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# The Reaction of Hexafluoroisopropyl Esters with Amines: A Fast, Easy, Solvent-Free Approach to the Synthesis of Amides

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**Abstract:** *A methodology is reported for the preparation of amides from hexafluoroisopropyl (HFIP) esters and amines. This involves initially producing the HFIP ester from hexafluoroisopropanol and an aldehyde using an oxoammonium salt as an oxidant. Amides could be prepared by solvent-free reaction of the HFIP esters with an amine for 30 minutes at 80 °C in the presence of triethylamine ($NEt_3$).This method was applicable over a wide range of esters and amines. Furthermore, the production of novel symmetrical diamides using this method was possible.*

**Keywords:** *Amidation, Esters, Amides, Diamides, Solvent-free reaction.*

## 1. INTRODUCTION

Amides are one of the most abundant class of compounds in both industry and pharmaceuticals [1-3]. The amide moiety can be found in many antibiotics due to its presence in the β-lactam ring, as well as in barbiturates such as phenobarbital, which is used to treat epilepsy in children, and in benzodiazepines such as diazepam, which can be used to treat anxiety. In industry, amides such as polyacrylamide can be used as a paint coating for household appliances and for dye applications. The traditional method of synthesising amides involves the coupling of an activated carboxylic acid and an amine. The carboxylic acid is activated either using an acyl chloride or a stoichiometric activating agent such as *N*,*N*' dicyclohexylcarbodiimide (DCC). This approach is often inefficient and is not considered to be 'green' due to the formation of unwanted by-products [4,5]. Finding an alternative method of synthesising amides has therefore been a much researched topic.

Employing esters in place of activated carboxylic acids as the starting material for amidation reactions has proven to be a successful way of producing amides (Fig. 1). There are a number of synthetic methods available (Fig 1), and a catalyst is required for most. *N*-Heterocyclic carbenes (NHCs) catalyze the amidation of unactivated esters with a high yield in a single step reaction [6, 7]. Metal catalysts are also successful at converting an ester to the corresponding amide. One example is lanthanum (III) triflate which was effective with a broad scope of substrates [8]. Similarly, it was shown that lithium hydroxide (LiOH) is also a useful catalyst in the amidation of primary and secondary amines and unactivated esters in a solvent free reaction [9]. Zinc dust can catalyze the conversion of aromatic carboxylic esters and amines to amides [10]. An example of the industrial relevance of this transformation is the production of cyanoacetamide CP-690,550-10 from its corresponding ester catalysed by 1, 8 diazabicycloundec-7-ene (DBU) [11]. At the time this transformation was discovered, the cyanoacetamide was under development for the treatment of autoimmune diseases, and has since been approved for the treatment of rheumatoid arthritis under the brand name Xelianz®. The traditional method of synthesis had low yield of 67% in the amidation step, which is too low for a large scale synthesis. The DBU catalysed approach allows for the desired cyanoacetamide to be prepared on a multi kilogram scale with a 90% yield in the amidation step.

