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Making Carbonyls of Amides Nucleophilic and Hydroxyls of Alcohols Electrophilic Mediated by SO_2F_2 for Synthesis of Esters from Amides

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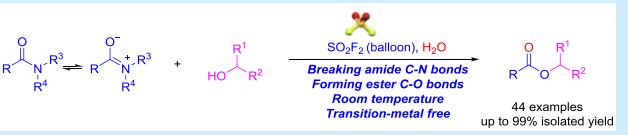
Supporting Information

ABSTRACT: We discovered that with the promotion of sulfuryl fluoride, the carbonyl groups of amides performed as nucleophiles while the hydroxyl groups of alcohols were activated to functionalize as electrophiles. This study displayed that the amide C−N bonds could be easily cleaved with delicate nucleophiles to form the ester C−O bonds at room temperature without using transition metals. The broad substrate scope and excellent functional group compatibility were proved with 44 examples in up to 99% yields.

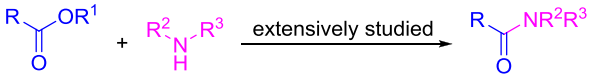


The discovery of new reactions for facile construction of various chemical bonds in molecules to achieve complexity lies at the center of organic chemistry.[1] Direct functionalization of sp^3 C−O bonds of aliphatic alcohols without excessive chemical transformations has been a long-lasting challenge for organic synthesis, because alcohols are usually unreactive as electrophiles and the hydroxyl (−OH) groups in alcoholic molecules cannot be easily replaced by nucleophilic reagents.[2] On the other hand, the electrophilic carbonyl groups are exceptionally reactive toward nucleophiles; therefore, scarce endeavors have been geared toward utilizing carbonyl groups as nucleophiles for chemical manipulations.[3]

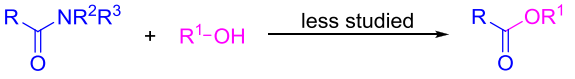
The amide motifs are ubiquitous in synthetic intermediates, natural products, proteins, and various other molecules of importance, which profoundly influence the biological and material properties of molecules.[4] To date, numerous methods for the formation of amide bonds have been extensively developed, which include the nucleophilic substitution of carboxylic esters with amines (Scheme 1a).[5] However, because of the high stability and rigidity of the amidic linkages, surmounting the high kinetic and thermodynamic barriers to harness amides as synthetic building blocks in C−N bond cleavage reactions has remained underdeveloped.[6] Recently, the transformation of amides to esters has gained significant attention (Scheme 1b)[7] since the seminal work by the Garg group.[8]

Scheme 1. Studies on the Formation of Amides and Esters

(a) nucleophilic acyl substitution of esters with amines:



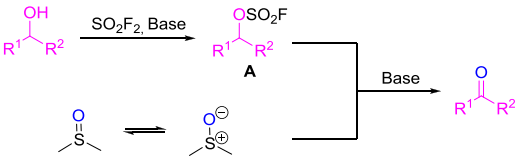
(b) nucleophilic acyl substitution of amides with alcohols:



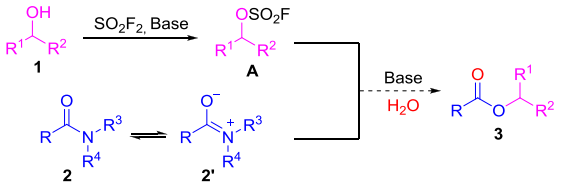
Our previous research revealed that under SO_2F_2 atmosphere,[9] the hydroxyl groups of alcohols were activated as leaving groups, and the oxygen anion tautomerized from sulfur−oxygen double bonds of DMSO served as a nucleophile to perform substitution reactions (Scheme 2a).[9m] We envision that oxygen anion tautomerized from carbon−oxygen double bonds of amides would also serve as nucleophiles to react with SO_2F_2-activated alcohols (Scheme 2b) in the consequence of breaking the amide C−N bonds with simultaneous formation of the ester C−O bonds. Herein, we report the exploration of amide carbonyls to functionalize as nucleophiles and SO_2F_2-

Scheme 2. Proposed Esterification of Alcohols Using Amides

(a) Our previous work on oxidation of alcohols using DMSO as oxidant and solvent:



(b) Proposed process on esterification of alcohols using amides as reactants and solvents:



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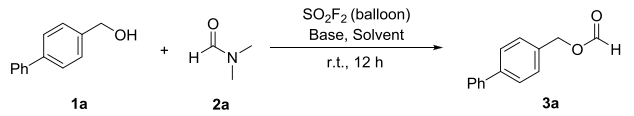
activated alcohols to perform as electrophiles for the synthesis of esters from amides.

