Harnessing the catalytic behaviour of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP): An expeditious synthesis of thioesters

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Graphical Abstract

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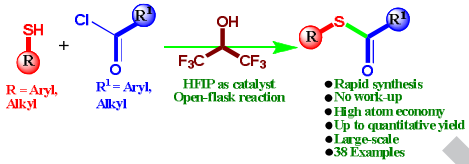

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Harnessing the catalytic behaviour of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP): An expeditious synthesis of thioesters

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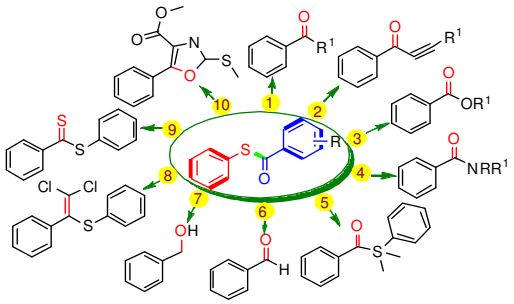
ABSTRACT

A novel, efficient, metal-, base- and acid-free straightforward protocol has been developed for the construction of useful thioesters. The immense catalytic potential of HFIP for promoting the thiocarbonyaltion of acyl halides and thiols is disclosed. HFIP was recovered with ease and reused for further reactions without any loss of reactivity. Both aryl and alkyl thiols bearing electron-donating and electron-withdrawing groups as well as aryl- and alkyl acyl halides worked well in this reaction. Inexpensive precursors, short reaction time, obviating workup, high atom economy, and gram-scale preparation are the significant features of the developed eco-friendly route for S-carbonylation of thiols.

As a category of activated carboxylic acid derivatives, the emergence of thioesters is a gift to synthetic chemist due to its acyl donor ability in organic syntheis and chemical biology.[1] Not only do they play important roles in various biological processes,[2] but they are highly desirable synthetic target for the construction of various natural products.[3] Moreover, substitution of sulfur-containing leaving group with a variety of nucleophiles can be achieved under relatively mild reaction conditions. Magnificent applications of thioester in organic synthesis are illustrated in Scheme 1. Palladium based catalytic system has been developed by Fukuyama and co-workers to facilitate the chemoselective synthesis of ketones by employing thioesters.[4] A variety of thioesters have been reported for the synthesis of acylsilanes,[5] acetylene ketones,[6] and amides.[7] In addition, the synthesis of aldehydes or alcohols in different experimental conditions from the carboxylic acid derivatives has been highlighted.[8] Sekiya and Laweson reported the successful replacement of oxygen atom of thioester by sulfur or CCl_2 group.[9] The benzothiolate product was also implemented for the excellent synthesis of sulfur-containing heterocyclic compounds. Furthermore, it is possible to synthesize 2-methylthio-1,3-oxazoles from both alkyl and aryl thioesters employing N-(ethoxycarbonylmethyl)-iminodithiocarbonate.[10]

Thiocarbonylation between thiols, acyl halides and acetic anhydride are clean and straightforward processes to construct the variety of thioesters. The S-carbonylation of thiols is commonly carried out by using acid chlorides or acid anhydrides in the presence of pyridine or triethylamine along with 4-(dimethylamino)pyridine[11] or Bu_3P.[12]



Scheme 1 Examples of application of thiolates as building blocks in organic synthesis

A wide range of Lewis acid catalysts are engaged for this purpose, such as $MgBr_2$,[13] $LiClO_4$,[14] $Sc(OTf)_2$,[15] $CoCl_2$,[16] $Sc(NTf_2)_3$,[17] $Bi(OTf)_3$,[18] TMSOTf,[19] $Cu(OTf)_2$,[20] $InCl_3$,[21]

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hydrotalcite,[22] tris(pentafluorophenyl)borane,[23] and heteropoly acids.[24] On the other hand, ruthenium(III) chloride has also been recognized for convenient synthesis of thioacetates in the presence of ionic liquids.[25] The use of CsF–celite and silica gel provide alternative protocol to afford the thioesters.[26] Albeit these are all certainly remarkable processes, the major concerns are the necessity of expensive metals and the toxicity associated with them, solvents, elevated temperature, long reaction time, special care for moisture/air sensitive reagents, use of non-green solvents and carcinogenic promoters. In view of the above limitations, there is a great desire of rapid, versatile, environmentally friendly, non-corrosive and reusable activator for the preparation of thioesters under mild reaction conditions.

