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Catalytic Nucleophilic Acyl Substitution of Anhydrides by Amphoteric Vanadyl Triflate

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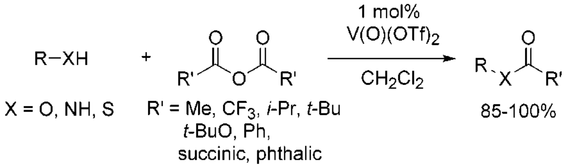
ABSTRACT



Among four vanadyl species examined, vanadyl triflate was the most efficient catalyst to facilitate nucleophilic acyl substitution of anhydrides with a myriad array of alcohols, amines, and thiols in high yields and high chemoselectivity. By using mixed-anhydride technique, one can achieve oleate and peptide syntheses. In marked contrast to common metal triflates, the amphoteric character of the V═O unit in vanadyl species was proven to be responsible for the catalytic profile in this process.

The acylations of alcohols, amines, and thiols are important and commonly used transformations in organic synthesis.[1] In these reactions, acid halides or anhydrides are often employed as the acyl source in basic media[2] or in the presence of Lewis base[3] or acid catalysts.[4] For the past five years, trimethylsilyl (TMS)[5] and metal triflates such as indium,[6] scandium,[7] copper,[8] and most recently bismuth triflate[9] have been found to be effective in catalyzing the acylation of alcohols with anhydrides. However, only a few of them have been studied with more complete anhydride scope,[5,7] and substrates bearing acid-sensitive groups, such as acetonide and allylic,[10] might not be fully compatible. In addition, their actual role in the catalytic pathway was not fully understood. Notably, the preparation of metal triflates often require direct mixing of metal oxides with excess of hot triflic acid. The incomplete removal of triflic acid from the metal triflates might limit the overall efficiency of the process. In this context, new mild and neutral catalysts, which can achieve general nucleophilic acyl substitution of anhydrides with protic nucleophiles, remain in great demand.

The synthetic utility of vanadium-containing compounds has been widely explored and utilized. Among them, oxovanadium(IV) (vanadyl) compounds were normally treated as precatalysts of the corresponding V^{V} species.[11] However, synthetic transformations that are directly catalyzed by vanadyl species were relatively unexplored.[11a,12] Notably, Togni in 1990 reported the uses of camphor-derived vanadyl

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(1) Green, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1991.

(2) Larock, R. C. In *Comprehensive Organic Transformations*; VCH Publisher Inc.: New York, 1989; p 980.

(3) For leading references, see: (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingvas, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286. (c) Verkade, J. G.; Ilankumaran, P. *J. Org. Chem.* **1999**, *64*, 9063.

(4) (a) Baker, R. H.; Bordwell, F. G. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 141. (b) Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001. (c) Chandrasekhar, S.; Ramachander, T.; Takhi, M. *Tetrahedron Lett.* **1998**, *39*, 3263.

(5) Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342.

(6) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743.

(7) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.

(8) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611.

(9) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2877.

(10) Jarowicki, K.; Kocienski, P. *Contemp. Org. Synth.* **1997**, 454.

