-isomer.

Our experimental results with other cyclic alcohols (Tables 1 – 3) also suggest that amidation reactions giving predominantly retention of configuration may not proceed by a classical S_N1 mechanism. Indeed, amidation studies of *l*-menthol under typical Ritter conditions (well known to proceed via classical carbocation intermediates) afforded amide products arising from a tertiary carbocation.^[21] Such products have never been observed in

our studies of 2-substituted cyclic alcohols. Instead, we suggest that our amidation reactions may involve a fast front-side attack of a carbocation intermediate such as **21** possessing pyramidal geometry as theorized by Sorensen and Schleyer (scheme 4).^{[12],[13]} Importantly, the cationic center in **21** is expected to maintain its configuration (as a single hyperconjugomer) through hyperconjugative stabilization.^[25] By contrast, there appears to be less of a barrier to carbocation planarization in acyclic systems possibly explaining the lack of stereospecificity in their amidation reactions.

Conclusions

We have discovered an exciting variation of the Ritter reaction using an inexpensive and unexplored Ti(IV)/nitrile reagent to prepare amides directly from cyclic secondary alcohols. Critical to the design of this new reaction is the first ever use of chlorosulfites, formed by the well-known reaction of alcohols and thionyl chloride, as in situ formed chelating leaving groups. Further mechanistic studies on this system are currently underway especially with a view to achieving sub-stoichiometric use of the reagents involved.

Experimental Section

General procedure for stereoretentive amidation reactions

To an ice-cold solution of alcohol (1.0 eq) in dichloromethane (1.0 M) was added thionyl chloride (1.5 eq) followed by stirring for 1 h to form the chlorosulfite. In a separate reaction vessel, nitrile (40 eq) was added to a TiF₄ (10 eq) suspension in dichloromethane (4.0 M) and allowed to stir at room temperature until complete dissolution (~15 min). Since TiF₄ is fairly moisture sensitive, it was quickly transferred to a reaction vessel under argon and then weighed. The amount of each remaining reagent was then based on the weight of the TiF₄. The titanium/nitrile solution was then cooled to 0 °C and to it was added the previously prepared chlorosulfite transferring by cannula under argon pressure. The chlorosulfite containing vessel was further washed with an amount of dichloromethane necessary to bring the final concentration of TiF₄ in the other vessel to the desired concentration (2.5 M). After stirring for 2 h, the reaction was quenched with deionized water and stirred (~30 min) until the organic layer became clear. The organic layer was removed and the aqueous layer was extracted twice with dichloromethane. All organic layers were combined, dried over anhydrous sodium sulphate, and concentrated in vacuo. Crude product was purified by silica gel flash chromatography using ethyl acetate-hexane as eluent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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23. Starting from the in situ formed chlorosulfite of cholestanol (0.1 M in CH_2Cl_2) and using TiCl_4 (5 eq) at 0 °C, the direct substitution chloride product was formed in 15 min as a single product in 80% yield with complete retention of configuration (see Supporting Information).
24. A rotation value -4.4 (c 5.5, CHCl_3). Pure inversion product was made by an alternative route in four steps from (S)-2-octanol via an $\text{S}_{\text{N}}2$ mechanism giving an optical rotation of -15.7 (c 3.55, CHCl_3).
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Scheme 1.

One-pot, stereoretentive amidation reaction of cyclic alcohols.

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Scheme 3.
Amidation in *cis*- and *trans*-3-methyl cyclohexanols.

Scheme 4.

Proposed mechanism and intermediates for the observed amidation reaction.

Table 1

Effect of Ti(IV) concentration on amidation yields.

entry	equiv		conc		Yield (%) ^a	
	PhCN	TiF ₄	PhCN	TiF ₄ (M)	1a	2 ^b
1	4	2	0.2	30	55	
2	4	2	1.0	45	43	
3	8	4	1.0	52	35	
4	8	4	2.5	56	33	
5	16	4	2.5	62	25	
6	24	6	2.5	67	22	
7	32	8	2.5	75	13	
8	40	10	2.5	84	5	

^a Isolated yield.

^b Chlorides formed with complete stereoretention

Table 2

Nitrile generality for stereoretentive amidation.

Entry	RCN	Product	Yield ^a
1		1b	65 ^b
2		1c	72 ^b
3		1d	85
4		1e	80
5	Cl_3CCN	1f	NR
6	H_3CCN	1g	92

^a Isolated yield.^b Reactions 1.0 M in TiF_4

Table 3

Substrate generality for stereoretentive amidation.

$\text{ROSOCl} \xrightarrow[\text{CH}_2\text{Cl}_2 (2.5 \text{ M}), 0^\circ\text{C}, 2.0 \text{ h}]{\text{PhCN (40 eq)}, \text{TiF}_4 (10 \text{ eq})} \text{R}-\text{N}(\text{H})-\text{C}(=\text{O})-\text{Ph}$			
Entry	ROH	Product	Yield ^a
1		3	88
2		4	94
3 ^b		5	75
4 ^b		6	76
5		7	63 ^c
6		n = 2 8	90
7		n = 3 9	80
8 ^b		n = 7 10	65
9		11	90
10 ^b		12	40
11	PhCH ₂ CH ₂ CH ₂ OH	-	NR

^aYield of retention product only.

^bIntermediate chlorosulfite prepared at $-78\text{ }^{\circ}\text{C}$ with TiF_4 conc. maintained at 1.0 M.

^cInversion product produced in 26% yield.