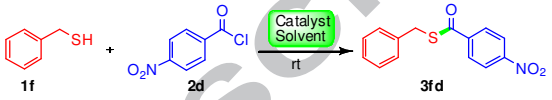
Polyfluorinated alcohols exhibit unique properties in various synthetic schemes.[27] 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) have emerged as remarkable solvents in the modern organic synthesis.[28] HFIP is flourished with intriguing set of properties, including low nucleophilicity, mild acidity, strong hydrogen bond donor ability, high ionizing power and ability to stabilize the cationic species.[29]

To date, several literature reports demonstrated that the HFIP has been used as a solvent, a promoter as well as an additive in numerous synthetic protocols.[30] However, the direct use of HFIP as a catalyst rather than additive or solvent in modern synthetic methodology is still surprisingly remained a tempting research field. Herein, we describe our advancement in HFIP chemistry and highly efficient, metal-free, base-free as well as acid-free expeditious protocol for the synthesis of thioesters is acknowledged.

Given the importance to thioesters and wide utility of HFIP, we envisaged that combining the catalytic as well as solvent effects of this polyfluorinated alcohol could facilitate the reaction between thiols and acyl halides. The direct thiocarbonylation of benzenemethanethiol (**1f**) and 4-nitrobenzoyl chloride (**2d**) was chosen as a model reaction to determine the optimal reaction conditions. Thus readily available and inexpensive fluorinated alcohol HFIP was added to a mixture of 4-nitrobenzoyl chloride and benzenemethanethiol. To our delight, the reaction afforded the thioester **3fd** in >99% yield within seconds at room temperature (Table 1, entry 1). Changing the loading of fluoroalcohol had virtually no effect on the yield of thioester in model reaction (entries 2 and 3). Excellent results were obtained when HFIP was used as an additive in CH_2Cl_2 where the addition of 10, 30, or 50 mol% of HFIP furnished the good amount of product (entries 4–6), although a qualitative decrease in rate was observed. Similar experiments were carried out using strong hydrogen-bond accepting solvents such as CH_3CN and THF, which had a deleterious effect in the thiocarbonyltion reaction[31] (entries 7 and 8). The lower amount of 4-nitrobenzoyl chloride surprisingly diminished the yield of the product (entry 9). TFE did not work well for C–S bond formation and **3fd** was obtained in modest yield in 5 h (entry 10). The reaction proceeded slowly by employing *i*-PrOH, the aliphatic analogue of HFIP, possessing hydrogen bonding properties and product **3fd** was obtained in 20% yield after long reaction time and the starting materials **2d** and **1f** were recovered (entry 11). When we used toluene as solvent for the thioesterification, a complex mixture was obtained in 12 h and no signal was observed in ^1H or ^{13}C NMR spectrum corresponding to product(s) from toluene or thiol **1f** (entry 12). This reaction failed to produce the corresponding product in the absence of HFIP, signifying the role of fluorinated alcohol in direct synthesis of thioester under mild conditions (entry 13).