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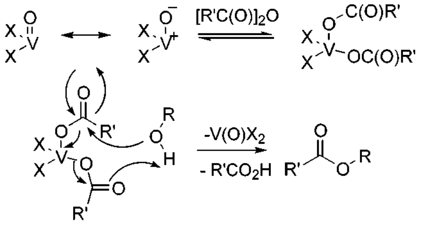
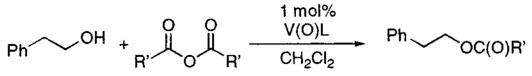
bis(1,3-diketonato) complexes as Lewis acid catalysts for asymmetric Diels−Alder reactions between Danishefsky dienes and aldehydes.[13] Although a concerted pathway was suggested in the report, the potential amphoteric character of the V═O unit (i.e., $^{+}V{-}O^{-}$) to facilitate a stepwise, push−pull type mechanism was overlooked. Namely, the (partial) positively charged V in V═O is Lewis acidic enough to activate the carbonyl oxygen of an aldehyde. In the meantime, the (partial) negatively charged O in V═O serves as a Lewis base to activate an enol silane with concomitant removal of its silyl group. The proposal was somewhat supported by a facile conversion of $V(O)(salen)_2$ to $VCl_2(salen)_2$ under the action of $SOCl_2$.[14] Therefore, we sought to examine if a vanadyl species can similarly react with an anhydride to establish a fast equilibrium with its anhydride adduct (Scheme 1). Under such circumstances, a protic nucleophile (e.g., an alcohol) may add to one of the two alkanoates in the adduct with a concomitant elimination of an alkanoic acid to regenerate the vanadyl species (i.e., a catalytic nucleophilic acyl substitution of an anhydride). We herein disclose our realization of this catalytic process.

Scheme 1. Proposed Equilibrium between an Amphoteric Vanadyl Species and an Anhydride in the Catalytic Acylation of an Alcohol



Four different vanadyl species were first tested in mediating the acetylation of 2-phenylethanol, Table 1. Initial trials with 5 mol % of vanadyl acetylacetonate ($VO(acac)_2$) and vanadyl sulfate were effective to complete the acetylation at ambient temperature in the presence of 1.5 equiv of Ac_2O in 5 and 24 h, respectively.

Table 1. Catalytic Acylations of 2-Phenylethanol with Various Anhydrides in the Presence of Various Vanadyl Species



entry	V(O)L	anhydride (R')	time (h)	yield,[a] %
1	$V(O)(acac)_2$[b,c]	CH_3	5	85
2	$V(O)Cl_2$	CH_3	7.5	94
3	$V(O)SO_4$[c,d]	CH_3[e]	24	92
4	$V(O)(OTf)_2$	CH_3	0.5	98
5	$V(O)(OTf)_2$[f]	CH_3	0.75	98
6	$V(O)(OTf)_2$	CF_3	3	98
7	$V(O)(OTf)_2$	*i*-Pr	1	98
8	$V(O)(OTf)_2$	*tert*-Bu	11	99
9	$V(O)(OTf)_2$	*tert*-BuO	28	95
10	$V(O)(OTf)_2$	Ph	26	92
11	$V(O)(OTf)_2$	succinic	42	93
12	$V(O)(OTf)_2$	phthalic	96	75[g]

[a] Isolated yields. [b] Acetylacetonate. [c] Five mol % catalyst was used. [d] The trihydrate was used. [e] CH_3CN was used as solvent. [f] Catalyst was recovered from aqueous layer and reused for five consecutive runs. [g] Diphenethyl ester was isolated in 16%.

Vanadyl chloride and triflate, which were prepared from vanadyl sulfate and suitable barium salts,[15] were found to be much more reactive. Acetylation using 1 mol % of $V(O)Cl_2$ and $V(O)(OTf)_2$ with 1.5 equiv of Ac_2O in CH_2Cl_2 were complete in 7.5 and 0.5 h, respectively, leading to phenethyl acetate in ≥94% yields. It should be noted that the corresponding VCl_3 and $V(OTf)_3$ are catalytically inactive, supporting the mechanistic role of the V═O unit in the vanadyl catalysts.[16] In addition, there is no need of chromatographic purification with the acetylation protocol since the remaining acetic anhydride and vanadyl triflate can be readily removed by direct aqueous wash. More importantly, $V(O)(OTf)_2$ is fully compatible with water. It can be recovered from the concentrate of the aqueous layer and reused for at least five consecutive runs with similar catalytic activity.

