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Electrophilic Activation of Carboxylic Anhydrides for Nucleophilic Acylation Reactions

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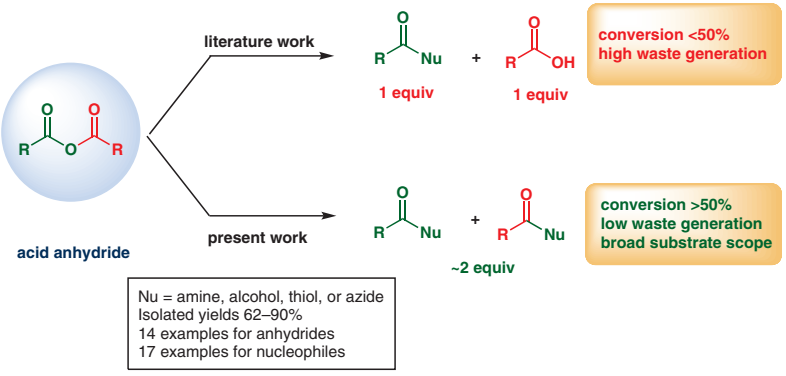

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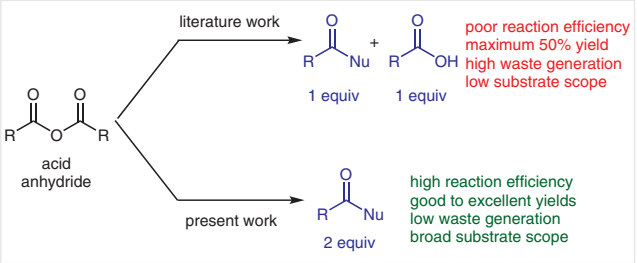
Abstract Nucleophilic acylation of symmetrical carboxylic anhydrides has inherited limitation of reaction efficiency along with relatively poor reactivity. Traditionally, one equivalent carboxylic acid is generated during nucleophilic acylation of a symmetrical anhydride, which always limits the yield of final product to 50% or less. This is a major drawback, which discourages the use of anhydrides for laboratory or industrial applications. Electrophilic activation of carboxylic anhydride using methanesulfonyl chloride is found to be an efficient method for nucleophilic acylation, which increases product yield by restricting the formation of corresponding acid as a side product. The developed protocol found to be a mild and high yielding methodology for one-pot nucleophilic acylation of carboxylic anhydrides with several type of N- and S-nucleophiles demonstrating appreciable functional group tolerance.

Key words nucelophilic acylation, electrophilic activation, anhydride activation, mesyl chloride

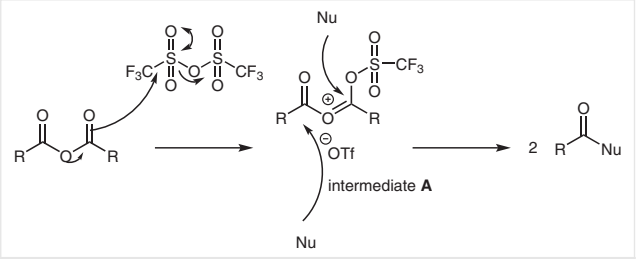
Carboxylic acids and their derivatives hold a special place in chemical arena due to their omnipresence as a key building block or structural motif in biomolecules, marketed drugs, drug intermediates, or chemical leads having therapeutic or commercial significance.[1] High prevalence of carboxylic acid and its derivatives is attributed to their ability for facile chemical transformations, mostly exploiting acyl substitution reaction with a variety of nucleophiles. Depending on choice of nucleophile, the nucleophilic acylation reaction of a carboxylic acid can potentially produce a diverse array of products, for example, amide, ester, thioester and acyl azide. Owing to these factors, nucleophilic acyl substitution is one of the most prolific reaction in various chemical processes employed either for laboratory research or commercial production.[2] For nucleophilic acylations, direct use of carboxylic acids is limited as one needs to pre-activate the acid before nucleophile addition. Traditionally, activated forms of carboxylic acids, namely acid halides, anhydrides, or esters are utilized for acyl substitution reactions. Among activated carboxylic acid derivatives, acid halides are highly espoused. Unfortunately, the requirement of special or stringent conditions for synthesis, handling, and storage of acid chlorides coupled with limited functional group tolerance, circumvent their synthetic application. Though esters are easily accessible, they are least preferred due to low reactivity compared to acid halides or anhydrides. Interestingly, anhydrides[3,4] (symmetrical or asymmetrical carboxylic anhydrides) seem to be excellent substrates owing to their moderate reactivity, ease of handling and milder conditions for activation. However, their synthetic applications are limited, mainly due to poor reaction efficiency, as one equivalent of carboxylic acid is generated as a major by-product and rejected as waste in the case of nucleophilic acylation reactions.[3] To the best of our understanding there is no relevant literature report on the activation of symmetrical carboxylic anhydride demonstrating no or limited wastage as acid by-product. We contemplated that it would be a considerable value addition to develop a methodology employing in situ activation of carboxylic acid anhydrides for nucleophilic acylation, which can restrict the generation of carboxylic acid as reaction waste (Scheme 1) and will increase overall reaction efficiency. The successful development of this anticipated strategy would provide inherited advantages like low waste generation and hence better reaction economy and yields.

