ORGANIC LETTERS

2009
Vol. 11, No. 22
5126−5129

Secondary Alcohol Hemiacetal Formation: An in Situ Carbonyl Activation Strategy

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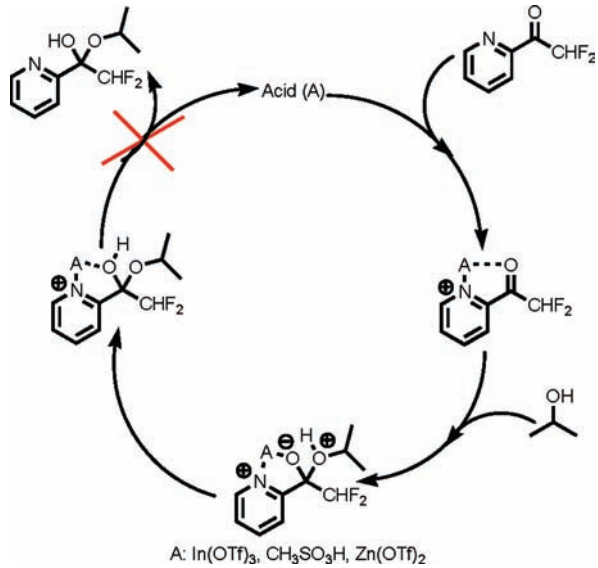
Received August 31, 2009

ABSTRACT



A simple strategy was studied for the reversible nucleophilic addition of secondary alcohols to carbonyl-based receptors to form hemiacetals. It involves the in situ binding of neighboring Brønsted and Lewis acids activators. The addition reaction was successfully observed by UV−vis spectroscopy, thereby laying the groundwork for alcohol optical sensor design.

The alcohol functional group is widespread in natural products such as terpenes, steroids, and saccharides, as well as being present in compounds that are components of complex mixtures, such as wine and perfume. In this regard, alcohols are attractive targets for molecular receptors. However, a mono-ol is a poor ligand and has low nucleophilicity. It also has very little molecular recognition contacts, being simply a hydrogen bond donor and acceptor. As a result, the molecular recognition of alcohols is challenging.

Efforts toward alcohol recognition using reversible covalent bond formation[1] have been reported.[2] In most cases, the receptor is based on trifluoroacetyl-substituted aromatics, where an equilibrium exists between the trifluoromethyl ketone and alcohol with the corresponding hemiacetal. Unfortunately, such carbonyl-based receptors have low sensitivity and long response times, even for simple primary alcohols. With secondary alcohols, the hemiacetals are normally only formed in neat solutions of alcohol.[3] Our goal was to develop a system that reversibly forms hemiacetals

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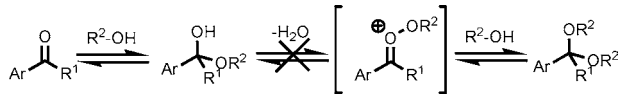
10.1021/ol9020207 CCC: $40.75
Published on Web 10/16/2009

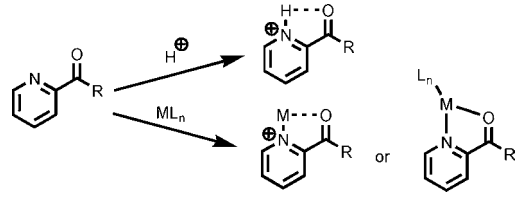
with secondary alcohols without acetal formation as a means to one-step binding equilibria. We sought to stop acetal formation by destabilizing the oxonium ion created during its formation[4] (Scheme 1).

Scheme 1. Hemiacetal Reaction



It is well-known that the extent of alcohol addition to carbonyls increases when electron-withdrawing groups, such as trifluoromethyl (CF_3), are placed in the α position.[5] Alternatively, electrophilic activation of the carbonyl, either through hydrogen bonding or acid coordination, should also increase addition. In this regard, we turned our attention to 2-acylpyridine derivatives. Because protonation with a Brønsted acid or coordination with a Lewis acid will place a formal positive charge on the pyridine nitrogen, the acids will afford a highly electron-withdrawing motif. Moreover, the neighboring carbonyl oxygen could be involved in either an intramolecular H-bond or metal coordination, respectively (Scheme 2). Further, the

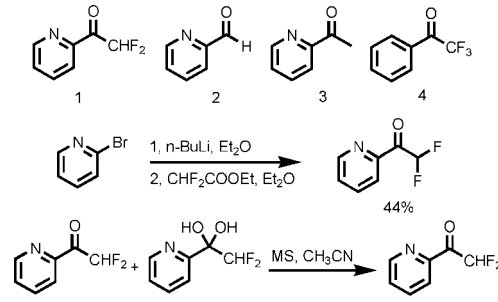
Scheme 2. Acid Activation



2-acylpyridine derivatives described here are analogous to α-imino esters,[6] which are known to be substrates for metal chelation.

