s-Triazene based fluorous coupling reagent for direct amide synthesis

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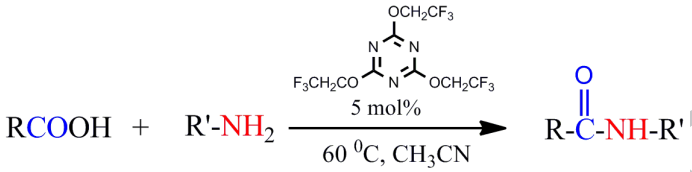

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s-Triazene based fluorous coupling reagent for direct amide synthesis

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ABSTRACT

A new simple and efficient fluorous coupling reagent TriTFET (2,4,6-Tris-(2,2,2-trifluoro-ethoxy)-[1,3,5] triazene) has been designed and synthesized for the direct amidation. The use of 5 mol % of TriTFET is good for the amide synthesis from carboxylic acids with amines in moderate to excellent yields (72-96 %).

Introduction

A simple and elegant approach for amide bond formation is often overlooked as a contemporary challenge in organic chemistry because of the widespread occurrence of amide bond in drugs, biomacromolecules, natural and synthetic polymers.[1-2] Amide bonds are more common in wide array of clinical drugs, for example; Bupivacaine, Mepivacaine, Lidocaine and Paracetamol (Figure 1). High polarity, stability and conformational flexibility allow versatile usage of amide bond for many applications.

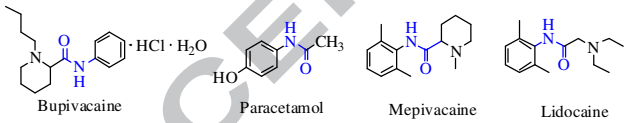

Figure 1. Amide linkage containing clinical drugs

Amide bond formation can occur *via* variety of chemical methods as well as enzymatic methods.[3] Direct approaches, metal-based catalytic approaches and use of suitable coupling reagents forms the bulk of reported procedures.[4-5] Further, for coupling between carboxylic acids and amines organocatalytic conditions have also been used in the presence of functionalized arylboronic acids and triphenylphosphines.[6] In addition, various acylating reagents such as thionyl chlorides, or coupling reagents such as 1-hydroxybenzotriazole (HOBt)[7a], 1, 1-carbonyldiimidazole (CDI)[7b], Uronium,[7c] and Phosphonium salts,[7d] triazene based micelles[7e] and thymine hydrochloride[7f] are generally utilized for activation of carboxylic acid in amide bond formation (Figure 2a-c).

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All the reported methods have some limitations, such as long reaction time, limited substance scope, modest yields, expensive coupling reagents and cumbersome work-up procedures.[8] Literature survey reveals that *s*-triazene based micelles has been widely used as powerful catalysts for many coupling reactions.[7e, 7f, 9] It is also used for amide coupling reactions between acids and amines. However, under similar conditions, *s*-triazine and long alkyl chain acid did not form micelles, hence no amide bond formation. For example; octanoate does not form micelles with *s*-triazine based reagent, therefore no amide bond formation with long chain acids. Thus, simple, efficient and economic approach for amide bond formation is still need in modern organic chemistry.

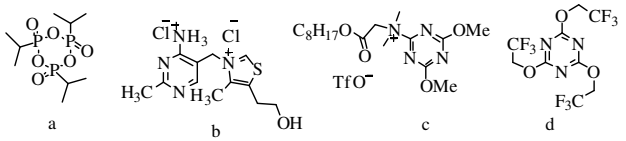

Figure 2. Amide coupling reagents (a) phosphorous containing reagent (b) VB catalyst (c) s-triazene base miceller reagent (d) TriTFET

Recently, we have reported a variety of effective catalytic systems for the synthesis of biological active molecule.[10] In this context, we further designed a new, stable fluorous coupling reagent TriTFET (Figure 2d). In this work TriTFET was utilized as a new coupling reagent for direct amidation from a large array of amines and carboxylic acids in acetonitrile under mild conditions and in lesser time. The coupling reagent was easily synthesized using commercially available *s*-triazene and trifluoroethanol in single step. Authenticity of TriTFET was

confirmed by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy (See supporting info).