Over the past few years, triflic anhydride (Tf_2O)-mediated electrophilic activation attained a great interest especially due to high electrophilic character of the Tf_2O reagent. Charrette et al. and Huang et al. demonstrated a successful activation and transformation of various carboxylic amides into different derivatives (aldehydes, ketones, esters, amines, imines, etc.) using the electrophilic nature of



Scheme 1 A comparison of reported versus developed synthetic protocol for nucleophilic acylation

Tf_2O.[5] We envisaged that it would be exciting to explore similar kind of activation for acid anhydrides. We hypothesized that treatment of an anhydride with Tf_2O would generate a highly electrophilic intermediate **A** (Scheme 2) that would subsequently undergo a facile condensation with any nucleophile to afford corresponding product without releasing acid as a by-product. Our initial investigation to explore this hypothesis started with amide bond formation using carboxylic anhydride and a secondary amine as a nucleophile. At the outset, the reaction of benzoic anhydride (**2**) was studied with piperidine in the presence of triethylamine (Et_3N) with varying concentration of Tf_2O at –78 °C (Table 1; entries 1–3). Progress of the reaction was monitored by TLC and Ultra Performance Liquid Chromatography (UPLC).



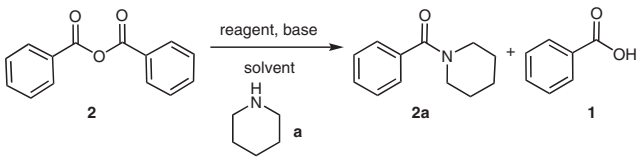
Scheme 2 Hypothesis involving electrophilic activation of anhydride

A UPLC-based method was developed to determine the quantitative conversion of anhydride **2** (Table 1) to the corresponding amide **2a** and acid **1** for each reaction attempt (see Supporting Information).[6] As anticipated, in the absence of an electrophilic activation, that is, without Tf_2O (Table 1, entry 1), anhydride **2** provided only 50% conversion to amide **2a** with generation of the corresponding acid **1** as the major by-product with complete consumption of anhydride. It was pleasant to observe that an incremental addition of Tf_2O from 0 to 1.1 equivalents enhances the desired conversion beyond 50% and restricted the formation of acid as a by-product. Notably, 1.1 equivalents of Tf_2O were found to be optimal for maximum conversion (entry 3). A brief study was planned to determine the effect of organic base. Replacing triethylamine with pyridine or one of its derivative was found to be detrimental (entries 3–6) for product yield. Also, the reaction performed at 0 °C afforded low yield with the corresponding acid as the major by-product. The isolation of pure product was not very efficient in spite of good to high conversion in most of these attempts. In order to find the milder conditions, we attempted a reaction with methanesulfonic anhydride (Ms_2O). To our dismay, the activation of benzoic anhydride was not significant and the yield of the desired product **2a** reduced drastically (entries 8, 9). However, methanesulfonyl chloride (MsCl) as a reagent of choice in place of Tf_2O afforded better yield with high conversion under similar conditions (entry 10). Considering the mild nature of the MsCl along with its lower cost, the outcome was very encouraging. A quick study to find an alternative for dichloromethane as reaction solvent was not noteworthy due to considerable yield loss (entries 11–13). The study of model reaction with different reaction parameters and their corresponding outcome (Table 1) concluded MsCl as the reagent of choice, triethylamine as the base, and dichloromethane as the preferred solvent for further exploration.

Further, a broad panel of different anhydrides (Scheme 3) was screened for a reaction with pyrrolidine using above optimized condition for corresponding amide formation. Notably, all the acid anhydrides on treatment with a secondary amine under above optimized reaction conditions, afforded good to excellent yields of the corresponding amides **3b–16b** with high chemical purity employing usual acid/base aqueous workup avoiding any major purification technique. Interestingly, this method also demonstrated a fair level of functional group tolerance for different functional groups attached to benzoic anhydride. For example, benzoic anhydride substituted with nitrile, acetyl, formyl, or Boc protecting group provided high yields of the corresponding amides **9b**, **11b**, **12b**, **14b**, **15b**, and **16b**, respectively. The developed protocol did not provide appreciable stereoselective outcome for the synthesis of amide **14b** having an α-stereogenic center. The reaction for the synthesis of **14b** led to a racemic product when attempted with a single enantiomer of the corresponding acid.

