Tetrahedron Letters 59 (2018) 1094–1098

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Hafnium inspired activation of highly hindered anhydrides in the acylation of alcohols and polyols

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ARTICLE INFO

Article history:
Received 27 December 2017
Revised 1 February 2018
Accepted 4 February 2018
Available online 7 February 2018

Keywords:
Acylation
Isobutyric anhydride
Pivalic anhydride
Hafnium triflate
Pivalation

ABSTRACT

A novel and highly efficient method for activating highly hindered acid anhydrides towards the acylation of alcohols and carbohydrate-derived polyols has been developed. This new method relies on the capacity of the hafnium triflate catalyst $Hf(OTf)_2$ to activate highly hindered acid anhydrides, and to direct the acylation reaction. This new acylation protocol is mild and proceed at room temperature with low catalyst loading. The method is versatile and has been extended to different alcohol substrates with different steric encumbrance as well as carbohydrate-derived polyols to afford the corresponding ester products in good to excellent yields.

Introduction

Acylation of hydroxyl groups to the corresponding esters and their subsequent deprotections has been widely utilized and remain popular in numerous organic synthetic protocols.[1–3] Some of the notable methods to protect hydroxyl groups employ the use of acetic anhydride and DMAP in pyridine.[4] While this reaction protocol works well, long reaction times coupled the noxious nature of pyridine has necessitated the need for other alternative acylation methods to complement the existing hydroxyl protection protocols.

Some of the notable acylation methods that utilizes acetic anhydride, acetic acid, acetyl chloride or other carboxylic acids as the acylating agent to protect hydroxyl groups include the use of magnesium perchlorate,[5] lithium perchlorate,[6,7] cobalt(II)chloride,[8] chlorotrimethylsilane,[9] zinc chloride,[10] iron(III)chloride,[11] magnesium bromide,[12] ruthenium(III)chloride,[13] tantalum(V)chloride,[14] vanadyl acetate,[15] *N*-bromosuccinamide (NBS),[16] 3-nitrobenzene boronic acid,[17] silica gel supported sodium hydrogen sulfate,[18] sodium acetate trihydrate,[2] dried sodium bicarbonate,[19] bromine,[20] iodine,[21,22] tributylphosphine,[23,24] *p*-toluene sulfonic acid,[25] alumina,[26] indium triflate,[27,28] scandium triflate,[29] bismuth triflate,[30] trimethylsilyl triflate,[31] copper triflate,[32] cerium triflate,[33] silver triflate,[34] bis(benzonitrile)palladium(II)bistriflate,[35] terakis(acetonitrile)copper(I)triflate,[36] montmorillonite K-10,[37] sulfamic acid,[38] molecular sieves,[39] hafnium(IV) and zirconium (IV) salts.[40,41]

While all these methods provide useful alternatives in protecting hydroxyl groups to the corresponding acetate esters, the extension of these protocols in activating hindered acid anhydrides are rarely reported. This becomes particularly crucial during long synthetic reaction sequence involving the manipulation of hydroxyl groups in various reaction media, where the usual ease of removal of the acetyl protecting group is undesirable, and therefore necessitating the use of a relatively more hindered and robust hydroxyl protecting groups.

Recently, hafnium triflate by virtue of its high stability in air, ease of handling and commercial availability has been utilized in many Lewis acid mediated organic synthetic transformations.[42] For example, Kobayashi research group in the past few years reported the development of a new protocol in the Friedel-Crafts acylation of arenes,[43,44] Fries rearrangement of acyloxybenzenes,[45] as well as C-acylation of phenol and naphthol derivatives,[46] all inspired by hafnium triflate in catalytic quantities.

In utilizing hafnium triflate in natural product synthesis, the Zhu research group reported the development of hafnium triflate inspired thioacetalization reactions of carbonyl compounds,[47] a strategy which was employed as one of the key steps in the synthesis of (−)-*rhazinilam* and (−)-*leucomidine B*.[48] In recent years, Movassaghi et al. employed hafnium inspired addition reactions of imine derivatives as one of its key steps in the total synthesis

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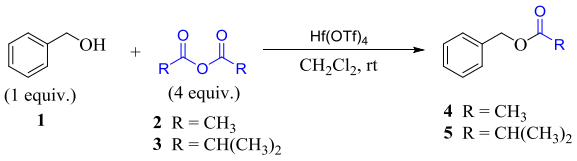
https://doi.org/10.1016/j.tetlet.2018.02.009
0040-4039/

of (+)-*gliocladin B* from *N*-protected L-tryptophan and sarcosine methylester.[49]

As a result of the excellent catalytic activity and versatility of hafnium triflate in many organic transformation reactions, we envisioned that this catalyst could potentially be effective in activating hindered acid anhydrides towards the masking of hydroxyl groups with more robust protecting groups.