With the emergence of several advancements in the dimension of HFIP chemistry,[32] we were delighted to demonstrate the exclusive tuning of HFIP with benzenemethanethiol (**1f**) and 4-nitrobenzoyl chloride (**2d**) that allowed optimum conditions for the direct and rapid

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Solvent (mL)	Time	Yield[b] (%)
1	HFIP (30)	–	<1 min	>99
2	HFIP (20)	–	<1 min	>99
3	**HFIP (10)**	**–**	**<1 min**	**>99**
4	HFIP (10)	CH_2Cl_2 (0.5)	2 h	90
5	HFIP (30)	CH_2Cl_2 (0.5)	2 h	92
6	HFIP (50)	CH_2Cl_2 (0.5)	2 h	98
7	HFIP (50)	CH_3CN (0.5)	6 h	85
8	HFIP (50)	THF (0.5)	6 h	31
9[c]	HFIP (10)	–	2 h	73
10	–	TFE (10)	5 h	34
11	–	*i*-PrOH (10)	26 h	20
12	–	Toluene (5)	12 h	nd
13	Neat	–	12 h	nd

The optimized condition is indicated in bold font.

[a]Conditions: **1f** (0.5 mmol) **2d** (0.6 mmol), HFIP catalyst stirred at rt. nd = not determined.

[b]Yield of isolated product.

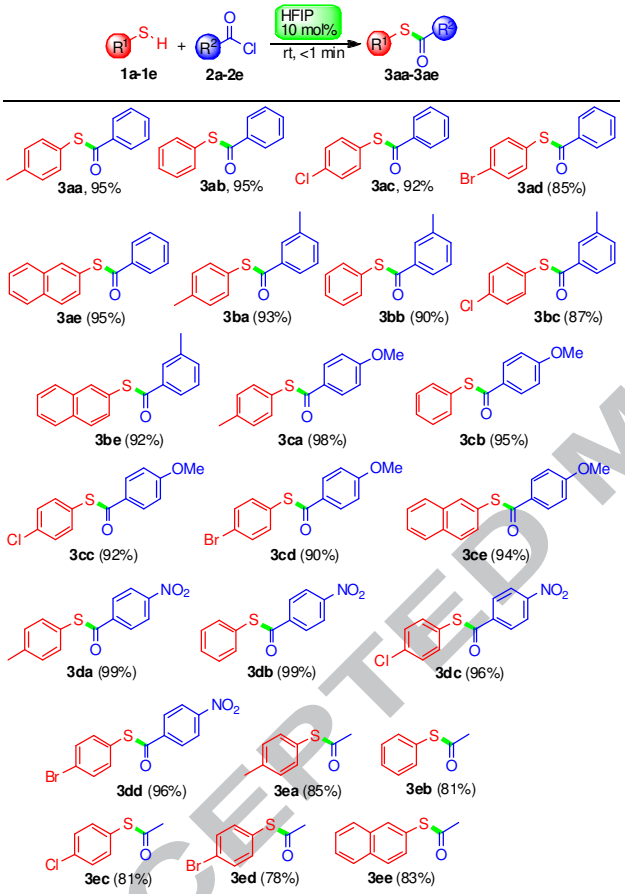
[c]0.4 mmol of **2d** was used.

synthesis of thioester **3fd**. It is of interest to note that HFIP played a dramatic role in the model scheme as a catalyst and not as a solvent. Presumably, the electrophilic activation of acyl halide contributed by the catalytic dynamism of HFIP facilitates the carbonylation of thiols. The whole reaction procedure was pleasant and no work-up was required for the rapid generation of thiolates in a high atom economical fashion.

Once the optimal conditions (Table 1, entry 3) was established and identified the catalytic behavior of hexafluoroisopropanol, the scope of this HFIP-catalyzed thioesterification reaction was probed to a range of substrates. With the optimized conditions in hand, different aryl thiols **1a**–**1e** were evaluated for direct thiocarbonylation reactions onto parent benzoyl chloride (**2a**). Delightedly, aryl thiol **1a** having electron-donating group at position 4 and thiophenol **1b** were able to react with benzoyl chloride to give the corresponding thioesters **3aa** and **3ab** in excellent yields. Other aryl thiols **1c** and **1d** bearing electron-withdrawing halo groups at position 4 of the aromatic ring, when tested for this simple protocol, provided