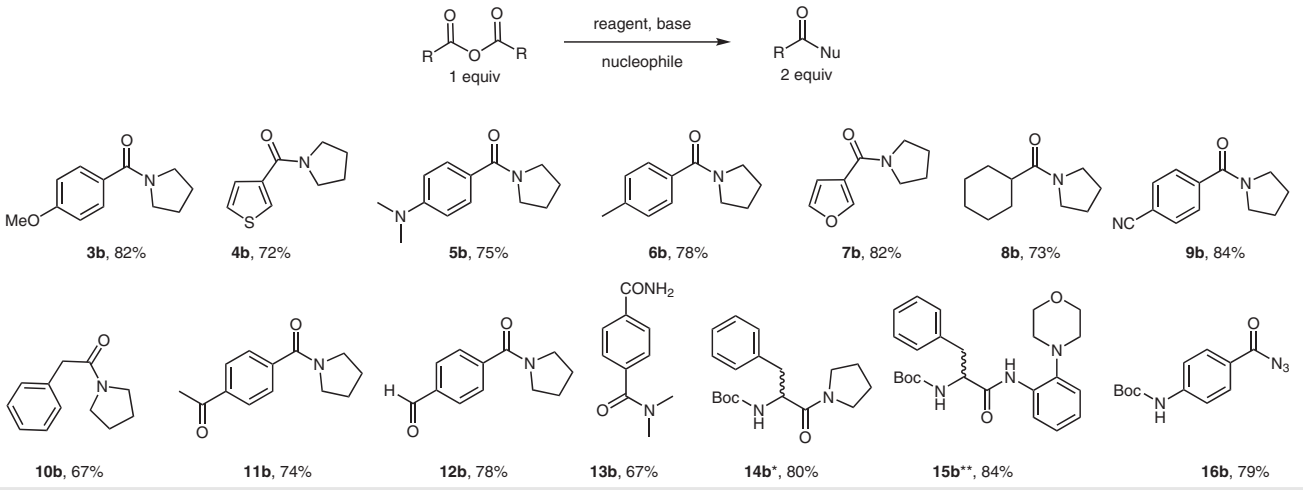
Based on literature understanding[5] and our observations during the course of this study, we conceived a reaction mechanism involving structures **A** and **B** as possible key intermediates (Scheme 4). We attempted to gather evidence corresponding to these intermediates by monitoring a reaction of benzoic anhydride with MsCl and Et_3N under developed protocols using mass spectrometric analysis. Reaction was initiated using standard protocol at –78 °C and two aliquots were extracted one each, after the addition of MsCl and Et_3N. Unfortunately, we could not observe any *m*/*z* peak corresponding to intermediate **A** after the addition of MsCl and **A1** after the addition of Et_3N under these conditions. A thin layer chromatographic analysis of the reaction mixture confirmed the presence of unperturbed anhydride. However, after the addition of Et_3N, we did observe *m*/*z* of 206.15, which probably corresponds to intermediate **B**.[6]

Table 1 Optimization of Reaction Conditions for Electrophilic Activation of Benzoic Anhydride (**2**)[a]



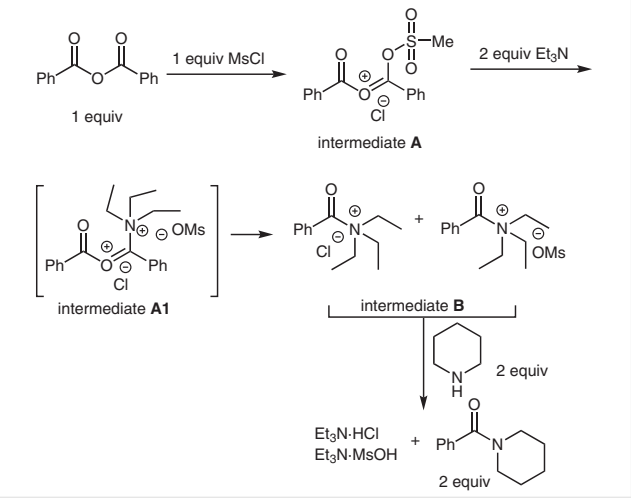
Entry	Reagent	Base	Solvent	Temp (°C)	Conversion[b] **2**/**2a**/**1**	**2a** Yield (%)[c]
1	–	Et_3N	CH_2Cl_2	0	00:48:52	45
2	Tf_2O (0.5 equiv)	Et_3N	CH_2Cl_2	–78	00:67:33	32
3	Tf_2O	Et_3N	CH_2Cl_2	–78	01:80:19	63
4	Tf_2O	pyridine	CH_2Cl_2	–78	23:56:21	38
5	Tf_2O	2-chloropyridine	CH_2Cl_2	–78	17:73:10	21
6	Tf_2O	2-fluoropyridine	CH_2Cl_2	–78	48:44:8	29
7	Tf_2O	Et_3N	CH_2Cl_2	0	00:64:36	45
8	Ms_2O	Et_3N	CH_2Cl_2	0	0:54:46	55
9	Ms_2O	Et_3N	CH_2Cl_2	–78	0:57:43	44
10	MsCl	Et_3N	CH_2Cl_2	–78	0:84:16	82
11	MsCl	Et_3N	CH_2Cl_2	0	0:71:29	64
12	MsCl	Et_3N	toluene	0	13:50:37	52
13	MsCl	Et_3N	$CHCl_3$	0	0:60:40	42

