A Conceptually New and Straightforward Method for the One-pot Transformation of Alcohols into Amines

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Abstract: A conceptually new amination method of alcohols has been developed using α-hydroxy esters as substrates and *N*-phenyl *bis*-trifluoromethanesulfonimide ($PhNTf_2$) as a test reagent. Playing two roles at once, $PhNTf_2$ activates the hydroxyl group as a highly reactive triflate intermediate and introduces the amino functionality through an in situ nucleophilic substitution by the anionic residue $PhTfN^-$. Two complementary procedures (methods A and B herein) have been developed, the latter permitting reaction of substrates with unstable alcoxides.

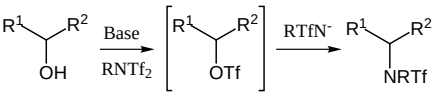
Key words: amination, amino esters, nucleophilic substitution, triflate, one-pot

α-Amino acids and their derivatives play a pivotal role in organic synthesis. The ease of preparation of α-hydroxy esters makes them ideal substrates for the preparation of α-amino esters.[1] Originally, such a functional group interconversion was achieved by means of the Mitsunobu reaction.[2] More recently, it has been demonstrated that a two-step procedure based on the activation of a hydroxyl followed by displacement by a nucleophilic nitrogen source was more widely applicable. In this case, the triflate group has been recognized as the most convenient leaving group by comparison with usual bromide, mesylate, sulfonate, both in terms of efficiency and chirality.[3]

Both methods, however, are not suitable for all circumstances.[4,5] Therefore, the development of new methodologies allowing for the direct transformation of an alcohol into an amine remains a subject of current interest.[6]

As part of an ongoing programme aimed at developing new methodologies in the chemistry of the trifluoromethanesulfonyl (triflyl) group, we envisaged that a process combining the advantages of both the Mitsunobu reaction (one step) and the triflate method (exceptional leaving group properties of OTf) would be of great benefit.

We have devised a conceptually new amination reaction whereby the same reagent would serve a dual function of triflating and aminating an alcohol in a single operation. By capitalizing on the routine use of *bis*-trifluoromethanesulfonimides (triflimides) $PhNTf_2$, *N*-pyridine *bis*-trifluoromethanesulfonimide ($PyNTf_2$) and *m*-chloro-*N*-pyridine *bis*-trifluoromethanesulfonimide (*m*-Cl-$PyNTf_2$) for trapping enolates to form vinyl triflates,[7,8] in conjunction with the good nucleophilic properties of triflamides $RNHTf$[9] and their anions,[10] we reasoned that triflimides of general formula $RNTf_2$ could met the criteria of our purpose. The first step of our planned reaction is proposed as follows: there is an initial addition of the alcoholate of the starting α-hydroxyester to a triflimide $RNTf_2$, which may provide a transient triflate along with a nucleophilic residue ^-NRTf. Subsequently, the latter may easily substitute the triflate group to give the expected amino ester (Scheme 1).



Scheme 1

Herein we wish to communicate our preliminary results establishing that the new concept exposed above can be accomplished, with the use of $PhNTf_2$ as a test reagent and α-hydroxy esters as substrates. To the best of our knowledge, the utilization of the crystalline, stable and commercially available $PhNTf_2$ for such a dual role of activating and aminating an hydroxyl group has not been previously reported.

The first part of this work was aimed at optimizing the conditions for the amination reaction.

Except for the commercially available methyl mandelate **1a** and ethyl lactate **3**, the α-hydroxy esters used in this study were readily prepared by conventional means (Scheme 2).[11,12]

We chose the crystalline methyl mandelate **1a** as our model substrate for reasons of ease of handling and availability. Bearing in mind that the elimination of TfH from triflamides (a class of compounds to which our desired amino esters belong) is a possible reaction,[10] NaH was preferred as the base over the usual metallic *bis*-trimethylsilylamidures (MHMDS, M = K, Na, Li) or lithium diisopropylamidure (LDA) or lithium isopropylcyclohexylamidure (LICA) because NaH does not generate a weak basic organic residue such as the others do. Following this logic, only a slight excess of NaH (1.2 equiv) was used. With the expectation that it would correctly solvate the anionic intermediates, THF was selected as the solvent. All the exploratory reactions were achieved on a 100