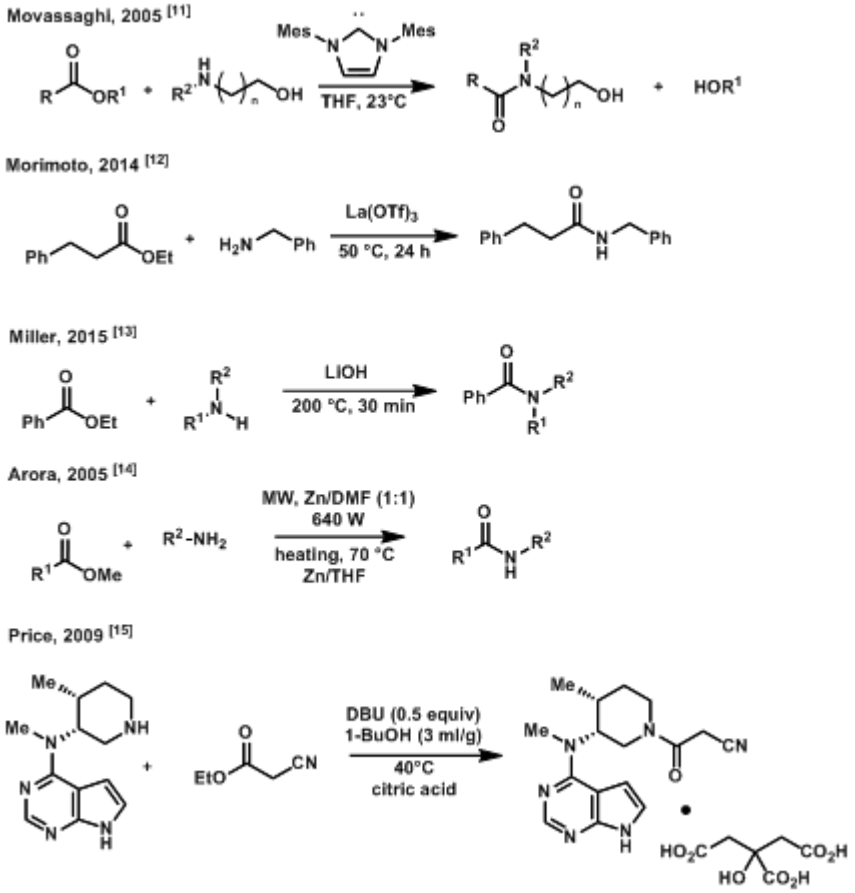



**Figure1.** *Amidation of Esters*

Our group has worked quite extensively on oxidative reactions using the oxoammonium salt 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate, also known as Bobbitt's salt [12]. This salt is a highly attractive reagent as it is able to oxidize substrates under mild conditions and it is metal-free. The spent oxidant can be easily regenerated using commercially available bleach making it recyclable [13]. Primary and secondary alcohols are readily oxidized to the corresponding aldehydes or ketones in the presence of the salt [14]. One area of interest to us has been the oxidative coupling of an aldehyde and an alcohol to form an ester [15]. We had previously demonstrated that aliphatic α-trifluoromethyl alcohols would not oxidize in the presence of the oxoammonium salt [16] and so could be possible candidates as reagents for oxidative esterification with aldehydes. We investigated the reaction between hexafluoroisopropanol and an aldehyde in the presence of the salt to form hexafluoroisopropyl (HFIP) esters (Fig. 2). The reaction works well with a broad scope of aldehydes, forming esters in high yields.

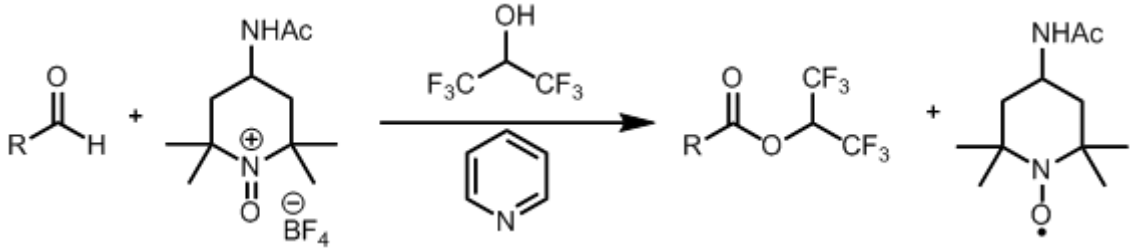


**Figure2.** *Conversion of an aldehyde and HFIP alcohol to the ester using Bobbitt's salt*

These fluorinated esters are very useful synthons as they are easily converted into other functional groups, including one example of an amide. Sparked by a recent report by Vatèle of a stepwise oxidative amidation of alcohols using trichloroisocyanuric acid, a catalytic amount of TEMPO in combination with pyridine and hexafluoroisopropyl (HFIP) alcohol followed by amines [17], we wanted to further explore the amidation of HFIP esters prepared via our oxidative esterification approach (Fig. 3). We report our results here. Following this, a range of HFIP esters and amines were screened to understand the scope of the reaction.