[a] Reaction conditions: Benzoic anhydride (0.5 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. Reagent (0.55 mmol, 1.1 equiv, unless specified) was added to this solution followed by addition of base (1.1 mmol, 2.2 equiv). After stirring for 30 min, the reaction mixture was treated with piperidine (1.1 mmol, 2.2 equiv) at the same temperature. The reaction mixture was slowly brought to r.t. and the progress of reaction was monitored by TLC. After completion of the reaction (5 min to 2 h), chemically pure product was obtained by acid/base workup.
[b] Conversion based on UPLC.
[c] Product yield based on UPLC.



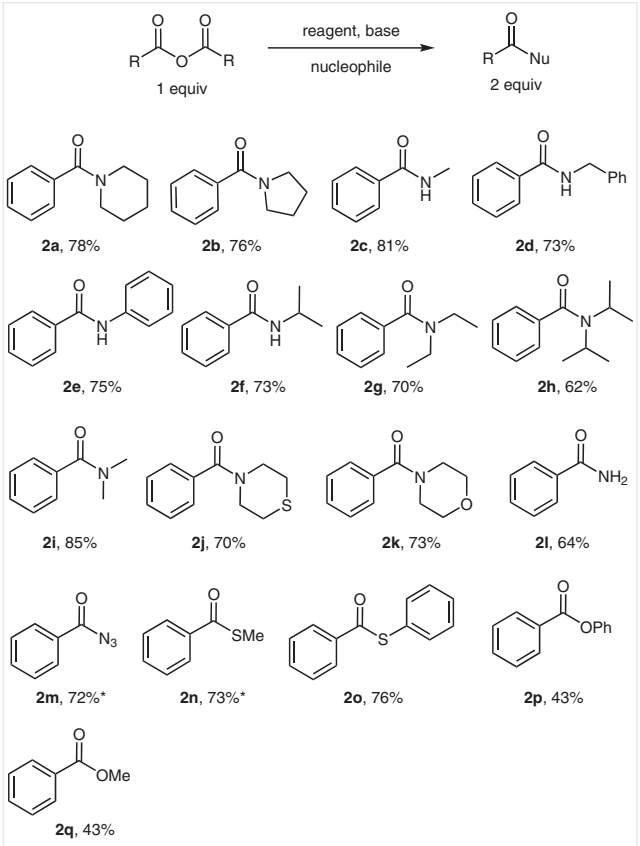
Scheme 3 Substrates scope for different carboxylic anhydrides. *Reagents and conditions*: Anhydride (0.5 mmol, 1 equiv) was dissolved in CH_2Cl_2 (5 mL) and cooled to –78 °C. To this solution was added MsCl (0.55 mmol, 1.1 equiv) followed by the addition of Et_3N (1.1 mmol, 2.2 equiv). After 30 min, the solution was treated with nucleophile (1.1 mmol, 2.2 equiv) at the same temperature. The reaction mixture was slowly brought to r.t. and the progress of reaction was monitored by TLC. After completion of the reaction (5 min to 2 h), chemically pure product was obtained by acid/base workup. * Racemization observed. ** Starting material was racemic mixture.

This indicates the possible involvement of intermediate **B**, which seems to be critical for high yields of nucleophilic acylation by restricting the release of carboxylate ion unlike traditional nucleophilic reactions of carboxylic anhydrides. It is also documented that MsCl can react with Et_3N to form sulfene even at low temperature.[7] We do not have enough evidence to rule out a partial involvement of electrophilic sulfene. However, a considerable amount of anhydride activation using Tf_2O and Et_3N (Table 1; entries 2, 3, conversion >50%) argues against the exclusive involvement of sulfene, as Tf_2O does not have acidic proton to facilitate sulfene formation. Also, we did a reference reaction of benzoic anhydride and piperidine with premixed MsCl and Et_3N to facilitate sulfene formation. This reference reaction afforded reduced yield of amide (>50%). This observation negates the involvement of sulfene under developed reaction conditions. This certainly demands for further investigations to make a conclusive understanding of reaction mechanism.