Initially, we optimized the favorable reaction conditions, such as best reaction solvent system, temperature and requisite amide coupling reagent for better results. To optimize the reaction conditions for the synthesis of amide bond, we conducted test reactions using phenylacetic acid and benzyl amine in different reaction conditions (Table 1). We selected three types of solvents viz; green solvent (ethanol), non polar solvent (toluene) and polar solvent ($CHCl_3$, DMF, DMSO, ACN). When we attempted the reaction of acid with amine in presence of 5 mol % of catalyst in ethanol at 80 °C yielded 30% of the desired product in 4 hours (Table 1, entry 2). Subsequently, we carried out the above reaction in non-polar solvent (toluene) at 90 °C gave 40% of product after 4 hours (Table 1, entry 3). Reaction of phenylacetic acid and benzyl amine in $CHCl_3$ at 60 °C gave trace amount of the desired product. Among polar solvents, we first selected acetonitrile due to ease of work up procedure. Interestingly, reaction of phenylacetic acid and benzyl amine in the presence of 5 mol % of TriTFET in acetonitrile at 60 °C gave 95 % of product after 2 hours (Table 1, entry 5) thus highlighting the role of TriTFET as a coupling reagent. Further studies in other polar solvents such as (1,4-dioxane, DMF and DMSO) revealed that the reactions were sluggish giving poor yields (Table 1, entries 4,6,7). Therefore, we selected acetonitrile as solvent choice for reaction due to lower boiling points, easy work up and high yield of product.

Scheme 1. Synthesis of amide 2a using phenylacetic acid and benzyl amine

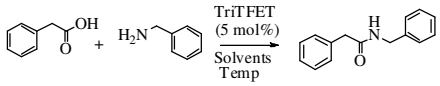

Table 1. Optimization of the reaction conditions[a] using different solvents

S. No.	Solvent	Temp (^{0}C)	Time (h)	Yield[b] (%)
1	$CHCl_3$	60	4	Trace
2	Ethanol	80	4	30
3	PhMe	90	6	40
4	1,4-Dioxane	90	8	65
5	**ACN**	**60**	**2**	**95**
6	DMF	110	8	85
7	DMSO	120	8	75

[a]Reaction conditions: Compound 2 (1 mmol), benzylamine (1 mmol), coupling reagent 5 mol %. [b]Isolated yields. Optimized reaction condition is shown in bold.

The next step was the optimization of coupling reagent loading for achieving high yield of amide synthesis. We carried out reaction with 1, 2, 5, 10, 15 & 20 mol % of catalyst. It is evident from the Table 2 that increase of calayst loading from 1 to 5 mole % result in increase in the yield of the desired product (Table 2, entries 2-4). Further increase of calatyst loading from 5 mol % to 20 mole % leads to decrease in the yield of final product from 90 % to 50 %. In fact the observation reveals that on increasing the amount of catalyst from 10 mol% to 20 mol%, the reaction mixture becomes cloudy and sticky mass formed instantly, thus it is impossible to stir the reaction for longer time consequently incomplete synthesis provides lesser yield (Table 2, entries 5-7). It means that 5 mol % of TriTFET is optimum amount for catalytic activity in amide synthesis. (Table 2, entry 4).

Table 2. Optimization of the reaction conditions[a] using different amount of reagent loadings in acetonitrile

S.No.	Mol% of TriTFET	Yield (%)
1	--------	NR
2	1	30
3	2	50
4	**5**	**95**
5	10	80
6	15	60
7	20	50

[a]Reaction conditions: Compound 2 (1 mmol), benzyl amine (1mmol), coupling reagent 5 mol %. [b]Isolated yields. Optimized reaction condition is in bold.