Our investigation of the esterification feasibility commenced with testing of reacting 4-biphenylmethanol (**1a**) with DMF (**2a**) under sulfuryl fluoride (SO_2F_2) atmosphere. Accordingly, a large variety of conditions were screened, and some representative examples were collected in Table 1 (see the Supporting Information for details). Pleasingly, the desired product ester **3a** was achieved in 34% HPLC yield when the transformation proceeded with the promotion of widely used organic base DMAP (4-dimethylaminopyridine) at room temperature for 12 h (Table 1, entry 1). Encouraged by the initial success, the subsequent screening of various inorganic bases was conducted because of their salient advantages on the easy workup and purification compared with organic bases. Among the examined inorganic bases, Cs_2CO_3 was found to be the most suitable base promoting the esterification efficiently to provide the product **3a** in quantitative yield, although good results were also obtained by using Na_2CO_3, K_2CO_3, and KF (Table 1, entries 2–5). Because solvents can act in a static sense to change the energies of the reactants and products,[10] the influence of the solvents was also assessed, and the research results indicated that the use of a large excess of amide (DMF) was essential since performing reactions with 10 equiv of DMF in other solvents provided the desired ester **3a** in moderate yields (Table 1, entries 6 and 7). Further optimization revealed that 1.2-fold excess of Cs_2CO_3 appeared to be crucial, as reducing the loading of base to 1.0 equiv slightly affected the efficiency of the esterification process (Table 1, entries 5, 8, and 9). Elevating the concentration of the reaction from 0.13 to 0.2 M slightly decreased the yield of ester **3a** (Table 1, entry 8 vs entry 10). In accordance with our expectation, ester **3a** was observed at an undetectable level without the presence of base as a promoter (Table 1, entry 11), and the condition of entry 8 was eventually taken as an optimal one for the substrate scope exploration and functional group compatibility examination.

Table 1. Reaction Conditions Optimization[a]

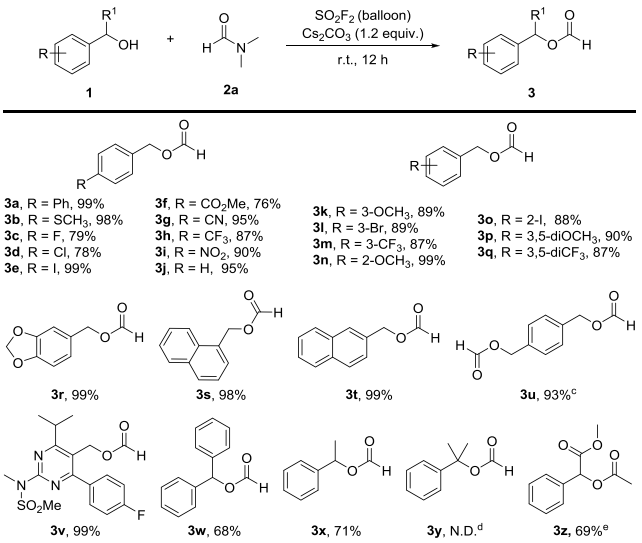


1a **2a** **3a**

entry	base (equiv)	solvent	conversion (**1a**, %)[b]	yield (**3a**, %)[b]
1	DMAP (2.0)	DMF (**2a**)	100	34
2	Na_2CO_3 (2.0)	DMF (**2a**)	76	75
3	K_2CO_3 (2.0)	DMF (**2a**)	84	83
4	KF (2.0)	DMF (**2a**)	92	91
5	Cs_2CO_3 (2.0)	DMF (**2a**)	100	99
6[c]	Cs_2CO_3 (2.0)	MeCN	97	54
7[c]	Cs_2CO_3 (2.0)	acetone	56	40
8	**Cs_2CO_3 (1.2)**	**DMF (2a)**	**100**	**99**
9	Cs_2CO_3 (1.0)	DMF (**2a**)	98	94
10[d]	Cs_2CO_3 (1.2)	DMF (**2a**)	93	90
11	none	DMF (**2a**)	0	0