Scheme 4 Proposed mechanism

To facilitate internal drug discovery efforts, we were interested in developing a general, mild and process friendly protocol for nucleophilic acylation having a wider scope for nucleophiles. To accomplish this, a study was executed to generalize the developed protocol for reaction of different nucleophiles on benzoic anhydride using MsCl as an activating reagent (Scheme 5, 2a–q). Various nucleophiles, such as primary amines (**2c–f**), secondary amines (**2g–k**), aromatic amine (**2e**), and thiophenol (**2o**) afforded good to excellent yields of the corresponding products. More importantly, relatively weak nucleophiles such as methanol (**2q**), phenol (**2p**), and ammonium hydroxide (**2l**) also afforded appreciable reaction yields. However, reactions attempted with poor nucleophiles such as ethanol, isopropyl alcohol, potassium thiocyanate, and potassium isocyanate did not lead to any product formation. Use of sodium azide and thiomethoxide as nucleophiles afforded poor yield of corresponding products **2m** (25%) and **2n** (30%) with a sluggish reaction profile (reaction time of 12 h). This was suspected due to poor solubility of these nucleophiles in reaction system. And rightly so, addition of DMSO as a co-solvent not only increased the reaction rate (2 h) but also improved the product yields (**2m**; 75% and **2n**; 73%). The study concluded in Schemes 3 and 5 generalized the present methodology with a wider substrate scope employing range of symmetrical anhydrides as well as nucleophiles.



Scheme 5 Substrates scope for different nucleophiles. For reagents and conditions, see Scheme 3. * DMSO (2 mL) was used as a co-solvent.

In summary, we have presented an unprecedented finding, involving activation of symmetrical carboxylic anhydride for nucleophilic acylation reactions by simple yet powerful electrophilic reagent such as MsCl in the presence of Et_3N. This activation is unique, as it produces two equivalents of acyl species from one equivalent of carboxylic anhydride and hence no acid waste unlike traditional nucleophilic acylations of anhydrides. There could be an argument that in current form, it is not an atom economic approach, but this study does open a possibility to have a new method where electrophilic activations of anhydrides can provide high efficiency for anhydride reactions. Intriguingly, we also observed a similar kind of electrophilic activation of anhydrides using $POCl_3$ as a reagent of choice and Et_3N as

an organic base (unpublished data).[8] This is important considering the fact that $POCl_3$ is a process-friendly reagent and preferred for industrial applications. We also demonstrated a practical ease as well as generality of the developed approach by evaluating this methodology across a range of anhydrides as well as different nucleophiles highlighting appreciable level of functional group tolerance and one-pot synthesis using inactivated but functionalized carboxylic acids.

Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. All reactions were performed under an inert atmosphere. Flash chromatography was carried out using silica gel (100–200 mesh). The reactions were monitored by TLC (Merck) and performed on silica gel and was visualized by staining with $KMnO_4$. The ^1H and ^{13}C NMR spectra were recorded either using a Bruker Avance DPX 400 (400 MHz for ^1H and 100 MHz for ^{13}C) or Bruker Avance 300 (300 MHz for ^1H and 75 MHz for ^{13}C) spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. The chemical shifts (δ) for ^1H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. Standard abbreviations are used to indicate the multiplicity. Evaporation of solvents was performed under reduced pressure using a Büchi rotary evaporator. IR spectra were recorded on a PerkinElmer Spectrum two FT-IR spectrophotometer. Samples were mixed with KBr and used as pellets for FT-IR analysis. Specific rotations were measured on a Rudolph Autopole IV instrument. Mass spectra were recorded on an Advion Mass Express CMS instrument and HRMS spectra were recorded on an Orbitrap Fusion mass spectrometer (Thermo) in positive ion mode through direct infusion by syringe. UPLC studies were carried out on a 1.7 µM C18 column stationary phase using MeCN/H_2O as the eluent.

Screening Reaction Conditions for Benzoic Anhydride (2); General Procedure (Table 1)

To a solution of benzoic anhydride (**2**; 0.113 g, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at –78 °C was added the corresponding reagent, followed by addition of a base. The reaction mixture was stirred for additional 30 min at the same temperature before the addition of piperidine (94 mg, 1.1 mmol, 2.2 equiv) was done. Progress of the reaction was monitored by TLC and UPLC. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed with 1 N aq HCl (10 mL). The organic layer was concentrated and 2 mg sample was submitted for UPLC analysis. Rest of the sample was diluted with EtOAc (20 mL) and washed with dilute $NaHCO_3$ (10 mL) followed by brine. The organic layer thus obtained was separated, dried (anhyd Na_2SO_4) and concentrated to get the desired product. If required, further purification was done using a hexane wash of the crude product. The overall yield and conversion was determined using UPLC (see Supporting Information).

