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Synthesis of *N*-Acyl-*N*,*O*-acetals Mediated by Titanium Ethoxide

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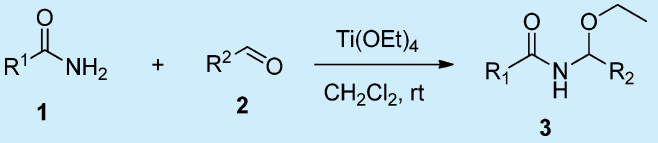
Supporting Information

ABSTRACT: *N*-Acyl-*N*,*O*-acetals are present in a number of bioactive natural products, and this unusual functional group can act as a synthetic precursor to unstable reactive *N*-acylimines. In this paper, a variety of *N*-acyl-*O*-ethyl-*N*,*O*-acetals was concisely prepared under mild conditions mediated by titanium ethoxide ($Ti(OEt)_4$). The method also offers a new strategy to make other *O*-alkyl-*N*,*O*-acetals. Furthermore, this strategy was extended to the synthesis of an analogue of the natural product turtschamide.



N-Acyl-*N*,*O*-acetals are important subunits in a number of bioactive natural products[1] including the antiproliferative mycalamide/pederin family,[2] psymberin,[3] and the microtubule-stabilizing zampanolide[4] (Figure 1). In some of these compounds, the structure−activity relationship studies indicated that the incorporation of the unique *N*-acyl-*N*,*O*-acetal motifs increased the potency.[1a,3a,5] Such acetals have in addition attracted attention as useful reactive intermediates and synthetic equivalents to unstable *N*-acylimines in organic synthesis.[6] The *N*,*O*-acetals are air, water, and light stable but can be activated to generate *N*-acylimines in situ under mild conditions, leading to further organic reactions.[7]

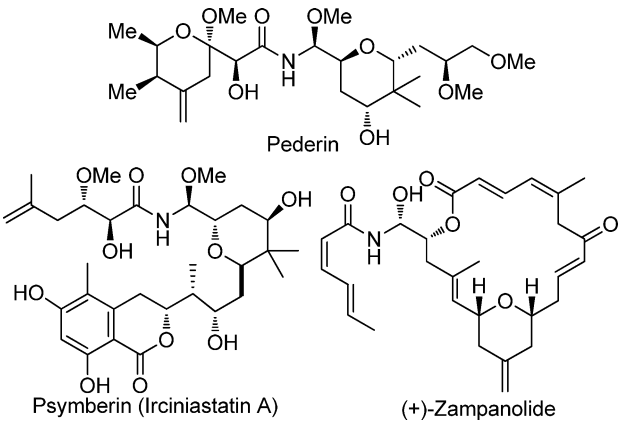
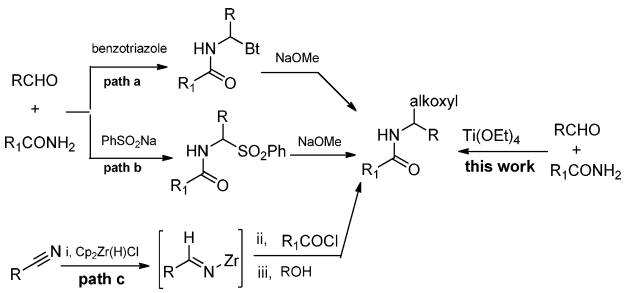


Figure 1. Natural products that contain *N*,*O*-acetals.

The presence of these unique *N*-acyl-*N*,*O*-acetals in intricate natural product structures and their value as synthons for reactive *N*-acylimine species has stimulated interest in the construction of this functional group. Asymmetric *N*,*O*-acetalization has been investigated in the construction of more stable as well as easily accessible cyclic *N*,*O*-acetals that are also found in pharmaceuticals.[8,9] These stable cyclic *N*,*O*-acetals were reportedly employed as reactive chemical reagents, undergoing ring-opening with allylsilane mediated by strong Lewis acids.[10]

Compared to cyclic *N*-acyl-*N*,*O*-acetals, the acyclic acetals are less stable and their preparation is more difficult. To date, several synthetic routes to *N*-acyl-*N*,*O*-acetals have been reported (Scheme 1). These unique structures can be generally constructed by Katritzky's benzotriazole method.[11] In this protocol, two steps are required. In the first step, the reaction was performed in refluxing toluene, and then a sodium alkoxide was employed to install the alkoxyl group of *N*,*O*-acetals (path a). A similar strategy with an α-amido sulfone as an intermediate was broadly employed to prepare *N*-acylimines in situ under basic conditions,[12] and *N*-acyl-*N*,*O*-acetals were reportedly obtained if sodium methoxide was used (path b).[13] However, the conditions also led to the formation of *N*-acylenamides exclusively in another report.[14] Wan and co-workers provided an alternative approach to form *N*,*O*-