[a]Reaction conditions: 4-biphenylmethanol (**1a**, 0.2 mmol), base, solvent (1.5 mL), SO_2F_2 (*Toxic by inhalation. Operate in fume hoods.*), r.t., 12 h. [b]The yields and conversions were determined by HPLC using **3a** or **1a** as the external standards, respectively (t_{3a} = 5.0 min, λ_{max} = 252 nm; t_{1a} = 3.4 min, λ_{max} = 289 nm; MeOH/H_2O = 75:25 (v/v)). [c]DMF (**2a**, 2.0 mmol, 10 equiv) was added to the reaction mixture. [d]DMF (**2a**, 0.2 M, 1.0 mL) was used as sole solvent.

Scheme 3. Esterification of Benzylic Alcohols[a,b]



[a]General conditions: benzylic alcohol (**1**, 2 mmol), Cs_2CO_3 (782 mg, 2.4 mmol), DMF (**2a**, 15 mL), and SO_2F_2 gas (balloon), r.t., 12 h. [b]Isolated yields. [c]Cs_2CO_3 (1.56 g, 4.8 mmol) and DMF (**2a**, 30 mL) were used. [d]N.D. = not detectable. [e]*N*,*N*-Dimethylacetamide (DMA) was used in the place of DMF.

Under the optimized reaction conditions, the generality of this SO_2F_2-mediated esterification was subsequently investigated using a large number of structurally and electronically diverse benzylic alcohols as summarized in Scheme 3. Not surprisingly, most of the alcohols reacted with DMF smoothly to deliver their corresponding esters (**3a**–**3v**) in good to excellent yields (76%–99%). Notably, the benzylic alcohols bearing electron-donating substituents on the aryl rings usually afforded the corresponding products in slightly higher yields than their electron-deficient counterparts (*e.g.*, **3b** compared to **3h** and **3p** compared to **3q**). Delightfully, the halogen motif and acetal skeleton on the substrates remained intact in a standard 2.0 mmol scale (**3c**–**3e**, **3l**, **3o**, and **3r**). The polycyclic benzylic alcohols (**1s** and **1t**) provided their esterified products (**3s** and **3t**) in nearly quantitative yields. For alcohol **1u** containing two hydroxyl groups, the efficiency of the desired transformation was not deteriorated when the stoichiometry of the reagents was adjusted accordingly to generate **3u** in 93% yield. Excitingly, the highly functionalized alcohol **1v**, a precursor to Rosuvastain (CrestorTM, a blockbuster HMG-CoA reductase inhibitor),[11] was also smoothly converted to its ester derivate **3v** in quantitative yield. Furthermore, secondary benzylic alcohols **1w** and **1x** were also smoothly esterified albeit in somewhat lower yields (**3w**, **3x** compared to **3j**), owing to the steric hindrance effect. The conversion of a tertiary benzylic alcohol **1y** to the corresponding ester **3y** was completely hampered. Switching the amide from DMF to DMA for reacting with secondary alcohol **1z** was also accomplished to provide the corresponding acetylated derivate **3z** in 69% yield.