Preparation of Precursor Special Anhydrides for 11b–16b; General Procedure

To a solution of the respective substituted carboxylic acid (2 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at –78 °C was added MsCl (126 mg, 1.1 mmol, 0.55 equiv) and Et_3N (444 mg, 4.4 mmol, 2.2 equiv), and the reaction mixture was stirred at –78 °C for 30 min and allowed to warm to r.t. Progress of the reaction was monitored by TLC. After completion of the reaction, the solution was diluted with Et_2O (40 mL) and filtered to remove the inorganic salt. The filtrate was washed with $NaHCO_3$ (20 mL), dried (anhyd Na_2SO_4), and then concentrated to obtain the desired product. If required, further purification were done using silica gel column chromatography using EtOAc/hexane as the eluent.

Nucleophilic Acyl Substitution of Benzoic Anhydride and Different Anhydrides with Different Nucleophiles; General Procedure (Schemes 3 and 5)

To a solution of the respective anhydride (0.5 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at –78 °C was added MsCl (60 mg, 0.52 mmol, 1.05 equiv) followed by Et_3N (111 mg, 1.1 mmol, 2.2 equiv). The reaction mixture was stirred for 30 min at –78 °C and the corresponding nucleophile (1.1 mmol, 2.2 equiv) was added. The progress of the reaction was monitored by TLC. After 2 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1 N aq HCl (10 mL) followed by aq $NaHCO_3$ (10 mL) and then brine (10 mL). The organic layer was dried (anhyd Na_2SO_4) and concentrated under reduced pressure to give the desired product. If required, a further purification was done using flash column chromatography using EtOAc/hexane as the eluent.

Phenyl(piperidin-1-yl)methanone (2a)[9]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and piperidine; transparent oil; yield: 150 mg (78%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 5 H), 3.70 (s, 2 H), 3.33 (s, 2 H), 1.67–1.51 (m, 6 H).

MS (APCI): m/z = 190.2 $[M + H]^+$.

Note: The reaction was repeated four times to give an average yield of 78%.

Phenyl(pyrrolidin-1-yl)methanone (2b)[10]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and pyrrolidine; yellow oil; yield: 133 mg (76%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 2 H), 7.39–7.37 (m, 3 H), 3.63 (t, J = 6.8 Hz, 2 H), 3.42 (t, J = 6.6 Hz, 2 H), 1.95–1.86 (m, 4 H).

MS (APCI): m/z = 176.2 $[M + H]^+$.

Note: The reaction was repeated four times to give an average yield of 76%.

N-Methylbenzamide (2c)[11]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and methylamine; white solid; yield: 109 mg (81%).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 6.8 Hz, 2 H), 7.46–7.37 (m, 3 H), 6.38 (s, 1 H), 3.00 (s, 3 H).

MS (APCI): m/z = 136.1 $[M + H]^+$.

Note: The reaction was repeated two times to give an average yield of 85%.

N-Benzylbenzamide (2d)[9]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and benzylamine; white solid; yield: 155 mg (73%).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.1 Hz, 2 H), 7.43–7.28 (m, 8 H), 6.31 (br s, 1 H), 4.60 (d, J = 5.7 Hz, 2 H).

MS (APCI): m/z = 212.2 $[M + H]^+$.

N-Phenylbenzamide (2e)[9]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and aniline; white solid; yield: 148 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.8 Hz, 2 H), 7.80 (s, 1 H), 7.64 (d, J = 6.0 Hz, 2 H), 7.56 (t, J = 5.6 Hz, 1 H), 7.49 (t, J = 6.6 Hz, 2 H), 7.36 (t, J = 5.1 Hz, 2 H), 7.16 (t, J = 5.6 Hz, 1 H).

MS (APCI): m/z = 198.2 $[M + H]^+$.

N-Isopropylbenzamide (2f)[12]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and isopropylamine; white solid; yield: 119 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.4 Hz, 2 H), 7.49–7.26 (m, 3 H), 5.92 (s, 1 H), 4.33–4.26 (m, 1 H), 1.26 (d, J = 6.6 Hz, 6 H).

MS (APCI): m/z = 164.2 $[M + H]^+$.

Note: The reaction was repeated two times to give an average yield of 73%.

N,N-Diethylbenzamide (2g)[11]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and diethylamine; white solid; yield: 124 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 5 H), 3.42 (s, 2 H), 3.14 (s, 2 H), 1.40–1.03 (m, 6 H).

MS (APCI): m/z = 178.2 $[M + H]^+$.

N,N-Diisopropylbenzamide (2h)[12]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and diisopropylamine; yellow oil; yield: 127 mg (62%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.38 (m, 3 H), 7.26–7.23 (m, 2 H), 3.60 (s, 2 H), 3.34 (s, 1 H), 1.36–1.12 (m, 12 H).

MS (APCI): m/z = 206.3 $[M + H]^+$.