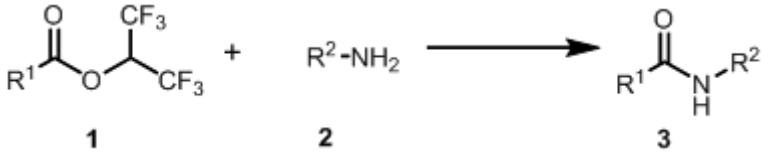



**Figure3.** *Proposed amidation of HFIP esters by amines*

## 2. METHODS

### 2.1. Materials and Measurements

NMR spectra ($^1$H, $^{13}$C) were performed at 298 K on a Brüker DRX-400 400MHz NMR. $^1$H spectra obtained in $CDCl_3$ were referenced to residual non-deuterated chloroform (7.27 ppm) in the deuterated solvent. $^{13}$C spectra obtained in $CDCl_3$ were referenced to residual non-deuterated chloroform (77.0 ppm) in the deuterated solvent. $^1$H spectra obtained in dimethyl sulfoxide (DMSO) were referenced to residual non-deuterated DMSO (2.50 ppm) in deuterated solvents. $^{13}$C spectra obtained in dimethyl sulfoxide (DMSO) were referenced to residual non-deuterated DMSO (39.51 ppm) in deuterated solvents.

Deuterated NMR solvents ($CDCl_3$ and DMSO) were purchased from Cambridge Isotope Laboratories. $CDCl_3$ was stored over 4Å molecular sieves and $K_2CO_3$. Pyridine was purchased from J.T. Baker (ACS Grade). Sodium sulfate, sodium bicarbonate and diethyl ether (ACS and reagent grade) were purchased from Sigma-Aldrich. Aldehydes and amines were purchased from commercial suppliers. Hexafluoroisopropanol and triethylamine were purchased from Oakwood Chemicals. The oxoammonium salt, 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (Bobbitt's salt) was prepared in house according to the literature procedure [18].

### 2.2. Synthesis

*Representative procedure for the synthesis of an HFIP ester: The HFIP ester of 4-methoxybenzoic acid (**1a**)* To a 50-ml round bottom flask equipped with a stir bar, 4-methyoxybenzaldehyde (0.681 g, 5 mmol, 1 equiv), pyridine (5.04 g, 63.75 mmol, 12.75 equiv) and hexafluoroisopropanol (2.94 g, 17.5 mmol, 3.5 equiv) were added. The mixture was allowed to stir at room temperature for approximately 5 min. Then Bobbitt's salt (4.5 g, 15 mmol, 3 equiv) was added at once and the flask was sealed with a rubber septum. The reaction mixture was stirred at room temperature as it turned red. When the reaction was complete, as characterised by a deep red colored solution (~1 hr), the hexafluoroisopropanol was removed *in vacuo* by rotary evaporation. Hexanes (30 ml) was added and allowed to stir for 5 min causing the precipitation of the nitroxide. The solids were filtered off using a medium porosity fritted funnel and washed with hexanes (250 ml). The filtrate was transferred to a separatory funnel and washed twice with 0.5 M HCl (150 ml). The organic layer was then washed with deionised water (150 ml) and brine (150 ml). The organic layer was then dried with $Na_2SO_4$ and the solvent removed via rotary evaporation affording ester **1a** as a clear orange liquid (1.203 g, 80% yield). $^1$H NMR ($CDCl_3$) δ 8.09 (d, 2H), 6.98 (d, 2H), 6.04-6.10 (m, 1H), 3.88 (s, 3H). $^{13}$C NMR ($CDCl_3$) δ 164.84, 162.77, 135.58, 122.07, 118.91, 114.03, 66.62, 55.25

*Hexafluoroisopropyl-2-ethylhexanoate* (**1b**) $^1$H NMR ($CDCl_3$) – δ 5.78-5.86 (m, 1H), 2.48-2.54 (m, 1H), 1.85-1.94 (m, 1H), 1.68-1.79 (m, 4H), 1.61-1.66 (m, 4H), 0.89 – 0.92 (m, 6H). $^{13}$C NMR ($CDCl_3$) – δ 172.91, 119.17, 66.13, 46.94, 31.49, 29.20, 22.43, 13.68, 11.30

*Hexafluoroisopropyl-3-phenylpropanoate* (**1c**) $^1$H NMR ($CDCl_3$) – δ 7.35-7.39 (m, 2H), 7.25-7.31 (m, 3H), 5.81-5.87 (m, 1H), 3.08 (t, 2H), 2.90 (t, 2H). $^{13}$C NMR ($CDCl_3$) – δ 169.56, 139.13, 128.68, 128.15, 126.7, 121.83, 66.66, 34.85, 30.46