Subsequent substrate examination revealed that the developed system was also suitable for preparation of esters from long-chain aliphatic alcohols in good to excellent yields (Scheme 4, **5a**–**5c**, 64%–96%). A slightly lower yield of ester

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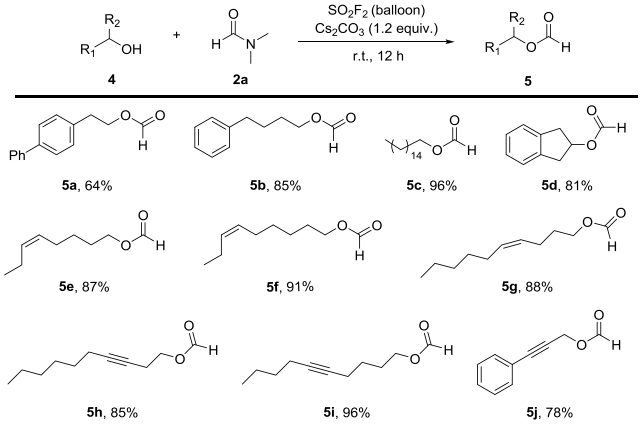
Scheme 4. Esterification of Aliphatic and Propargylic Alcohols[a,b]



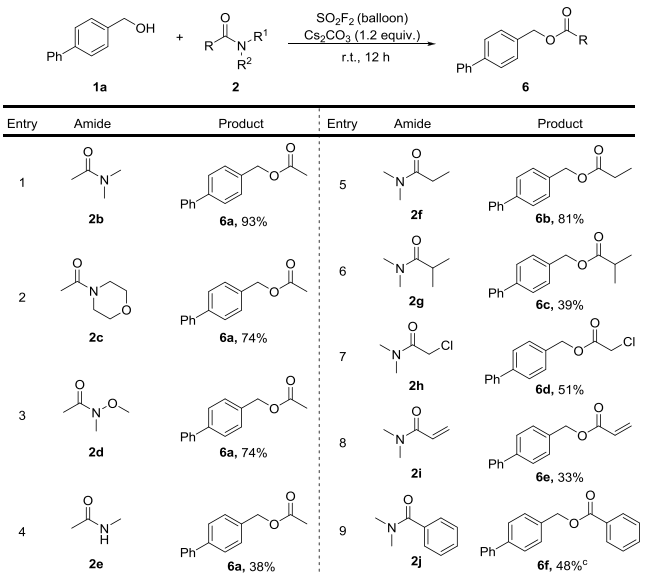
[a]General conditions: aliphatic or propargylic alcohol (**4**, 2 mmol), Cs_2CO_3 (782 mg, 2.4 mmol), DMF (**2a**, 15 mL), and SO_2F_2 gas (balloon), r.t., 12 h. [b]Isolated yields.

5d was observed for the secondary alcohol **4d** bearing some steric hindrance. Pleasingly, the long-chain alcoholic substrates possessing unsaturated moieties (**4e**−**4i**) were also smoothly converted to their corresponding ester products (**5e**−**5i**) without destroying the double or triple bond scaffolds. More importantly, the *Z*-configuration of C═C bonds of alcohols **4e**−**4g** remained the same after being converted to their corresponding esters **5e**−**5g**. Furthermore, propargylic alcohol **4j** which is fragile to various reaction conditions was also smoothly transformed to the corresponding ester **5j** under this condition.

As depicted in Scheme 5, evaluation of various liquid amides (**2b**−**2i**) was further conducted to demonstrate good functional group compatibility of this esterification method. Delightfully, acetyl amides (**2b**, **2c**, and **2d**) functionalized with different substituents on the nitrogen-atom center were all transformed to [1,1′-biphenyl]-4-ylmethyl acetate **6a** in good to excellent yields (74−93%) after reacting with 4-biphenylmethanol **1a**. It is worth noting that the secondary amide **2e** was also converted to acetate **6a** although a lower yield was obtained compared to its tertiary amide counterparts (**2b**, **2c**, and **2d**). However, the primary amides were not suitable for synthesizing their corresponding esters using this developed method. In addition, the examination of the carbonyl part of amides (**2f**−**2i**) was also performed under optimized reaction conditions, and their corresponding products (**6b**−**6e**) were subsequently furnished in moderate to good yields (33−81%). Remarkably, the melted solid amide **2j** also reacted with 4-biphenylmethanol **1a** at 50 °C to afford the desired ester **6f** in 48% yield.