thiocarbonylated products **3ac** and **3ad** in high yields. Similarly, the reaction of bulky substrate 2-naphthalenethiol also gave the corresponding product **3ae** in excellent yield. Encouraged by these results, benzoyl chlorides **2b** and **2c** bearing electron-donating groups were next investigated to check the efficiency of HFIP. Thus thioester products **3ba**, **3bb**, **3bc**, **3be** and **3ca**–**3ce** were obtained in high to excellent yields. Under these optimal conditions, 4-NO_2 benzoyl chloride (**2d**) led to the formation of thioesters **3da**–**3dd** in excellent to quantitative yields. Aryl alkyl thioesters **3ea**–**3ee** were isolated in 78–85% yields from the ethanoyl chloride and a variety of thiophenols.

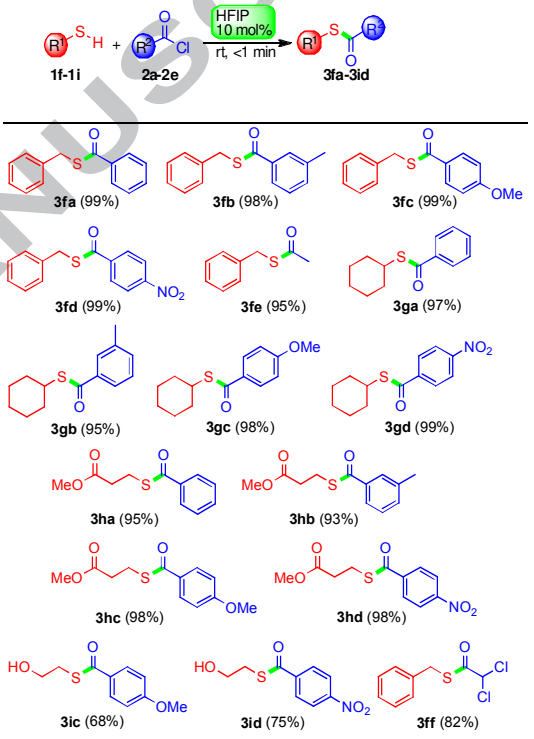
Table 2 HFIP–Catalyzed thioesterification using aryl thiols[a]



[a]Reaction conditions: Arylthiol (0.5 mmol), acyl halide (0.6 mmol), HFIP (0.05 mmol).

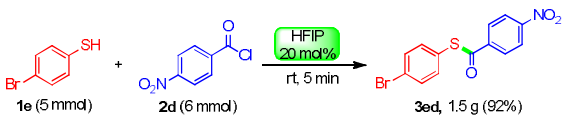
On the basis of promising results obtained in the case of aryl thiols, we turned our attention towards aliphatic thiols to broaden the scope of base and acid-free eco-friendly protocol for the synthesis of thioesters (Table 3). Thus HFIP–catalyzed thioesterification reaction onto benzene methanethiol (**1f**) was examined. When parent benzoyl chloride was employed, the product **3fa** was isolated in 99% yield. Subsequently, a variety of benzoyl chlorides possessing electron-donating groups (**2b** and **2c**) and electron-withdrawing group (**2d**) were successfully reacted with compound **1f** under the optimized conditions providing thioesters **3fb**, **3fc** and **3fd** in excellent to quantitative yield. The use of ethanoyl chloride (**2e**) was also furnished the product **3fe** in excellent yield. Moreover, cyclohexylthiol (**1g**) was tested under aforementioned conditions and the products **3ga**, **3gb**, **3gc** and **3gd** were obtained in high yield. Ester functionalized thiol **1h** worked well to yield the products **3ha**, **3hb**, **3hc** and **3hd**. More importantly, hydroxyl group-containing alkyl thioesters **1ic** and **1id** could be synthesized in 68–75% yield when the reaction was carried out by employing 2-mercaptoethanol (**1i**) as a substrate for this novel transformation. Finally, the reactivity of dichloroacetyl chloride (**2f**) was also examined in acylation of thiols. Dichloroacetyl chloride was found to be very reactive with different thiols. Interestingly, when benzyl mercaptan (**1f**) was the nucleophile of choice, high yield of **3ff** was obtained within seconds.