*Hexafluoroisopropyl-4-nitrobenzoate* (**1d**) $^1$H NMR ($CDCl_3$) – δ 8.38 (d, 2H), 8.32 (d, 2H), 5.99-6.08 (m, 1H). $^{13}$C NMR ($CDCl_3$) – δ 161.65, 151.56, 132.02, 131.62, 123.93, 121.74, 67.45

*Hexafluoroisopropyl-3-chlorobenzoate* (**1e**) $^1$H NMR ($CDCl_3$) – δ 8.10 (s, 1H), 8.02 (d, 1H), 7.65 (d, 1H), 7.47 (t, 1H), 6.01-6.07 (m, 1H). $^{13}$C NMR ($CDCl_3$) – δ 162.25, 134.81, 134.33, 130.44, 130.15, 128.54, 126.88, 119.13, 67.24

*Hexafluoroisopropyl-3-methoxybenzote* (**1f**) $^1$H NMR ($CDCl_3$) – δ 7.74 (d, 1H), 7.43 (t, 1H), 7.22 (dd, 1H), 6.01-6.10 (m, 1H), 3.89 (s, 3H). $^{13}$C NMR ($CDCl_3$) – δ 163.20, 159.89, 129.85, 128.09, 122.78, 121.11, 119.24, 114.92, 67.02, 55.36

*Representative procedure for the amidation of an HFIP ester: N-Benzyl-4-methoxybenzamide (**3aa**)* To a 10-ml vial equipped with a stir bar, the HFIP ester of 4-methoxybenzoic acid **1a** (0.302 g, 1 mmol, 1 equiv) and triethylamine (0.111 g, 1.1 mmol, 1 equiv) were added. The vial was sealed with a cap and stirred at room temperature for 5 min. Benzylamine, **2a**, (0.268 g, 2.5 mmol, 2.5 equiv) was added dropwise to the reaction mixture. The cap was replaced on the vial and the reaction was stirred for 30 min at 80 °C. When the reaction was completed, the product mixture was diluted with dichloromethane (25 mL) and transferred to a separatory funnel. It was washed three times with 2 M HCl (18 mL) and then $NaHCO_3$ (50 mL). The organic layer was then washed with water (25 mL) and brine (25 mL) and dried over $Na_2SO_4$. The solvent was removed via rotary evaporation affording the amide, **3aa**, as a white solid (0.178 g, 74 %). $^1$H NMR ($CDCl_3$) δ 7.77 (d, 2H), 7.36 (m, 4H), 7.29-7.33 (m, 1H), 6.92 (d, 2H), 6.40 (bs, 1H), 4.64 (d, 2H), 3.85 (s, 3H). $^{13}$C NMR ($CDCl_3$) – δ 166.83, 162.20, 138.40, 128.74, 127.88, 127.52, 126.64, 113.74, 55.38, 44.05

*N-Butyl-4-methoxybenzamide* (**3ac**) $^1$H NMR ($CDCl_3$) – δ 7.73 (d, 2H), 6.89 (d, 2H), 6.30 (bs, 1H), 3.82 (s, 3H), 3.41 (m, 2H), 1.58 (m, 2H), 1.39 (m, 2H), 0.94 (t, 3H) $^{13}$C NMR ($CDCl_3$) – δ 166.96, 161.89, 128.49, 127.00, 113.52, 55.26, 39.67, 31.71, 20.00, 13.68

*2-Chlorobenzyl-4-methoxybenzamide* (**3ae**) $^1$H NMR ($CDCl_3$) – δ 7.76 (d, 2H), 7.45-7.48 (m, 1H), 7.38-7.40 (m, 1H), 7.23-7.25 (m, 2H), 6.90-6.94 (d, 2H), 6.58 (bs, 1H), 4.72 (d, 2H), 3.85 (s, 3H). $^{13}$C NMR ($CDCl_3$) – δ 166.82, 162.26, 135.79, 133.67, 132.72, 130.38, 129.52, 128.93, 127.13, 126.52, 114.16, 55.38, 41.96