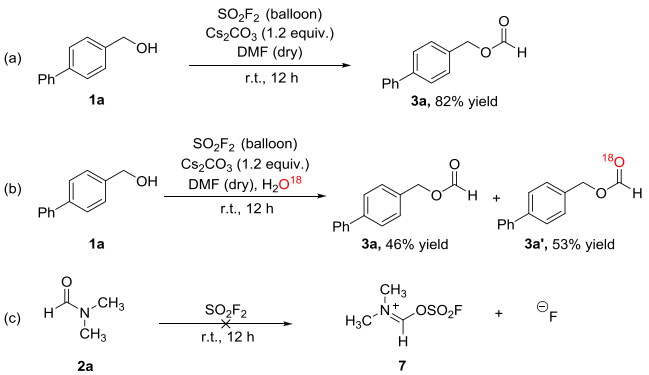
As illustrated in Scheme 6, in order to gain more insight into the mechanism of this SO_2F_2-mediated esters formation

Scheme 5. Substrate Scope Examination with Different Amides[a,b]



[a]General conditions: 4-biphenylmethanol (**1a**, 2 mmol), Cs_2CO_3 (782 mg, 2.4 mmol), amide (**2**, 15 mL), and SO_2F_2 gas (balloon), r.t., 12 h. [b]Isolated yields. [c]The reaction was performed at 50 °C using solid amide (**2j**, 10 g).

Scheme 6. Mechanism Studies



process, several investigations were conducted accordingly. Performing the reaction of alcohol **1a** in dry DMF resulted in the formation of product **3a** in 82% yield (Scheme 6a). The use of ^{18}O-labeled water provided ester in nearly quantitative yield (99%), in which, 53% was the ^{18}O-labeled ester product **3a′**, revealing that a trace amount of H_2O also played an important role in this transformation to facilitate the formation of ester (Scheme 6b). Bubbling the SO_2F_2 into DMF at room temperature for 12 h did not form the intermediate **7**, which excluded the generation of the Vilsmeier-type reagent[12] during this ester formation process (Scheme 6c).

Based on the results of mechanism investigations and previous studies,[9g,j,m,p] a plausible mechanism of this SO_2F_2-mediated coupling of alcohols with amides for generation of esters was proposed in Scheme 7. The hydroxyl of alcohol **1** initially proceeded a nucleophilic substitution with sulfuryl fluoride (SO_2F_2) in the presence of base to afford the fluorosulfate **A** together with releasing of the fluoride ion to serve as an additional base[13] to participate in the following chemical transformations. The iminium **2′** tautomerized from amide **2** functionalized as an oxygen nucleophile to undergo a S_N2 type of nucleophilic displacement with fluorosulfate **A** to generate the iminium intermediate **B**. In wet solvent, the addition of water to iminium **B** provided the corresponding adduct **C**, which was subsequently cleaved to ester **3** with the promotion of base (**Path 1**); alternatively, in dry solvent, this reaction could proceed through **Path 2**, in which the OSO_2F anion underwent a nucleophilic addition to iminium **B** to form

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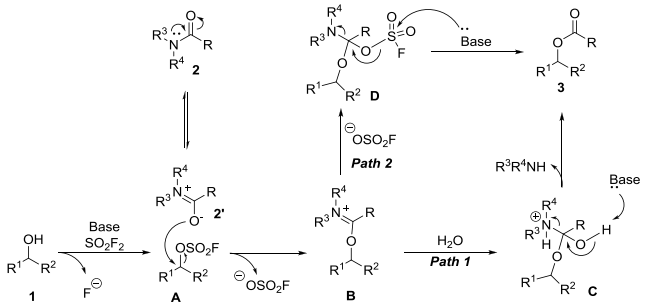
Scheme 7. Proposed Reaction Pathway



the corresponding intermediate **D**, whose S−O bond was further cleaved under basic conditions to generate the corresponding ester **3**.

In summary, we have discovered an unusual reaction, in which, with the assistance of SO_2F_2, the carbonyls of amides performed as nucleophiles while the hydroxyl groups of alcohols were activated to play as electrophiles to break the amide C−N bonds and form the ester C−O bonds. The versatility of this reaction feathered with wide substrate scope (44 examples) and excellent functional group compatibility provides a new portal to esters construction from readily available alcohols and amides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03274.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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