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Tf_2O/Amide Adducts: Versatile Reagents for the Synthesis of Imidates and Amidines

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Abstract: The Vilsmeier reagents generated from tertiary and secondary aliphatic and aromatic amides and trifluoromethanesulfonic anhydride (Tf_2O) reacted with different nucleophiles (ROH, RSH, RNH_2) affording the relative iminium and amidinium salts. The former, stable at room temperature, were easily transformed into the corresponding esters or O-alkyl thioesters by treatment with OH^- or SH^-.

Vilsmeier-Haack reagents, obtained by reacting N,N-dimethylformamide with acyl chlorides, have been widely employed in organic synthesis as formylating agents for different substrates (aromatic compounds, alkenes, ketones, etc.)[1-4]. Formation of five- or six-membered rings was observed under the same conditions[2]. Moreover, Vilsmeier-Haack reagents were reported to react with alcohols to obtain acetates and formates[5-7]. However, in some cases, the reaction did not occur on account of the competitive formation of the relative chlorohydrocarbons. Formates and acetates were obtained in acceptable yields only when using phosgene or benzoyl chloride as reagents, long reaction times and, in some cases, low temperatures. More recently, trifluoromethanesulfonic anhydride (Tf_2O) has been used to activate dimethylformamide (DMF), producing an iminium salt (**1**) able to perform formylation also of the less reactive aromatic substrates[8].

In this paper we report that the iminium salts (**1**) derived from tertiary and secondary aliphatic and aromatic amides are versatile reagents which react with different nucleophiles (ROH, RSH, RNH_2) leading to new iminium salts (**2**) in good yields, subsequently converted into esters (**3**) and O-alkyl thioesters (**4**) by hydrolysis or thiolysis (Scheme 1).

N,N-dimethylformamide (DMF), and N,N-dimethylacetamide (DMA) gave good results with primary and secondary alcohols, benzyl alcohols, naphthols, thiols, thionaphthols and primary amines. A series of imidate ester triflates (**2a**), imidate thioester triflates (**2b**) and amidinium triflates (**2c**) were obtained, which, being stable at room temperature, could be isolated and characterized spectroscopically (NMR, IR and mass spectrometry) (Table 1). The very low nucleophilic character of the trifluoromethanesulfonate anion present in intermediates (**2**) prevented the occurrence of undesired side reactions[9-10].

Higher yields of (**2**) were obtained by adding a stoichiometric amount (10 mmol) of 2,6-di-*tert*-butylpyridine to the intermediates (**1**) before the addition of the nucleophile, in order to neutralise the triflic acid generated in the reaction.

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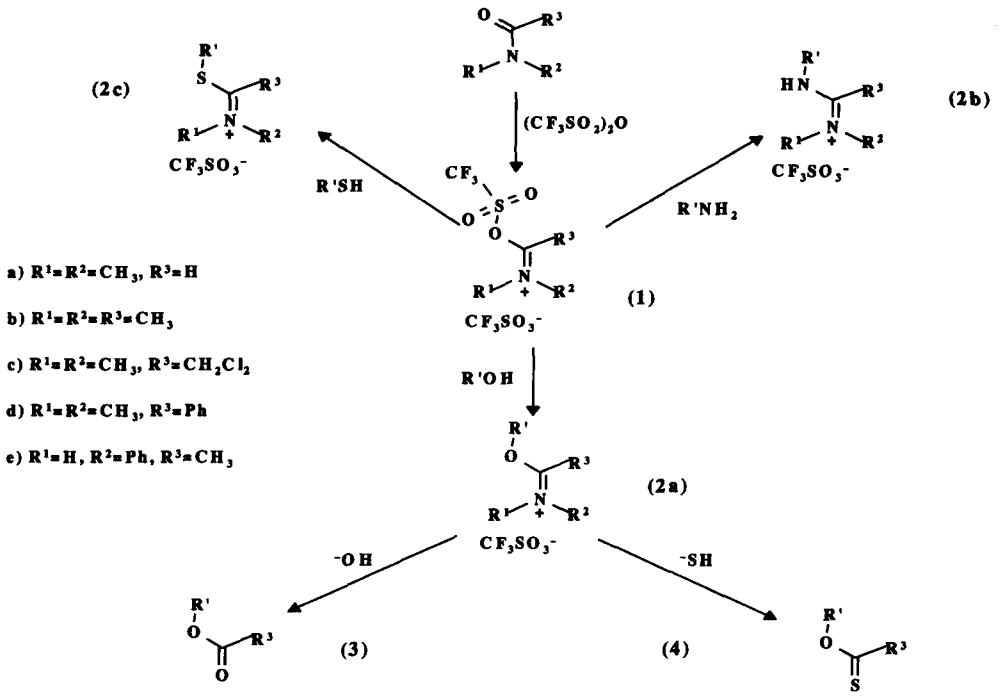