*N-Cyclohexyl-4-methoxybenzamide* (**3ag**) $^1$H NMR ($CDCl_3$) – 7.72 (d, 2H), 6.91 (d, 2H), 5.93 (bs, 1 H), 3.91-4.03 (m, 1H), 3.84 (s, 3H), 2.03 (dd, 2H), 1.75 (dt, 2H), 1.65 (d, 1H), 1.37-1.49 (m, 2H), 1.17-1.29 (m, 3H). $^{13}$C NMR ($CDCl_3$) – δ 166.12, 161.99, 128.59, 127.42, 113.67, 55.40, 48.58, 33.33, 25.62, 24.95

*(4-Methoxyphenyl)-piperidin-1-ylmethanone* (**3ah**) $^1$H NMR ($CDCl_3$) – δ 7.32 (d, 2H), 6.86 (d, 2H), 3.77 (s, 3H), 3.50 (bs, 4H), 1.54-1.63 (m, 6H). $^{13}$C NMR ($CDCl_3$) – δ 170.11, 160.35, 128.62, 113.43, 55.10, 48.51, 53.31, 25.43

*(4-Methoxyphenyl)(morpholin-4-yl) methanone* (**3ab**) $^1$H NMR ($CDCl_3$) – δ 7.31 (d, 2H), 6.84 (d, 2H), 3.74 (s, 1H), 3.55-3.60 (m, 8H). $^{13}$C NMR ($CDCl_3$) – δ 170.03, 160.60, 128.88, 127.05, 113.47, 66.56, 55.02

*2-Ethyl-N-propyl-hexanamide* (**3bc**) $^1$H NMR ($CDCl_3$) – δ 5.59 (bs, 1H), 3.23—3.28 (m, 2H), 1.85-1.91 (m, 1H), 1.26-1.70 (m, 12H), 0.84-0.93 (m, 9H). $^{13}$C NMR ($CDCl_3$) – δ 172.88, 49.84, 38.95, 32.51, 29.84, 26.05, 22.70, 20.02, 13.88, 13.63, 12.03

*N-Butyl-3-phenylpropionamide* (**3cc**) $^1$H NMR ($CDCl_3$) – δ 7.21-7.33 (m, 5H), 5.53 (bs, 1H), 3.20-3.25 (m, 2H), 2.99 (t, 2H), 2.49 (t, 2H), 1.39-1.47 (m, 2H), 1.24-1.33 (m, 2H), 0.92 (t, 3H). $^{13}$C NMR ($CDCl_3$) – δ 171.98, 140.89, 128.43, 128.28, 126.14, 39.16, 38.50, 31.75, 31.55, 19.91, 13.65

*N-Butyl-4-nitrobenzamide* (**3dc**) $^1$H NMR ($CDCl_3$) – δ 8.27 (d, 2H), 7.92 (d, 2H), 6.35 (bs, 1H), 3.45-3.50 (m, 2H), 1.59-1.66 (m, 2H), 1.36-1.47 (m, 2H), 0.96 (t, 3H). $^{13}$C NMR ($CDCl_3$) – δ 165.47, 149.47, 140.42, 128.03, 123.75, 40.13, 31.55, 20.10, 13.7

*N-Butyl-3-chlorobenzamide* (**3ec**) $^1$H NMR ($CDCl_3$) – δ 7.75 (s, 1H), 7.63 (d, 1H), 7.46 (d, 1H), 7.31-7.36 (m, 1H), 6.20 (bs, 1H), 3.42-3.48 (m, 2H), 1.59-1.64 (m, 2H), 1.39-1.44 (m, 2H), 0.95-0.99 (m, 3H). $^{13}$C NMR ($CDCl_3$) – δ 166.50, 136.72, 134.60, 131.14, 129.68, 127.54, 125.27, 40.06, 31.66, 20.25, 13.84

*N-Butyl-3-methoxybenzamide* (**3fc**) $^1$H NMR ($CDCl_3$) – δ 7.33 (s, 1H), 7.18-7.22 (m, 1H), 6.92 (m, 2H), 3.72 (s, 3H), 3.31-3.36 (m, 2H), 1.47-1.55 (m, 2H), 1.26-1.35 (m, 2H), 0.86 (t, 3H). $^{13}$C NMR ($CDCl_3$) – δ 167.39, 159.47, 136.03, 129.16, 118.66, 117.11, 112.13, 55.04, 39.65, 31.42, 19.91, 13.50