We first studied 2-trifluoroacetylpyridine, but it was far too hygroscopic and difficult to dehydrate.[7] We therefore turned to 2-difluoroacetylpyridine (**1**). Compound **1** was prepared from ethyl difluoroacetate and 2-bromopyridine (Scheme 3)[8] and characterized (see Supporting Information).

Scheme 3. Receptors and Synthesis



Compound **1** is moisture-sensitive but can be dehydrated using 3 Å molecular sieves (MS). 2-Picolinaldehyde (**2**) and 2-acetylpyridine (**3**) were also studied. These three compounds afforded us the possibility to probe the effect of induction on the reactivity and the position of equilibrium. Trifluoroacetophenone (**4**) served as a control because it lacks the nitrogen near the carbonyl group that coordinates an acid activator.

To test our design criteria and elucidate the role of acids to promote alcohol addition to 2-acylpyridine derivatives, NMR titrations were conducted in CD_3CN. The reaction of **1** and 2-propanol (5 equiv) in the presence of 3 Å MS and different concentrations of methanesulfonic acid (MsA) was monitored (Figure 1). Only tiny resonances for the hemiacetal

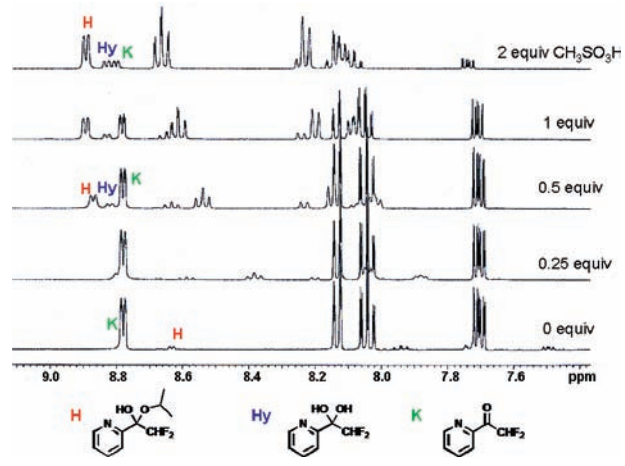


Figure 1. ^{1}H NMR spectra of the reaction of host **1** (~36 mM) and 2-propanol (5 equiv) in the presence of varied concentrations of methanesulfonic acid in CD_3CN. H = hemiacetal; Hy = hydrate; K = ketone.

were observed in the absence of acid, indicating binding constants far less than 1. As the concentration of acid increased, the amount of hemiacetal increased accordingly. The hydrate was also seen due to residual water in the alcohol

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and acid, but the acetal was not observed. Therefore, the electron-withdrawing difluoromethyl group did sufficiently destabilize the oxonium intermediate required for acetal formation. All of the aromatic signals of the hemiacetal were shifted downfield as the equivalents of acid increased, whereas the peaks from the ketone receptor were shifted only slightly. This indicates that the hemiacetal pyridine is protonated by MsA while most of compound **1** is not protonated during this titration. The hemiacetal unit is less electron-withdrawing than a carbonyl, and as a result, the pyridine nitrogen in the hemiacetal is a better base than that in **1**. Therefore, the acid acts as a thermodynamic activator rather than as a catalyst that more rapidly establishes equilibrium.