Scheme 1. Strategies To Synthesize *N*-Acyl-*N*,*O*-acetals



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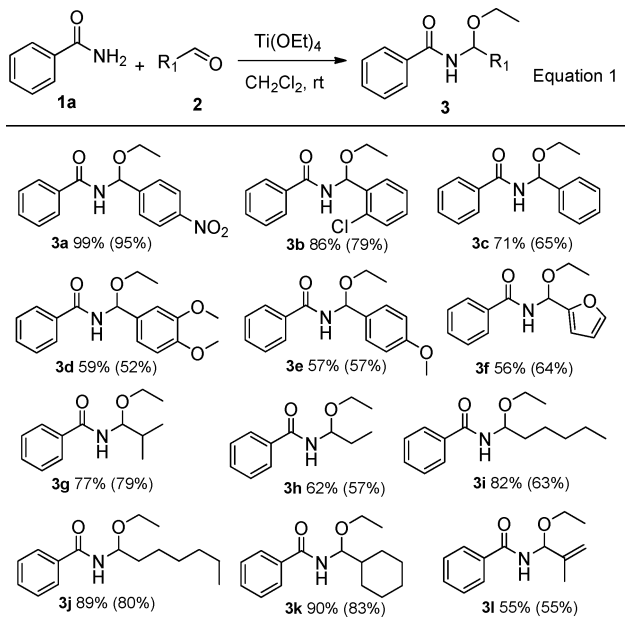
acetals.[15] In their method, three successive steps, i.e., nitrile hydrometalation, acylation, and nucleophile addition were carried out in one pot (path c). Other methods to prepare *N*-acyl-*N*,*O*-acetals are often limited to a certain substrate, for example, resin-supported aromatic amides[7] and chloral.[16] Recently, Antilla and co-workers reported the synthesis of enantiomeric *N*-acyl-*N*,*O*-acetals but started with freshly prepared unstable *N*-benzoylimines.[17] Some strategies including Curtius rearrangement to form these unique motifs in total synthesis of several natural products were also reported.[18] Here, we report a general concise method to prepare these unique species with a broad range of substrates under mild conditions mediated by $Ti(OEt)_4$.

$Ti(OEt)_4$ and other titanium alkoxides have been reported to prepare *N*-*tert*-butylsulfinylimines from aldehydes or ketones with *N*-*tert*-butylsulfinamide.[19] We reasoned that it would be similarly suitable for synthesis of *N*-acylimines from aldehydes and amides. A preliminary investigation was initiated using *p*-nitrobenzaldehyde with benzamide employing $Ti(OEt)_4$. To our surprise, the reaction provided *N*-benzoyl-*O*-ethyl-*N*,*O*-acetal (**3a**) instead of *N*-benzoylimine (Scheme 2, eq 1).

Scheme 2. Reaction of Aldehydes with Benzamide To Give *N*-Acyl-*N*,*O*-acetals[a,b]



[a]Representative procedure: To a solution of aldehyde **2** (1.0 equiv) and benzamide **1a** (1.2 equiv) in anhydrous dichloromethane was added $Ti(OEt)_4$ (1.5 equiv) dropwise at rt, followed by stirring for 8 h. [b]HPLC yields. Isolation yields given in parentheses.

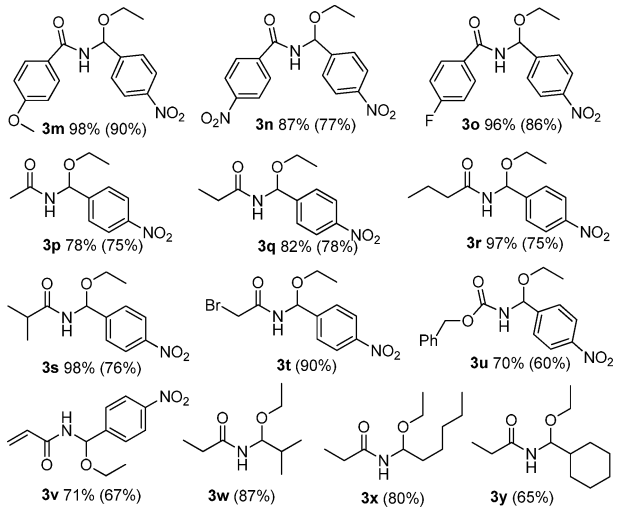
However, these more stable *N*-acyl-*N*,*O*-acetals can be considered as an equivalent reagent to the *N*-acylimine.[9b] Encouraged by the result, we investigated the reaction conditions and the scope of aldehydes and amides.