*Representative procedure for the preparation of a diamide: N-ethyl-4-methoxybenzdiamide* (**3aj**) To a 10 ml vial equipped with a stir bar, the HFIP ester of 4-methoxybenzoic acid, **1a**, (1.209 g, 4 mmol, 2 equiv) and triethylamine (0.226 g, 2.2 mmol, 1.1 equiv) were added. The vial was sealed with a cap, and the reaction mixture was allowed to stir for 5 min at room temperature. Ethylenediamine (0.122 g, 2 mmol, 1 equiv) was added and the reaction was stirred for 30 min at 80 °C. When the reaction was completed, the white solid formed was filtered and washed with hexanes affording diamide (**3aj**) as a

white solid (0.546 g, 83%). $^{1}$H NMR ($d_6$-DMSO) – δ 8.46 (bs, 2H), 7.83 (d, 4H), 6.98 (d, 4H), 3.80 (s, 6H), 3.41 (t, 4H). $^{13}$C NMR ($d_6$-DMSO) – δ 166.19, 161.67, 129.17, 126.93, 113.62, 55.50

*N-Ethyl-3-phenylpropiondiamide* (**3cj**) $^{1}$H NMR ($d_6$-DMSO) – δ 7.83 (bs, 2H), 7.18-7.26 (m, 10H), 3.04 (s, 4H), 2.80 (s, 4H), 2.35 (t, 4H). $^{13}$C NMR ($d_6$-DMSO) – δ 171.61, 141.50, 128.42, 126.02, 38.48, 37.23, 31.20

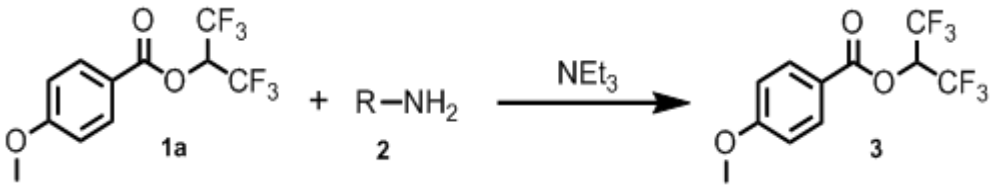
*N-Ethyl-4-nitrobenzamide* (**3dj**) $^{1}$H NMR ($d_6$-DMSO) – δ 9.03 (bs, 2H), 8.31 (d, 4H), 8.09 (d, 4H), 3.49 (s, 4H). $^{13}$C NMR ($d_6$-DMSO) – δ 165.05, 149.15, 140.36, 128.94, 123.65, 45.56

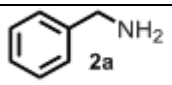
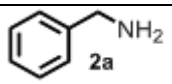
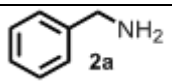
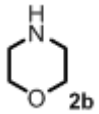
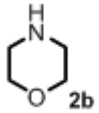
*N-Ethyl-3-methoxybenzamide* (**3fj**) $^{1}$H NMR ($d_6$-DMSO) – δ 8.58 (bs, 2H), 7.35-7.43 (m, 6H), 7.08 (dd, 2H), 3.79 (s, 6H), 3.44 (t, 4H). $^{13}$C NMR ($d_6$-DMSO) – δ 166.45, 159.31, 136.18, 129.54, 119.60, 117.13, 112.58, 55.41

## 3. RESULTS AND DISCUSSION

Using the procedure developed previously by our group [15], a series of six hexafluoroisopropyl esters (**1a**-**f**) were prepared. Using one of these esters, the hexafluoroisopropyl-4-methoxybenzoic acid (**1a**), and benzylamine (**2a**) as starting materials, conditions for the amidation reaction were optimised as outlined in Table 1. Reactions were performed in the presence of one equivalent of triethylamine. By varying temperature, reaction time, and performing the reaction in the presence of a solvent and solvent-free we determined the optimal conditions to be: solvent-free at 80 °C for 30 min (Entries 1-3). Morpholine (**2b**) was also screened against **1a** to probe whether the reaction would proceed with a secondary amine as the substrate. The amide was indeed, but a lower conversion of 60 % (Entry 4). Repeating the reaction but doubling the reaction time to 1 hour increased the conversion to 96 % (Entry 5). This suggests that for primary amines, a reaction time of 30 min is sufficient, however for secondary amines such as morpholine, the reaction should be run for one hour.