Beside acetic anhydride, the catalytic system is amenable to acyclic and cyclic, aliphatic, and aromatic anhydrides, Table 1. In general, the more hindered the anhydride, the slower the acylation rate (i.e., CH_3 > *i*-Pr > *t*-Bu; entries 4, 7, and 8). Acylation with an aromatic anhydride (e.g., R = Ph, entry 10) is up to 50 times slower than those with aliphatic anhydrides (entries 4 and 6−8). Acylation with di-*tert*-butyl dicarbonate also proceeds well and with a rate similar to that of benzoylation (entry 9). Cyclic anhydrides such as succinic and phthalic anhydride are the least reactive. Acylations took 2−4 days (entries 11 and 12).

With the optimal catalyst-vanadyl triflate in hands, nucleophilic acyl substitutions of both acetic and pivalic anhydride (representing two steric extremes) with protic nucleophiles (e.g., alcohols, amines, and thiols) of varying steric and electronic demands were examined. In almost all

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(11) For a general review, see: (a) Hirao, T. *Chem. Rev.* **1997**, *97*, 2707. (b) For oxidative couplings, see: Hwang, D. R.; Chen, C. P.; Uang, B. J. *J. Chem. Soc. Chem. Commun.* **1999**, 1207. (c) Hon, S.-W.; Li, C.-H.; Kuo, J.-H.; Barhate, N. B.; Liu, Y.-H.; Wang, Y.; Chen, C.-T. *Org. Lett.* **2001**, *3*, 869. (d) For vicinal dialkylation of cyclic enones, see: Hirao, T.; Takada, T.; Sakurai, H. *Org. Lett.* **2000**, *2*, 3659.

(12) For recent applications, see: (a) Belokon, Y. N.; North, M.; Parsons, T. *Org. Lett.* **2000**, *2*, 1617. (b) Ishii, Y.; Matsunaka, K.; Sakaguchi, S. *J. Am. Chem. Soc.* **2000**, *122*, 7390.

(13) Togni, A. *Organometallics* **1990**, *9*, 3106.

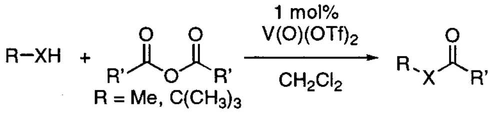
(14) Schmidt, H.; Bashirpoor, M.; Rehder, D.*J. Chem. Soc., Dalton Trans.* **1996**, 3865.

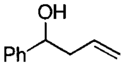
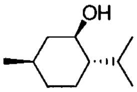
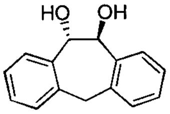
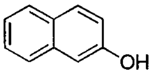
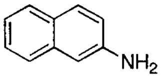
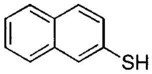
(15) See Supporting Information.

(16) $V(O)Cl_3$ is moisture-sensitive but was found to be catalytically active (100% yield, 1.5 h).

cases except in the pivalations of cinnamyl alcohol (85%) and (−)-menthol (84%), the chemical yields of acylation were ≥95%, Table 2. In general, acetylations proceed much faster than the corresponding pivalations. Acylations went smoothly with primary, secondary, and acid-sensitive allylic and benzylic alcohols. No trace of allylic[7,17] or pinacol[18] rearrangement byproducts was observed in the case of cinnamyl alcohol and 10,11-dihydroxy-dibenzosuberane (entries 2 and 5). Tertiary alcohols such as *tert*-butyl alcohol and trityl alcohol are inactive. Nevertheless, the corresponding *tert*-butanethiol is fairly reactive (entry 10). Aromatic alcohols, amines,[19] and thiols (e.g., 2-hydroxy, 2-amino, and 2-thio-naphthalenes) are amenable to acylations in essentially quantitative yields (entries 6−8).