Considering $Ti(OEt)_4$ can be applied as a Lewis acid, an initial study was conducted on benzamide and *p*-nitrobenzaldehyde with a variety of Lewis/Bronsted acids in order to determine the influence of the acidity of the titanium reagent on the reactivity (Table S1, Supporting Information). In the presence of $CuSO_4$ and $Zn(OTf)_2$, no *N*,*O*-acetal was observed. Only a trace amount of the *N*,*O*-acetal was formed in the cases of strongly acidic $BF_3{\cdot}Et_2O$, TFA, and *p*-TsOH as catalysts. The fact that $Ti(OEt)_4$ mediated the formation of *N*,*O*-acetals with its weak Lewis acidicity in high yield implied that the ortho group effect of incorporated ethoxide might play a big role. It is worth mentioning that the *N*-acyl-*O*-isopropyl-*N*,*O*-acetal was also easily obtained by substituting $Ti(i\text{-}OPr)_4$ for $Ti(OEt)_4$.

With the conditions using $Ti(OEt)_4$ in hand, we investigated the scope of aldehydes in the reactions with benzamide and found the *N*,*O*-acetalization to be general (Scheme 2). Both aromatic and aliphatic aldehydes gave the respective acetals in modest to high yields. The electronic properties of substituted benzaldehydes have an obvious influence in the formation of *N*,*O*-acetals (**3a**–**f**). With electron-withdrawing groups, the reactions usually gave high yields (**3a**,**b**). It seemed that steric hindrance did not play a crucial role in the reactions. Both aliphatic unbranched and branched aldehydes were converted into *N*,*O*-acetals with good yields (**3g**–**k**). An *α*,*β*-unsaturated aldehyde also provided the expected product in moderate yield (**3l**).

To explore the reaction scope, a variety of amides including aromatic, aliphatic amides, and carbamates were investigated first to react with *p*-nitrobenzaldehyde. The results show that the structural variations in the amides were broadly tolerated (**3m**–**v**, Scheme 3). Aromatic and aliphatic amides and even

Scheme 3. Scope of Reaction of Amides with *p*-Nitrobenzaldehyde (3m–v) and Aliphatic Aldehydes with Propionamide (3w–y)[a,b]



[a]Reaction conditions: aldehyde **2** (1.0 equiv), amide **1** (1.2 equiv), $Ti(OEt)_4$ (1.5 equiv), CH_2Cl_2, 8 h, rt. [b]HPLC yields. Isolation yields given in parentheses.

the carbamate $CbzNH_2$ proved to be suitable for the reactions in good to excellent yields. Acrylamide also gave the expected acetal in a good yield without observed polymerization (**3v**). More interestingly, 2-bromoacetamide furnished the expected acetal (**3t**) without competing nucleophilic attack of the *α*-bromocarbonyl. Furthermore, the aliphatic *N*,*O*-acetals (**3w**–**y**) were also successfully obtained in good isolated yields with both aliphatic amides and aldehydes as starting materials. A primary amide appears essential as no *N*,*O*-acetal was obtained when *N*-methylacetamide served as a substrate.

We also explored the possibility of using $Ti(OEt)_4$ as a general reagent for other *O*-alkyl-*N*,*O*-acetals via alkoxide exchange. Thus, *N*-benzoyl-*O*-methyl-*N*,*O*-acetal **4a** was successfully obtained in good yield by the addition of excess

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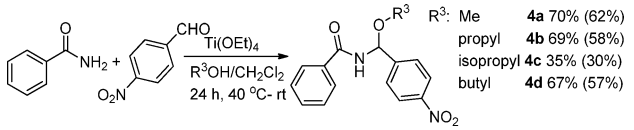
methanol (16 equiv) during the reaction (Scheme 4). Other *O*-alkyl-*N*,*O*-acetals **4b–d** were also easily made in moderate

Scheme 4. Preparation of *N*-Acyl-*O*-alkylacetal 4[a,b]