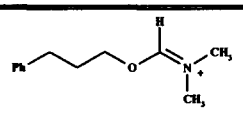
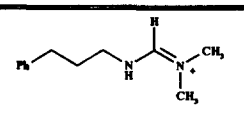
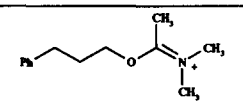
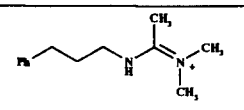
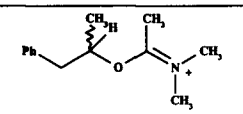
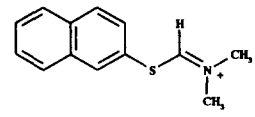
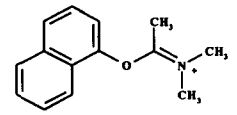
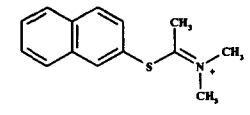
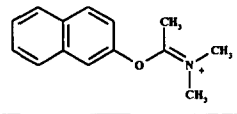
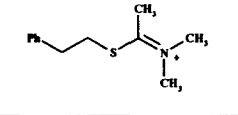
Scheme 1

Several studies were reported concerning the kinetics and the mechanism of hydrolysis of N,N–disubstituted imidate esters[10–14], suggesting that the yields of esters decrease as the pH increases. Actually, we observed a quantitative conversion to the esters when the hydrolysis of the imidate esters (**2a**) was performed in a biphasic solution (H_2O and CH_2Cl_2) at basic pH (7–8) in 30 minutes. Instead, the rate of the hydrolysis was very low at acidic pH. The overall synthesis of esters (**3**) and thioesters (**4**) could be performed as a one–pot reaction. The yields reported in Table 2 can be further optimized by carefully controlling the pH during the hydrolysis by using suitable buffers.

The reaction here reported is a simple and mild method to convert alcohols and thiols into the corresponding esters or O–alkyl thioesters via imidate triflates and can be extended to the synthesis of S–alkyl esters and S–alkyl thioesters via thioimidate triflates. Moreover, it allows a facile preparation of stable amidinium salts, which are powerful synthetic intermediates in organic synthesis.

General procedure. In a typical procedure, trifluoromethanesulfonic anhydride (Tf_2O, 10 mmol) was added dropwise to a stirred solution of the amide (10 mmol) in anhydrous CH_2Cl_2 at 0°C under nitrogen. The reaction was left under stirring for 30 minutes at room temperature, until a white precipitate of iminium trifluoromethanesulfonate (**1**) was formed. First, 2,6–di–*tert*–butylpyridine (10 mmol), then the nucleophile (either alcohol, amine or thiol) were added dropwise under vigorous stirring. The reaction was maintained for 30 minutes at room temperature until the precipitate disappeared. The organic phase was extracted with water, dried over Na_2SO_4, evaporated to a small volume and treated with Et_2O to obtain the imidate salts (**2**) as white precipitates. Amidinium salts were obtained as oils. All compounds were reliably characterized by NMR (^1H, ^{13}C) and IR spectroscopy, mass spectrometry and satisfactory elemental analysis (δ (C,H) 0.5%).

Table 1. Intermediates formed by reacting the Tf_2O/amide adducts with O-, S- and N-Nucleophiles.

Nucleophile	Amide	Intermediate (2)	Yield % [a]	Nucleophile	Amide	Intermediate (2)	Yield % [a]
3-Phenyl-1-propanol	DMF		60 %	3-Phenyl-propylamine	DMF		59%
3-Phenyl-1-propanol	DMA		72%	3-Phenyl-propylamine	DMA		57%
1-Phenyl-2-propanol	DMA		50%	Thio-2-naphthol	DMF		70%
α-Naphthol	DMA		54%	Thio-2-naphthol	DMA		60%
β-Naphthol	DMA		35%	2-Phenyl-ethanethiol	DMA		30%

a – Yields of isolated products.

Table 2. One-Pot Synthesis of Esters and O-Alkyl Thioesters.

Amide	Alcohol	Product (3) or (4)	Yields, % [a]
DMF	3-Phenyl-1-propanol	Formate	86%
DMF	Benzyl alcohol	Formate	72%
DMF	Cholesterol	Formate	73%
DMF	2-Phenyl-1-ethanol	Formate	78%
DMF	1-Phenyl-2-propanol	Formate	83%
DMF	2-Methyl-1-phenyl-2-propanol	Formate	20%
DMF	3-Phenyl-1-propanol	O-Alkyl thioformate	70%
DMA	3-Phenyl-1-propanol	Acetate	77%
DMA	1-Phenyl-2-propanol	Acetate	50%
DMA	1-Phenyl-2-ethanol	Acetate	62%
DMA	p-Nitrobenzyl alcohol	Acetate	68%
DMA	3-Phenyl-1-propanol	O-Alkyl thioacetate	55%
2-Chloro-DMA	3-Phenyl-1-propanol	2-Chloroacetate	30%
Dimethylbenzamide	3-Phenyl-1-propanol	Benzoate	35%
Acetanilide	3-Phenyl-1-propanol	Acetate	30%

a – Yields of isolated products.

One-pot hydrolysis of the iminium salts (**2a**) was alternatively performed by adding to the solution an aqueous solution of saturated $NaHCO_3$, or an equimolar amount of aqueous NaOH or NaSH 0.1M (pH 7-8). After 15 minutes the mixture was extracted twice with CH_2Cl_2 and the combined organic phases were dried and evaporated to small volume. Purification of esters and O-alkyl thioesters was performed by silica gel chromatography.

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