Moreover, we also compared the feasibility of amide synthesis with previously known methods which are summarized in Table 3. Most of the reported methods worked at higher temperature or longer reaction time compared to TriTFET catalyzed method. In entry 1 (Table 3), amidation proceeded without any catalyst but it occurs at high temperature and longer reaction time. Other catalysts mentioned in the Table 3 require high temperature, longer reaction time, and gave moderate yields (Table 4, entries 1-8). Interestingly, *s*-triazine based catalyst works at low temperature, shorter reaction time (Table 3, entry 7). But it suffers from cumbersome synthesis of catalyst. CAL-B also works at low temperature and longer reaction time and gave moderate to good yields (Table 3, entry 8). On the other hand, in this work synthesis of TriTFET catalyst is more economical. It requires low temperature, shorter reaction time, and moderate to excellent yields. (Table 3, entry 7). On comparison, it appears that TriTFET is better than existing catalysts.

Table 3.

Comparative overview of the present method with little previously known methods

S. No.	Catalyst	Temp (°C)	Time (h)	Yield (%)	Ref.
1	Without catalyst	110	22	90	5b
2	Nano-sulfated TiO_2	115	6-12 h	70-98	11b
3	Boronic acid	100	16-24	44-73	6a
4	$ZrCl_4$	110	4-24	70-94	8
5	Zeolite-Hy	120	5-24	40-99	8
6	Phosphorous catalyzed	175	7h	80	8
7	Triazene based micceller catalyst	25	1-4	16-88	8
8	CAL-B	40	20-30	60-90	11a
9	**TriTFET**	**60**	**2-3**	**95**	**Current study**

Thus, using optimized reacton conditions *i.e.* 5 mol % of catalyst, in acetonitrile at 60 °C, we then successfully synthesized a variety of substituted amides using different carboxylic acids and amine derivatives (Scheme 2). The results are summarized in Table 4. In all the studied examples, the aromatic and aliphatic amines (Primary and secondary) could react smoothly to give the corresponding amide derivatives in good to excellent yields (76 to 95%). However, a synthesis of dipeptide between suitably protected α-amino acids under similar reaction conditions were unsuccessful.

Scheme 2. Synthesis of amide derivatives using acids and amines

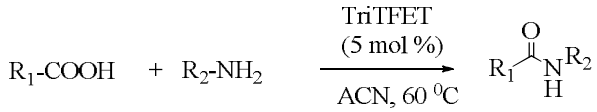

Table 4. Synthesis of amide derivatives from carboxylic acids and amines using TriTFET