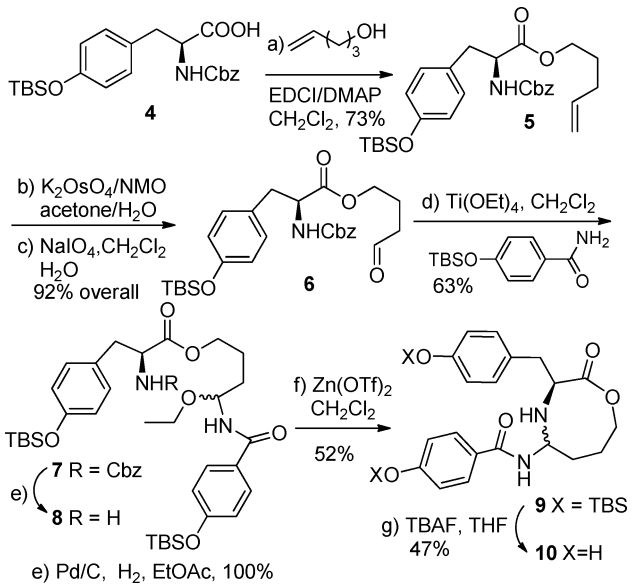


[a]Reaction conditions: *p*-nitrobenzaldehyde **2a** (1.0 equiv), amide **1a** (1.5 equiv), $Ti(OEt)_4$ (2.0 equiv). [b]HPLC yields. Isolation yields given in parentheses.

yields with $Ti(OEt)_4$ by the addition of other alcohols as cosolvents. It was noteworthy that steric hindrance of acohols seemed to play an important role. The yield of *O*-propyl-*N*,*O*-acetal (**4b**) was almost twice as that of *O*-isopropyl-*N*,*O*-acetal **4c**. Meanwhile, *N*-acyl-*N*,*O*-hemiacetal can be obtained by removing ethyl from **3k** using $Zn(OTf)_2$ in acetonitrile (Figure S1, Supporting Information).

Having established a general concise method for the formation of *N*-acyl-*N*,*O*-acetals from aldehydes and amides catalyzed by $Ti(OEt)_4$, we sought to employ our method for target-oriented synthesis. A recently reported natural product turtschamide is a cyclic putrescine bisamide with anticancer activity.[20] It has incorporated an unusual *N*,*N*-aminal motif which we reasoned could be constructed from *N*,*O*-acetals. To confirm the concept, we first investigated the synthesis of a simpler analogue, compound **10** in which oxygen was installed to replace nitrogen for the ease of synthesis (Scheme 5).

Scheme 5. Synthesis of *O*-Turtschamide 10



Initially, an easily obtained L-tyrosine derivative protected with Cbz and TBS was esterified using EDCI to give ester **5**. Dihydroxylation of **5** and subsequent oxidative cleavage afforded aldehyde **6**. Applying our $Ti(OEt)_4$ protocol, *N*,*O*-acetal **7** was prepared in a moderate yield. Cleavage of Cbz with Pd/C afforded a free amine in a quantitive yield. Then, methods for the formation of a cyclic *N*,*N*-aminal were studied.[21] After extensive experimentation using a variety of acids including $BF_3{\cdot}Et_2O$, TMSCl, TFA, PPTS, $Zn(OTf)_2$, and $Ti(OEt)_4$, we finally found that a treatment with $Zn(OTf)_2$ led to cyclic product **9** in a moderate yield. Final deprotection of TBS from **9** successfully afforded *O*-turtschamide **10**. The stereochemical configuration of **10** could not be assigned by NOESY spectra, and we are currently attempting to obtain an X-ray structure.

In conclusion, we have discovered a novel concise method to construct *N*-acyl-*O*-ethyl-*N*,*O*-acetals from both aliphatic and aromatic aldehydes with a broad range of amides and carbamates, mediated by $Ti(OEt)_4$. Our method also offers access to other *O*-alkyl-*N*-acyl-*N*,*O*-acetals, either by the use of other titanium alkoxides or by incorporating other alcohols during the reaction. In our further study, these special functional groups can be converted into *N*-acyl-*N*,*O*-hemiacetals, another important motif present in some natural products, such as zampanolide. Finally, the methods were successfully applied to the synthesis of turtschamide analogue **10**. Further investigation to synthesize enantiomeric *O*-alkyl-*N*-acyl-*N*,*O*-acetals is underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for all reactions and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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