N,N-Dimethylbenzamide (2i)[11]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and dimethylamine; white solid; yield: 126 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (s, 5 H), 3.11 (s, 3 H), 2.97 (s, 3 H).

MS (APCI): m/z = 150.1 $[M + H]^+$.

Note: The reaction was repeated two times to give an average yield of 90%.

Phenyl(thiomorpholino)methanone (2j)[13]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and thiomorpholine; transparent oil; yield: 144 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 5 H), 3.99–3.64 (m, 4 H), 2.69–2.55(m, 4 H).

MS (APCI): m/z = 208.2 $[M + H]^+$.

Morpholino(phenyl)methanone (2k)[11]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and morpholine; transparent oil; yield: 139 mg (73%).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.46–7.39 (m, 5 H), 3.58 (br s, 8 H).

MS (APCI): m/z = 192.2 $[M + H]^+$.

Note: The reaction was repeated two times to give an average yield of 76%.

Benzamide (2l)[14]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and ammonium hydroxide; white solid; yield: 78 mg (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.2 Hz, 1 H), 7.54–7.41 (m, 2 H), 6.21 (br s, 2 H), 5.80 (br s, 1 H).

MS (APCI): m/z = 122.1 $[M + H]^+$.

Benzoyl Azide (2m)[15]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and sodium azide; white solid; yield: 106 mg (72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.8 Hz, 2 H), 7.53–7.47 (m, 1 H), 7.42–7.37 (m, 2 H).

MS (APCI): m/z = 148.1 $[M + H]^+$.

S-Methyl Benzothioate (2n)[16]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and sodium thiomethoxide; transparent oil; yield: 110 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.2 Hz, 2 H), 7.58–7.42 (m, 3 H), 2.47 (s, 3 H).

MS (APCI): m/z = 153.2 $[M + H]^+$.

S-Phenyl Benzothioate (2o)[17]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and thiophenol; transparent oil; yield: 163 mg (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 7.5 Hz, 2 H), 7.67–7.47 (m, 8 H).

MS (APCI): m/z = 215.2 $[M + H]^+$.

Phenyl Benzoate (2p)[18]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and phenol; white solid (85 mg, 43%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (dd, J = 8.4, 2.0 Hz, 2 H), 7.62 (t, J = 6.0 Hz, 1 H), 7.54 (t, J = 6.8 Hz, 2 H), 7.46 (t, J = 8.4 Hz, 2 H), 7.28–7.20 (m, 3 H).

MS (APCI): m/z = 199.2 $[M + H]^+$.

Methyl Benzoate (2q)[19]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from benzoic anhydride and methanol; transparent oil; yield: 58 mg (43%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.4 Hz, 2 H), 7.58–7.42 (m, 3 H), 3.91 (s, 3 H).

MS (APCI): m/z = 137.1 $[M + H]^+$.

(4-Methoxyphenyl)(pyrrolidin-1-yl)methanone (3b)[10]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 4-methoxybenzoic anhydride and pyrrolidine; transparent oil; yield: 168 mg (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.7 Hz, 2 H), 6.89 (d, J = 9.0 Hz, 2 H), 3.83 (s, 3 H), 3.63 (t, J = 6.9 Hz, 2 H), 3.48 (t, J = 6.9 Hz, 2 H), 1.95–1.86 (m, 4 H).

MS (APCI): m/z = 206.2 $[M + H]^+$.

Note: The reaction was repeated four times to give an average yield of 80%.

Pyrrolidin-1-yl(thiophen-3-yl)methanone (4b)[10]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from thiophene-3-carboxylic acid anhydride and pyrrolidine; transparent oil; yield: 130 mg (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.65 (m, 1 H), 7.37 (d, J = 5.1 Hz, 1 H), 7.30 (d, J = 4.8 Hz, 1 H), 3.65–3.57 (m, 4 H), 1.94–1.92 (m, 4 H).

MS (APCI): m/z = 182.2 $[M + H]^+$.

[4-(Dimethylamino)phenyl](pyrrolidin-1-yl)methanone (5b)

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 4-dimethylaminobenzoic anhydride and pyrrolidine; transparent oil; yield: 163 mg (75%); mp 82–85 °C.

IR (KBr): 3437, 2960, 2864, 1598, 1416, 1190, 946 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, J = 9.0 Hz, 1 H), 6.66 (d, J = 9.0 Hz, 2 H), 3.56 (br s, 4 H), 2.98 (s, 6 H), 1.87 (br s, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 151.5, 129.2, 124.1, 110.9, 46.4, 40.2, 24.46.

HRMS (APCI): m/z $[M + H]^+$ calcd for $C_{13}H_{19}N_2O$: 219.1497; found: 219.1492.