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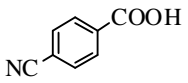
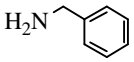
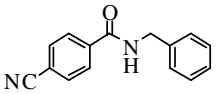
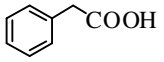
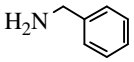
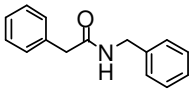
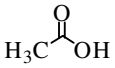
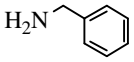
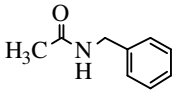
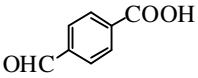
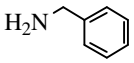
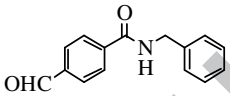
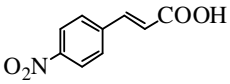
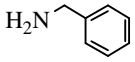
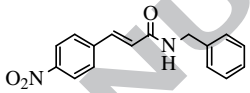
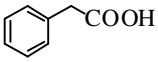
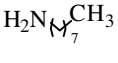
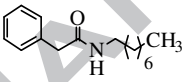
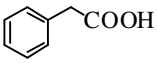
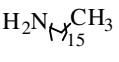
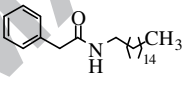
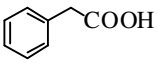
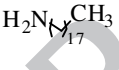
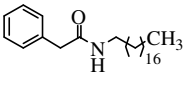
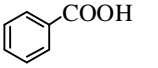
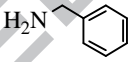
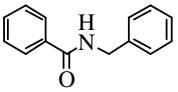
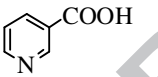
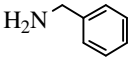
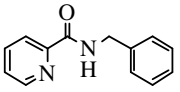
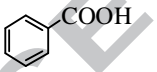
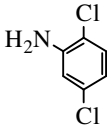
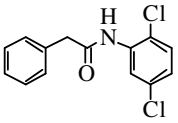
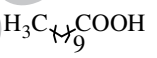
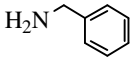
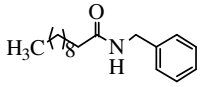
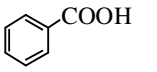
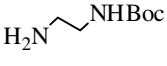
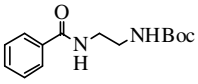
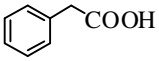
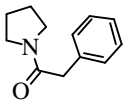
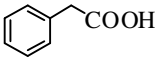
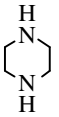
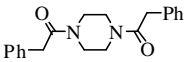
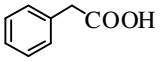
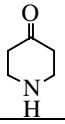
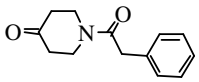
1				1a	2	92
2				2a	2	95
3				3a	2	72
4				4a	3	90
5				5a	4	86
6				6a	2	95
7				7a	2	94
8				8a	2	82
9				9a	2	88
10				10a	3	83
11				11a	3.5	93
12				12a	4	81
13				13a	4	76
14				15a	2.5	86
15				16a	2	84

16				17a	2.5	84
17				18a	3	88
18				19a	3.5	80

[a]Reaction conditions 1mmol of acids and 1mmol of amines in the acetonitrile solvent using 5 mol % of TriTFET .[b]Isolated yield.

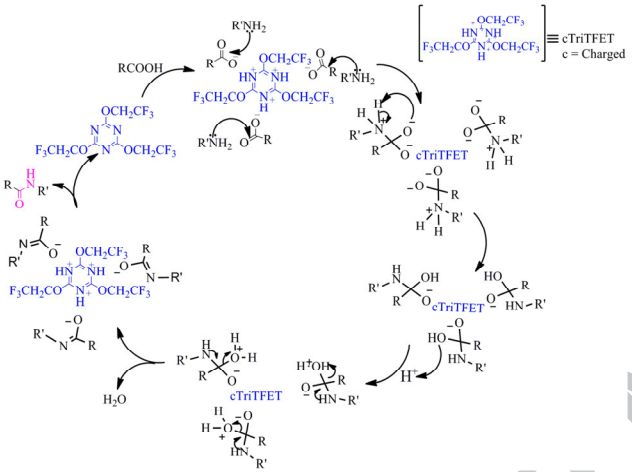


Figure 3. Activation of acids using TriTFET

On the basis of the represented results, a mechanism is proposed for the direct amidation. Acids first activated with TriTFET to give intermediate stages. Finally, amine combines with an acid molecule to produce corresponding amide by regenerating the TriTFET as a catalytically active species.

In conclusion, we successfully synthesized a variety of functional amides through direct amidation of acids and amines (primary and secondary) in moderate to excellent yield (72-95%) by a new fluorous reagent under mild conditions. The scope of this methodology has been demonstrated in (i) primary and secondary aliphatic amines (ii) aromatic amines with carboxylic acids (aliphatic and aromatic). Moreover, it is also useful for the synthesis of amide bond between long alkyl chain acid and amine. Considering the economic attractiveness and operational simplicity, we strongly believe that the procedure is of important synthetic value for access to a variety of functionalized amides.

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Supplementary Material

Experimental protocols and copies of ^{1}H and ^{13}C NMR spectra of all compounds are provided.