Table 2. Vanadyl Triflate-Catalyzed Acetylation and Pivalation of Alcohols, Amines, and Thiols

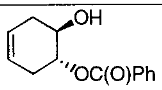
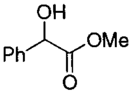
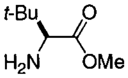
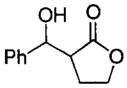
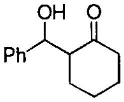
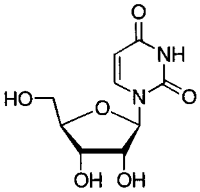
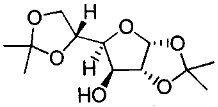
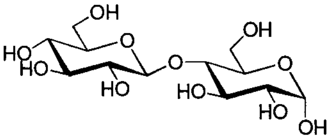
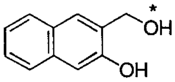
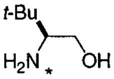


entry	substrate[a]	time, h	yield,[b] %
1	Ph(CH$_2$)$_2$OH	0.5 (11[c])	99 (99)
2	PhCH=CHCH$_2$OH	3.5[d] (72[e])	98 (85)
3		10 (24)	97 (97)
4		1 (96[f])	97 (84)
5		1 (5 [g])	98 (95)
6		5 (36)	99 (99)
7		8 (42)	99 (99)
8		40 (96)	99 (98)
9	(*i*-Pr)$_2$NH	3	97
10	*tert*-BuSH	12 (24)	99 (95)

[a] A total of 1.5 equiv of anhydride was used unless otherwise stated. [b] Isolated yields and characterized spectroscopically. [c] The data in parentheses correspond to pivalations. [d] A total of 2 equiv of anhydride was used. [e] A total of 3 equiv of anhydride was used. [f] THF was used as solvent. [g] Toluene was used as solvent.

The acylation protocol is tolerant to protic nucleophiles bearing functional groups such as alkene, ester, lactone, ketone, imide, acetonide, and lactol (entries 1−9, Table 3). Their acylations proceeded smoothly in 75−100% yields. Side reactions such as oxidation (dehydrogenation) and dehydration[4b] were not observed in the case of α-hydroxy,

Table 3. Acetylation and/or Pivalation of Functionalized Substrates

entry	substrate[a]	time, h	yield,[b] %
1		0.5 (48[c])	99 (99)
2		2 (3)	96 (95)
3		0.5[d] (1.5)	100 (85)
4		12 (24)	95 (95)
5		6 (12)	100 (100)
6		96[e]	90
7		49[f]	75
8		60[e,g]	85
9	β-cyclodextrin	96[g]	90
10		3[h](48)	95 (96)
11		2[h,i] (15)	60[j] (97)

[a] A total of 1.5 equiv of anhydride was used unless otherwise stated. [b] Isolated yields and characterized spectroscopically. [c] The data in parentheses correspond to pivalations. [d] A total of 2 equiv of anhydride was used. [e] A total of 3 equiv of anhydride was used. [f] Carried out at −5 °C. [g] No solvent was used. [h] Asterisk signifies the reactive site. [i] For effective monoacylation, 0.95 equiv of anhydride was used. [j] Diacetylated product was isolated in 10% yield.

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(17) A mixture of products was obtained under usual conditions (acid chloride/pyridine). For its effective acetylation mediated by TMSOTf, lower reaction temperature (−10 °C in ethyl acetate) was required (ref 5).

(18) Conventional procedure (acid chloride/pyridine) led to only pinacol rearrangement product.

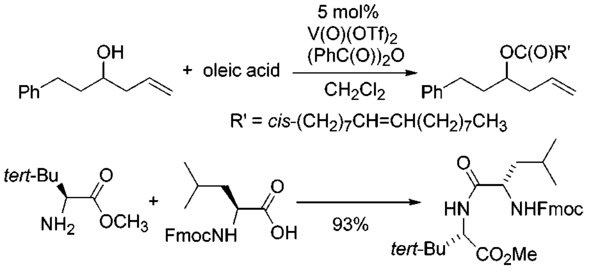
(19) (a) Aniline has failed to produce acetanilide in Cp*$_2$Sm(thf)$_2$-mediated acetylation. (b) Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, *61*, 3088.