**Table1.** *Optimization of reaction conditions*[a]




| Entry | Amine | Solvent | Temp. (°C) | Time (h) | Conversion (%) |
|---|---|---|---|---|---|
| 1 |  2a | $CH_2Cl_2$ | RT | 12 | 29 |
| 2 |  2a | $CH_2Cl_2$ | 70 | 0.5 | 0 |
| 3 |  2a | - | 80 | 0.5 | 100 |
| 4 |  2b | - | 80 | 0.5 | 60 |
| 5 |  2b | - | 80 | 1 | 96 |

*a) Reactions were performed on the 1 mmol scale using 1 eq. of the ester partner and 2.5 eq. of the amine. Triethylamine (1.1 eq.) was added to the reaction mixture. Product conversion was obtained using $^{1}$H-NMR spectroscopy.*

We decided to focus initially on screening the hexafluoroisopropyl ester of 4-methoxybenzoic acid (**1a**) against nine amines (Table 2, Entries 1-9). The range of amines chosen allowed us to broaden of the methodology, testing both primary and secondary aromatic and aliphatic amines. The reaction was successful in most cases. Benzylic and primary and secondary amines reacted with **1a** to yield the desired amide in good to excellent yield. When using diisobutylamine and aniline, no product was

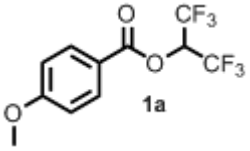
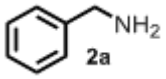
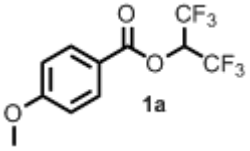
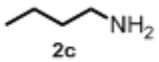
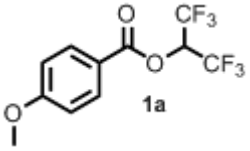
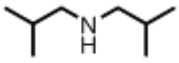
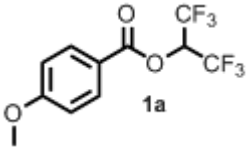
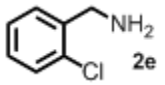
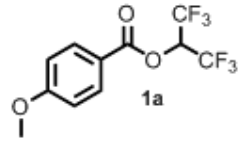
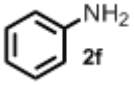
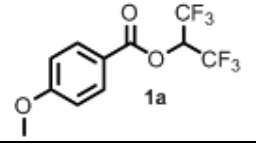
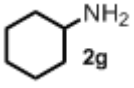
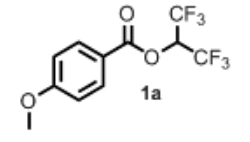
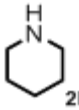
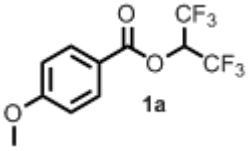
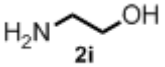
formed. In the case of the former, this is likely due to steric hindrance and, in the case of the latter, due to electronic nature of the aromatic substrate.