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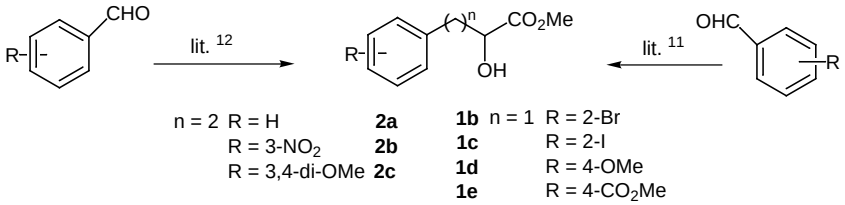


Scheme 2

mg scale. After exploring numerous sets of conditions, it was found that the isolated yield of amino ester **4a** could not exceed 40% (Scheme 3).[13] All preliminary attempts featured a rapid consumption of starting material (less than 5 min, TLC monitoring). GC/MS and ^{1}H NMR analyses on the crude mixtures revealed a partial recovery of both **1a** (5–50%) and triflimide $PhNTf_2$, as well as marginal production of both triflamide PhTfNH and imine **7a** plus other unidentified by-products. As judged from the ^{1}H NMR spectra, **7a** was present as a sole stereomer whose stereochemistry has not been determined at this time. The temperature proved, at least to a certain extent, to be an important factor, which permitted us to minimise the formation of the by-products without affecting the reaction rate (Scheme 3). Under optimal conditions (method A),[13] 80% of conversion was achieved and the imine was isolated in 15% yield.

From these results, it clearly appears that the amino ester **4a** formed was continuously undergoing a basic-driven elimination of TfH, thus leading to the imine **7a**. The recovery of amounts of both **1a** and PhTfNH in the medium suggests that the related anionic forms (alcoholate and $PhTfN^-$) were mainly responsible for this undesired process. As a result, we felt that introducing some differences in the electronic and steric environment surrounding the enolizable position in the benzylic series (type **1** substrates) may have a deep impact on the reaction profile. For instance, it was anticipated that substrates bearing an electron-donating substituent on the aromatic nucleus would decrease the rate of the deprotonation, and subsequently provide the amino esters in higher yields. Considering the steric demand of the bases mediating the elimination, it was also anticipated that more crowded substrates such as ortho substituted alcohols **1b** and **1c** would also prevent the imine formation.

Only the second scenario was proved as shown from the results summarized in Table 1. Under similar conditions as described above, the amino esters **4b**–**c** were indeed produced in decent yields from the suitably substituted substrates **1b**–**c** (entries 1–3), whereas the electron-rich alcohol **1d** gave the expected amine **4d** in only 29% yield along with the usual side-products. Apparently, electronic donation of a *para* methoxy group was not sufficient to prevent the side-reactions. In the two former cases, the starting material was totally consumed and the imines **7b**–**c** were only detected in trace amount. Scaling-up these successful reactions to 1 g did provide **4b** and **4c** in yields superior to those obtained from the test reactions. As expected, the diester **1e** led to **4e** also in poor yield, the imine **7e** plus other side-products being dominant (entry 4).

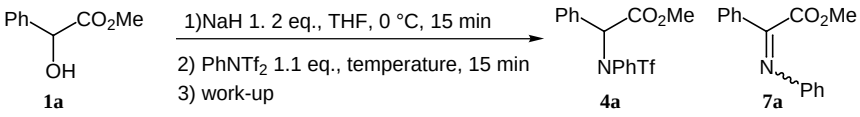
Apparently, only those mandelates having the *ortho* position congested proved synthetically useful in this reaction.

Table 1 Reaction of substituted Mandelates **1b**–**e** using Method A

Entry	α-Hydroxy Ester	Product (Yield %)[a]
1[b]	**1b**	**4b** (65)
2[b]	**1c**	**4c** (60)
3[b]	**1d**	**4d** (29)
4[b]	**1e**	**4e** (30)
5[c]	**1b**	**4b** (78)
6[c]	**1c**	**4c** (64)

[a] Isolated yields are given.
[b] Reaction performed on a 100 mg scale.
[c] Reaction performed on a 1 g scale.