α-amino esters (entries 2 and 3), *β*-hydroxy esters and ketones (entries 4 and 5). No trace of the glycosidic C−O cleavage was observed in the acetylation of diacetone-D-glucose (entry 7) at −5 °C, although 22% of acetylation at the primary hydroxy group with concomitant migration of the acetonide unit could not be prevented.[15]

The high catalytic efficacy of vanadyl triflate was further demonstrated in the peracetylations of polyhydroxyl molecules such as uridine, lactose, and cyclodextrin (21 OH groups!). In all cases, reactions went to completion in acetic acid or in neat acetic anhydride, albeit with longer reaction time (2.5−4 days).[20] By taking advantage of the differential reactivity between nucleophiles, we were able to carry out chemoselective acylation of 3-hydroxymethyl-2-naphthol. Its primary hydroxyl group was acylated with complete chemoselectivity and in ≥95% yields (entry 10).[21] Acetylation of *tert*-leucinol at the sterically hindered amino moiety was moderately selective. The corresponding *N*-acetylated product was furnished in 60% yield. Nevertheless, the analogous *N*-pivalation proceeded with complete selectivity (97%).[22]

Since benzoic anhydride[23] is the least reactive acyclic anhydride, one may carry out acylation directly with fatty acid in the presence of benzoic anhydride. By this protocol, the in-situ-generated mixed anhydride acts as the real acylation reagent.[7] As an example, 1-phenethyl-3-buten-1-ol was treated with a mixture of oleic acid and benzoic anhydride (1.1 equiv) in CH_2Cl_2 with 5 mol % of vanadyl triflate for 2 h. The resultant oleate was produced smoothly in 82% yield, Scheme 2. More importantly, the mixed-anhydride technique can be applied to dipeptide synthesis, as illustrated in the direct coupling of Fmoc-L-leucine and methyl L-*tert*-leucinate in 94% yield.

Scheme 2. Acylations with Mixed-Anhydride Approaches in Oleate and Dipeptide Syntheses



To support the mechanistic proposal in Scheme 1, vanadyl triflate was first heated in refluxing trifluoroacetic anhydride ($R' = CF_3$) for 12 h and then concentrated. The resultant adduct was treated with a stoichiometric amount of 2-phenylethanol ($R = Ph(CH_2)_2$) in CH_2Cl_2 for 3 h. The corresponding 2-phenethyl trifluoroacetate was isolated in 87% yield.[15]

In conclusion, we have unraveled the amphoteric catalytic behavior of vanadyl triflate in nucleophilic acyl substitutions with various anhydrides. It can be readily prepared and represents a new type of water-tolerant metal triflate.[24] The acylation protocol allows for chemoselective acylation and tolerates many structural and substrate variations. Mixed-anhydride technique allows for acylations with commercially unavailable anhydrides. Investigations toward solution and solid-state peptide syntheses by this catalytic process are underway.

Acknowledgment. We are grateful to the National Science Council of the Republic of China for generous support of this research. We thank reviewers and Professor Alois Fürstner for enlightening suggestions on this work.

Supporting Information Available: Representative experimental procedures, spectral data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Pivalations did not work properly because of the poor solubility of these substrates in pivalic anhydride.

(21) (a) Further stirring with excess of acetic and pivalic anhydride (10 equiv) for another 18 and 72 h (50 °C) furnished the corresponding diacetylated and dipivalated products in 87% and 89% yields, respectively. (b) In DMAP catalyzed acylation in pyridine, reversed chem-selectivity was observed in this case as a result of the more acidic nature of phenolic OH.

(22) By using the pivalic anhydride/pyridine protocol, the desired product was isolated in only 20% yield.

(23) It was found that amines, thiols, and primary and aromatic alcohols are amenable to benzoylations. Benzoylations of secondary alcohols are rather limited and require harsher reaction conditions. So far, the only workable substrate is as shown in entry 1, Table 3, which underwent benzoylation at 50 °C in 52% yield.

(24) For an elegant survey of other water-tolerant metal salts, see: Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.