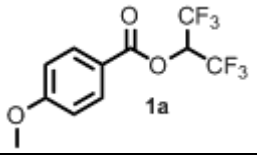
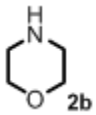
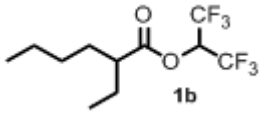
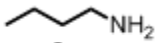
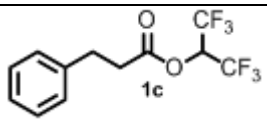
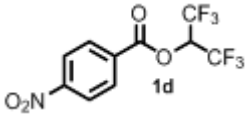
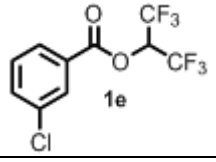
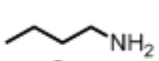
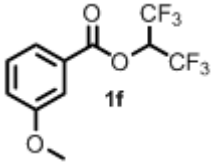
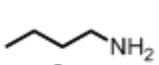
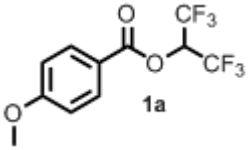
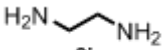
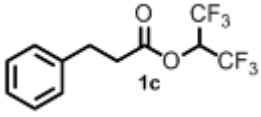
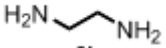
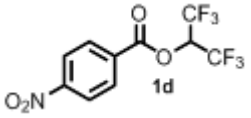
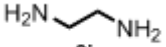
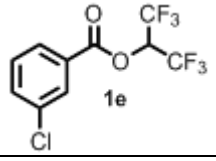
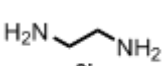
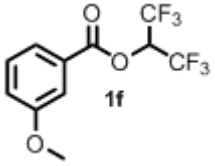
We screened the reaction of **1a** with ethanolamine (**2i**). There are two possible products from the reaction, one being the amide and the other being an ester formed by reaction of the alcohol functionality in **2i**. We found that a mixture of the two was formed, the amide being the major (Entry 8).

Varying the ester component and using butylamine as the amine coupling partner, we found that the reaction was again broadly successful (Entries 10-14). Aliphatic and aromatic esters can be coupled effectively and the reaction tolerates changes in the steric and electronic nature of the substrate. In most cases, isolation of the product was simple with the exception of the reaction of the hexafluoroisopropyl ester of 4-nitrobenzoic acid where the work-up procedure resulted in significant product loss. This was attributed to the reactivity of the amide product.

We expanded the scope of the reaction to the preparation of diamides, a class of compound that has proven to be an area of current research due to their use as insecticides [18]. We were able to prepare a range of diamides using our methodology by coupling hexafluoroisopropyl esters with ethylenediamine (Table 2, entries 15-19). Yields were generally somewhat lower than in the case of the monoamide analogs.

**Table2.** *Substrate scope of the amidation reaction*

| Entry | Ester | Amine | Product | Conversion (yield) (%) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** | **3aa** | 100 (74) |
| 2 |  **1a** |  **2c** | **3ac** | 100 |
| 3 |  **1a** |  **2d** | **3ad** | 0 |
| 4 |  **1a** |  **2e** | **3ae** | 89 (75) |
| 5 |  **1a** |  **2f** | **3af** | 0 |
| 6 |  **1a** |  **2g** | **3ag** | 96 |
| 7[b] |  **1a** |  **2h** | **3ah** | 100 |
| 8 |  **1a** |  **2i** | **3ai** | 2 products formed |

| | | | | |
|---|---|---|---|---|
| 9[b] |  1a |  2b | **3ab** | 99 (90) |
| 10 |  1b |  2c | **3bc** | 68 |
| 11 |  1c |  2c | **3cc** | 100 (90) |
| 12 |  1d |  2c | **3dc** | 100 (55) |
| 13 |  1e |  2c | **3ec** | 100 (88) |
| 14 |  1f |  2c | **3fc** | 100 (88) |
| 15[c] |  1a |  2j | **3aj** | 100 (83) |
| 16[c] |  1c |  2j | **3cj** | 75 |
| 17[c] |  1d |  2j | **3dj** | 51 |
| 18[c] |  1e |  2j | **3ej** | 0 |
| 19[c] |  1f |  2j | **3fj** | 61 |

*a) Reactions were performed on the 1 mmol scale using 1 eq. of the ester partner and 2.5 eq. of the amine. Triethylamine (1.1 eq.) was added to the reaction mixture. The reaction mixture was stirred for 30 min at 80 C. Product conversion was obtained using $^1$H-NMR spectroscopy. Yield data (in parentheses) corresponds to isolated yield of the amide product. b) The reaction time was increased to one hour. c) The ester to amine reagent stoichiometry was changed to 4:1.*

## 4. CONCLUSION

A rapid, easy, solvent-free approach to the synthesis of amides from esters and amines is presented here. The reaction involves the use of hexafluoroisopropyl esters, a class of compounds that are shelf-stable but react readily with amines. Our methodology has a broad scope and allows for the preparation not only of monoamides but also diamides.

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