A corresponding ^{19}F NMR titration of **1** and 2-propanol with MsA is shown in Figure 2. The doublet splitting

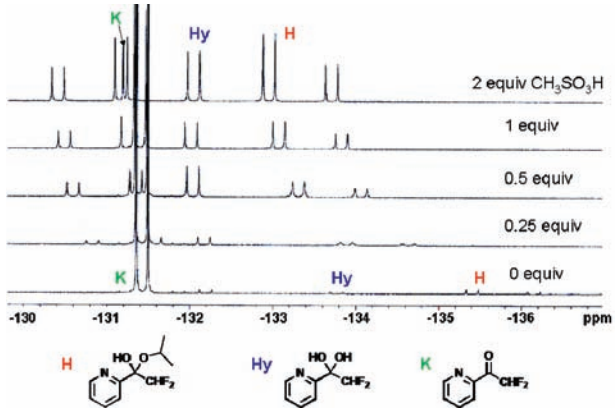

Figure 2. ^{19}F NMR spectra of the reaction of host **1** (~36 mM) and 2-propanol (5 equiv) in the presence of varied concentrations of methanesulfonic acid in CD_3CN. H = hemiacetal; Hy = hydrate; K = ketone.

pattern for each peak results from H−F coupling ($J_{H-F} \approx$ 58 Hz). The doublets confirm the presence of an α-hydrogen and not an enol form of compound **1**. In the resulting hemiacetal, the newly formed stereocenter makes the two fluorine atoms (and the two methyl groups of the added 2-propanol) diastereotopic, and therefore, two sets of similar dd patterns are observed ($J_{F-F} \approx$ 300 Hz and $J_{H-F} \approx$ 58 Hz). The ^{19}F peaks in the hemiacetal are shifted downfield relative to ketone **1**, and this is in agreement with the ^{1}H NMR titration results. The binding constant of **1** with 2-propanol in the presence of CH_3SO_3H is estimated to be around 4×10^2 M^{-2} from the integrations of ^{1}H and ^{19}F NMR. This indicates that the binding of **1** toward secondary alcohols is dramatically improved upon activation with methanesulfonic acid.

Indium triflate was also studied because of its high Lewis acidity and water tolerance.[9] In the presence of $In(OTf)_3$ (1 equiv) and 2-propanol (5 equiv, host concentration 30−40 mM), both hemiacetal and hydrate were observed (Table 1).

Table 1. Reaction of **1** (30−40 mM) with 2-Propanol (5 equiv) in the Presence of Lewis Acids (1 equiv) at Equilibrium[a]

acid	MS	K, %	H, %	Ac, %	Hy, %
$In(OTf)_3$	no	tiny	68	tiny	32
$In(OTf)_3$	yes	tiny	76	17	7
$Zn(OTf)_2$	no	17	69	tiny	14
$Zn(OTf)_2$	yes	24	66	7	3

[a] K = ketone; H = hemiacetal; Ac = acetal; Hy = hydrate.

When the reaction was performed in the presence of 3 Å MS, the hydrate was diminished, but the acetal was observed. Nevertheless, the hemiacetal was still the major product. The 2-propanol used contained about 0.15% water as indicated from a Karl Fischer titration, and this accounts for some of the hydrate formation. $Zn(OTf)_2$ is less effective than $In(OTf)_3$. Even with 10 equiv of 2-propanol present, a substantial amount of host **1** still remains at equilibrium. At the same time, the hydrate formation is reduced.

To better understand the necessity of the fluorine atoms in **1**, we ran analogous reactions with less activated carbonyls. The equilibrium constant for reaction of picolinaldehyde (**2**) with methanol in CD_3CN was found to be less than 1 M^{-1}, which is similar to what has been previously reported for pyridine-4-carboxaldehyde.[10] Yet, **2** is activated in situ upon addition of acids (see Supporting Information). However, the formation of the corresponding 2-propanol acetal was substantial after several hours. Therefore, the reaction does not equilibrate at the desired hemiacetal because the H on the aldehyde is not electron-withdrawing enough to prevent subsequent acetal formation. For 2-acetylpyridine (**3**), only a slight addition of 2-propanol was observed at equilibrium, even in the presence of acid. The equilibrium of trifluoroacetophonone (**4**) with 2-propanol under similar conditions was also negligible because **4** lacks the nitrogen for chelation-controlled activation.

We also undertook a study of the equilibrium between secondary alcohols and our carbonyl-based receptors using UV−vis spectroscopy as a presage to creating optical sensors for alcohols. Upon addition of 2-propanol into host **1** and MsA, $In(OTf)_3$ or $Zn(OTf)_2$, a new peak at 255 nm appeared, while the intensity of two original peaks decreased (for $Zn(OTf)_2$, see Figure 3). The new peak indicates the formation of hemiacetal. The blue shift (269 nm−255 nm) is reasonable because the conjugation decreases upon changing from 2-acylpyridine to the hemiacetal. However, from the titration curves it is clear that substantial amounts of ketone remain unreacted, which is evidence for an equilibrium. These results are consistent with the NMR studies and demonstrate that the equilibrium shifts toward the reactants at the lower concentrations used in UV−vis spectroscopy.