To the best of our knowledge, the use of this catalyst in activating hindered acid anhydrides in the protection of hydroxyl groups has not been studied. We report herein a new method that utilizes hafnium triflate as catalyst in the acylation of alcohols and polyols using hindered acid anhydrides.

Table 1
Hafnium triflate catalyzed acylation of benzyl alcohol.[a]



Entry	Acylating agent	Catalyst loading (mol%)	Time (min)	Product	Yield (%)[b]
1	2	10	1	4	95
2	2	7	1	4	93
3	2	5	1	4	96
4	2	2	1	4	95
5	2	1	1	4	95
6	**3**	**1**	**15**	**5**	**97**
7	3	0.5	45	5	82

The bold values represents the optimum reaction condition identified during our preliminary studies and was subsequently used to run the acylation reactions.

[a] Reactions were conducted on 0.5 mmol scale with benzyl alcohol in dried CH_2Cl_2 (2.5 M).

[b] Isolated yield.

Results and discussion

Preliminary studies to investigate the effectiveness of hafnium triflate in activating hindered acid anhydrides began using benzyl alcohol **1** as the starting substrate. An acetic anhydride **2** and a relatively more hindered isobutyric anhydride **3** were used as the acylating agents in a bid to study their relative rates of acylation at different catalyst loading. (Table 1).

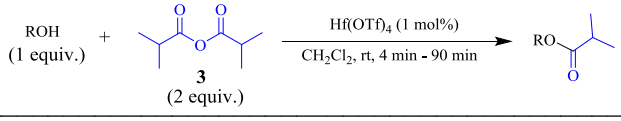
Conversion of benzyl alcohol **1** to the corresponding ester **4** using acetic anhydride **2** as the acylating agent proceeded smoothly and rapidly even at 1 mol% catalyst loading to afford the benzyl acetate in excellent yields (Table 1, entry 1–5). This encouraging results prompted us to investigate the efficacy of this catalyst in activating a relatively more hindered acid anhydride such as isobutyric anhydride towards the protection of hydroxyl groups.

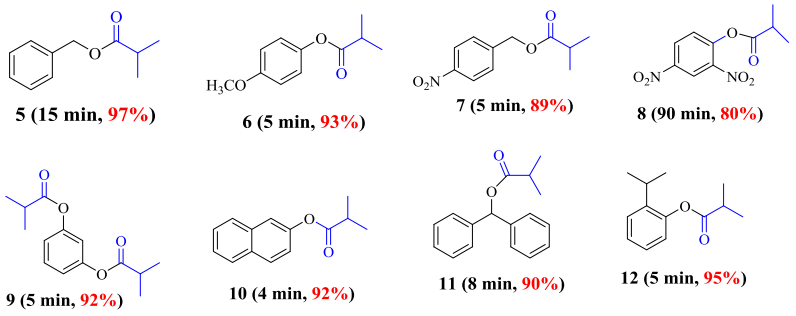
Upon treatment of benzyl alcohol **1** with isobutyric anhydride **3**, to our amazement, the acylation reaction proceeded to completion within 15 min at 1 mol% catalyst loading, affording the corresponding ester **5** in excellent yield (Table 1, entry 6). Further reduction in the catalyst loading resulted in a sluggish reaction rate and reduced isolated yield (Table 1, entry 7). These results were significant because it demonstrate the capacity of hafnium triflate to activate not only simple acid anhydrides such as acetic anhydride but also a relatively more hindered acid anhydrides as well.

To investigate the generality and scope of this method, the new acylation protocol was extended to a wide variety of different alcohols using isobutyric anhydride **3** as the acylating agent (Table 2).

Upon treatment of the alcohols with isobutyric anhydride using 1 mol% of the catalyst, the acylation reactions proceeded smoothly with shorter reaction times, affording the corresponding esters **6**–**15** in good to excellent yields (Table 2). Of particular note is the use of 2,4-dinitrophenol as a substrate, although quite deactivated and less nucleophilic, the acylation reaction still proceeded affording the corresponding ester **8** in good yields (Table 2).

Table 2
Acylation of alcohols with isobutyric anhydride catalyzed by $Hf(OTf)_4$.[a]





[a] Reactions were conducted in dried CH_2Cl_2 (2.5 M).