Table 2 HFIP–Catalyzed thioesterification using aliphatic thiols[a]



[a]Reaction conditions: Aliphatic thiol (0.5 mmol), acyl halide (0.6 mmol), HFIP (0.05 mmol).

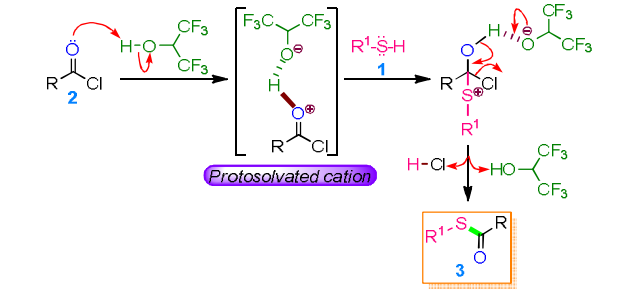
Moreover, this elegant and green protocol for the preparation of thioesters can be readily scaled up to prove the catalytic efficacy of HFIP which can be recovered easily. We then conducted the reaction of 4-bromothiophenol **1e** (5.0 mmol) with 4-NO_2 benzoyl chloride **2d** (6.0 mmol) in the presence of HFIP (1.0 mmol) under the mild reaction condition which afforded the thioester **3ed** in 92% yield (Scheme 2). Distillation of HFIP directly from the reaction



Scheme 2 Gram-scale synthesis of thioester **3ed**.

pot afforded 80 microlitres of a fluorinated solvent. Notably, the recovered solvent can be used for other occasions in synthetic chemistry and be equally as good at catalyzing C–S bond formation to synthesize thiolates as the store bought material.

The plausible mechanism for HFIP catalyzed thiocarbonylation between thiol and acyl halide is depicted in Scheme 3. On the basis of previous reports for acyl halide activation[33] we contemplate that the addition of HFIP to acyl chloride **2** may result in the formation of protosolvated cation due to the strong H-bonding with the oxygen atom of acyl halide. Further, nucleophilic attack of sulfur from thiol **1** onto protosolvated cation can take place. This transition state could be stabilized by high polarizing and low nucleophilic HFIP to afford the corresponding thioester **3**.



Scheme 3 Plausible reaction mechanism

This work reveals that HFIP is particularly pertinent catalyst for the synthesis of thioesters. The reaction is assumed to proceed through in situ generated protosolvated cation intermediates from substrate acyl halides. Direct use of HFIP as catalyst allows the S-carbonylation of thiols in green, clean and atom economical fashion, favouring over the other tedious and traditional protocols. Thus metal-, base- and acid-free, novel protocol also greatly expanded the scope of thiols and acyl halides that are compatible for the expeditious synthesis of thioesters in good to quantitative yields. Further, the development of simple, efficient and eco-friendly novel synthetic protocols employing HFIP under progress in our laboratory.

Acknowledgment

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Supplementary Material

^{1}H NMR and ^{13}C NMR data and copies of spectra of all products are available.

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Highlights

Ms. Title: *Harnessing the catalytic behaviour of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP): An expeditious synthesis of thioesters*

- Acid-, base- and metal-free and expeditious synthesis of thioesters is unravelled.
- Novel HFIP-catalyzed synthesis of thioesters in excellent yields is reported.
- Proceeds under aerobic conditions at room temperature with wide substrate scope.
- No additional reagent/solvent, no workup required in this clean method.
- Reuse of HFIP, high atom economy, gram-scale synthesis are noteworthy.