Satisfied that competitive elimination was not a significant problem, we shifted our attention to type **2** substrates as well as to the unsubstituted ethyl lactate **3** with the expectation that imine formation should be electronically prevented. While **3** and methyl phenyl propionate **2a** did lead predominantly to the desired products **6** and **5a** in good yields (Table 2, entries 1, 2), the substituted analogues **2b**–**c** both failed to react as expected (entries 3, 4). During the deprotonation step of the nitro substrate **2b**, the color rapidly turned brown, indicating a decomposition of the alkoxide. This was supported by analyses on the crude (GC/MS and ^{1}H NMR) from which only $PhNTf_2$ could be detected. The same pattern featured on spectra of products



temperature			
	0 °C	35%	21%
	-20 °C	40%	15%
	-60 °C	42%	13%

Scheme 3

formed from the reaction of the electron-rich alcohol **2c** although in this case no significant visual change in the medium was observed.

Table 2 Reaction of Ethyl Lactate **3** and α-Hydroxy Esters **2a–c** under Method A

Entry	α-Hydroxy Ester	Product (Yield %)[a]
1	**3**	**6** (75)
2	**2a**	**5a** (71)
3	**2b**	**5b** (0)
4	**2c**	**5c** (0)

[a] Isolated yields are given.

An alternative method (method B) was then devised whereby the alkoxide formed would be immediately trapped by the triflimide. This could be made possible by premixing the substrate and triflimide and then adding the resulting THF solution to a suspension of NaH. When method B was applied to **2b**,**c**,[14] **5b**,**c** could now be secured in fair yields (Table 3, entries 1, 2). This procedure could also be successfully scaled-up to 1 g (entries 3, 4).

The latter results from substrates **2a–c** and **3** are extremely encouraging and predict the effectiveness of the reaction when simpler, less functionalized alcohols will be addressed.

Table 3 Reaction of α-Hydroxy Esters **2b**,**c** using Method B

Entry	α-Hydroxy Ester	Product (Yield %)[a]
1[b]	**2b**	**5b** (63)
2[b]	**2c**	**5a** (75)
3[c]	**2b**	**5b** (85)
4[c]	**2c**	**5c** (69)

[a] Isolated yields are given.
[b] Reaction performed on a 100 mg scale.
[c] Reaction performed on a 1 g scale.

In summary, we have accomplished the amination of α-hydroxy esters using for the first time the concept of derivatization and amination by a single reagent, employing the commercially available $PhNTf_2$ as a test reagent. Two complementary procedures (methods A and B) have been developed, the latter allowing conversion of substrates with unstable alcoholates. Further work aimed at expanding the synthetic potentiel of this reaction (base, substrate, triflimide), as well as revealing its mechanistic picture (SN_2 *vs.* SN_1) are being pursued in our laboratory and will be reported in due course.

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(13) **Typical Procedure (Method A)**: A tetrahydrofuran (1 mL) solution of methyl mandelate (100 mg, 0.6 mmol) was added under argon at 0 °C to a suspension of sodium hydride (29 mg, 60% in oil, 0.72 mmol) in tetrahydrofuran (1 mL). After stirring 15 min, this alkoxide solution was added dropwise at –20 °C to a tetrahydrofuran (1 mL) solution of triflimide (236 mg, 0.66 mmol). After 15 min, the solution was hydrolyzed with water (5 mL) and extracted with diethyl ether (3 × 5 mL). Combined organic layer was dried over magnesium sulfate and concentrated under vacuum to give the desired amine which was purified from side-products by flash-chromatography on a silica gel column (eluant: cyclohexane–ethyl acetate (9–1 to 7–3).
(14) **Typical Procedure for the Amination of 3-[3-Nitrophenyl]-2-hydroxy-methyl Propanoate (Method B)** A tetrahydrofuran (1 mL) solution of α-hydroxy ester (100 mg, 0.43 mmol) and triflimide (167 mg, 0.47 mmol) was added dropwise under argon at –20 °C to a suspension of NaH (20 mg, 60% in oil, 0.51 mmol) in tetrahydrofuran (1 mL). After 15 min the solution was hydrolyzed with water (5 mL) and extracted with diethyl ether (3 × 5 mL). Combined organic layer was dried over magnesium sulfate and concentrated under vacuum to give the desired amine which was purified by flash-chromatography on a silica gel column (eluant: cyclohexane–ethyl acetate (9–1 to 7–3).