When 2-propanol is in a large excess and the acid is either in a large excess or is very strong, the reaction conditions can be manipulated to give pseudo-first-order kinetics. When

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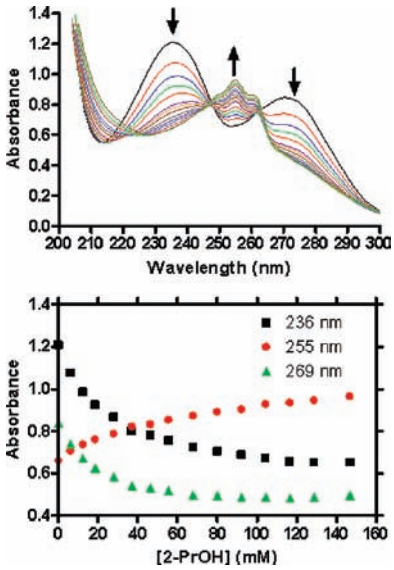


Figure 3. Titration of 2-propanol into the solution of **1** (0.17 mM) in the presence of $Zn(OTf)_2$ (8.89 mM) in CH_3CN (top panel) and its binding isotherm (bottom panel). After each addition, the sample was sonicated for ~10 s and allowed to equilibrate for ~5 min before measurement.

host **1** (0.17 mM), 2-propanol (4.78 mM), and $In(OTf)_3$ (0.17 mM) were mixed, the reaction was complete within 3 min as monitored via UV−vis spectroscopy (Figure 4). This

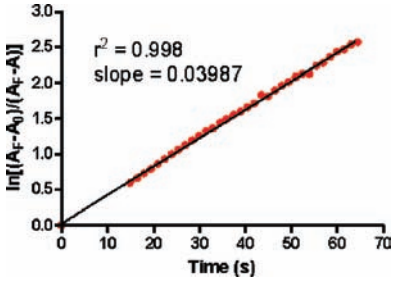
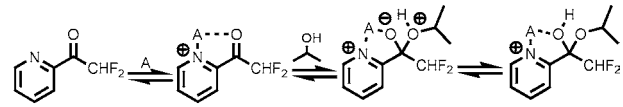


Figure 4. First-order kinetics of the reaction of host **1** (0.17 mM) and 2-propanol (4.78 mM) activated by $In(OTf)_3$ (0.17 mM) in CH_3CN. The absorbance at 255 nm was monitored.

confirms the powerful activating ability of the indium salt. When host **1** (0.17 mM), 2-propanol (19.25 mM), and methanesulfonic acid (9.40 mM) were mixed together, the equilibrium was reached after approximately 2 h (see Supporting Information). Therefore, the kinetics of our system is improved significantly over previous studies[3] considering the relatively low alcohol concentration used.

Based on the discussions above, the reaction sequence in Scheme 4 is proposed. Host **1** is activated in situ through

Scheme 4. Proposed Reaction Sequence



acid chelation, and this activated complex is attacked by the alcohol, followed by proton transfer. The resulting acid-hemiacetal complex is thermodynamically favored relative to the starting acid-ketone complex. As a result, the acid is not regenerated to catalyze the reaction.

In summary, we have discovered conditions for the binding of secondary alcohols to carbonyl derivatives through reversible covalent bond formation. The scenario of in situ carbonyl activation is achieved through chelation control. Although this is one of the few strategies that are successful for secondary alcohols, water and primary alcohols would be major competitors in mixtures of alcohols. A series of acids (both Brønsted and Lewis acids) were screened, and $In(OTf)_3$ was found to be the most effective. The reaction can also be stopped at the hemiacetal stage when an appropriate R group is chosen. The creation of an acid-hemiacetal complex compared to acid-host complex supplies a driving force for the reaction. Only millimolar to submolar ranges of alcohol concentration are required to induce a signal change in UV−vis spectroscopy. Further alcohol receptor designs should benefit from the physical organic details revealed here and will be reported in due course.

Acknowledgment. We thank Charles Shannahan for helpful discussions. We thank the NIH (GM077437) and Welch Foundation for support of this work.

Supporting Information Available: Experimental section, selected ^1H NMR and ^{19}F NMR spectra, and UV−vis titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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