(4-Methylphenyl)(pyrrolidin-1-yl)methanone (6b)[10]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 4-methylbenzoic anhydride and pyrrolidine; transparent oil; yield: 147 mg (78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 7.5 Hz, 2 H), 7.19 (d, J = 7.8 Hz, 2 H), 3.64 (t, J = 6.9 Hz, 2 H), 3.45 (t, J = 6.6 Hz, 2 H), 2.38 (s, 3 H), 1.98-1.86 (m, 4 H).

MS (APCI): m/z = 190.2 $[M + H]^+$.

Note: The reaction was repeated two times to give an average yield of 80%.

Furan-3-yl(pyrrolidin-1-yl)methanone (7b)[10]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 3-furoic anhydride and pyrrolidine; transparent oil; yield: 135 mg (82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 7.05 (d, J = 3.4 Hz, 1 H), 6.48 (s, 1 H), 3.82 (t, J = 6.6 Hz, 2 H), 3.65 (t, J = 6.6 Hz, 2H), 2.01–1.87 (m, 4 H).

MS (APCI): m/z = 166.1 $[M + H]^+$.

Cyclohexyl(pyrrolidin-1-yl)methanone (8b)[20]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from cyclohexanecarboxylic acid anhydride and pyrrolidine; transparent oil; yield: 132 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.45–3.39 (m, 4 H), 2.34–2.26 (m, 1 H), 1.93–1.19 (m, 14 H).

MS (APCI): m/z = 182.2 $[M + H]^+$.

4-(Pyrrolidine-1-carbonyl)benzonitrile (9b)[21]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 4-cyanobenzoic anhydride and pyrrolidine; transparent oil; yield: 168 mg (84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.4 Hz, 2 H), 3.64 (t, J = 6.6 Hz, 2 H), 3.36 (t, J = 6.6 Hz, 2 H), 1.98–1.86 (m, 4 H).

MS (APCI): m/z = 201.2 $[M + H]^+$.

2-Phenyl-1-(pyrrolidin-1-yl)ethanone (10b)[22]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from phenylacetic anhydride and pyrrolidine; yellow oil; yield: 126 mg (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 3.68 (s, 2 H), 3.53–3.42 (m, 4 H), 1.95–1.81 (m, 4 H).

MS (APCI): m/z = 190.2 $[M + H]^+$.

1-[4-(Pyrrolidine-1-carbonyl)phenyl]ethan-1-one (11b)[10]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 4-acetylbenzoic anhydride and pyrrolidine; transparent oil; yield: 160 mg (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.2 Hz, 2 H), 7.60 (d, J = 8.1 Hz, 2 H), 3.63 (t, J = 6.8 Hz, 2 H), 3.36 (t, J = 6.8 Hz, 2 H), 2.57 (s, 3 H), 1.95–1.82 (m, 4 H).

MS (APCI): m/z = 218.2 $[M + H]^+$.

4-(Pyrrolidine-1-carbonyl)benzaldehyde (12b)[11]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from 4-formylbenzoic anhydride and pyrrolidine; transparent oil; yield: 158 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.06 (s, 1 H), 7.95 (d, J = 6.6 Hz, 2 H), 7.69 (d, J = 6.6 Hz, 2 H), 3.70 (t, J = 6.8 Hz, 2 H), 3.42 (t, J = 6.8 Hz, 2 H), 2.02–1.90 (m, 4 H).

MS (APCI): m/z = 204.2 $[M + H]^+$.

***N*,*N*-Dimethylterephthalamide (13b)**

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from the corresponding benzoic anhydride with ammonium hydroxide; yellow solid; yield: 130 mg (67%); mp 131–134 °C.

IR (KBr): 3351, 3167, 2933, 1685, 1620, 1384, 1140, 863 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.8 Hz, 2 H), 6.24 (br s, 1 H), 5.72 (br s, 1 H), 3.12 (s, 3 H), 2.95 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.67, 168.7, 139.6, 134.4, 127.6, 127.2, 39.3, 35.3.

HRMS (APCI): m/z $[M + H]^+$ calcd for $C_{10}H_{12}N_2O_2$: 193.0975; found: 193.0972.

Boc-Phenylalanine Pyrrolidine Amide (14b)[22]

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from the corresponding carboxylic acid anhydride and pyrrolidine; colorless oil; yield: 256 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21–7.12 (m, 5 H), 5.35 (br d, *J* = 8.7 Hz, 1 H), 4.52–4.49 (m, 1 H), 3.38–3.20 (m, 3 H), 2.92–2.83 (m, 2 H), 2.52–2.47 (m, 1 H), 1.70–1.49 (m, 4 H), 1.34 (s, 9 H).

tert-Butyl {1-[(2-Morpholinophenyl)amino]-1-oxo-3-phenylpropan-2-yl}carbamate (15b)

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from the corresponding carboxylic acid anhydride and 2-morpholinoaniline; white solid; yield: 357 mg (84%); mp 121–124 °C.

IR (neat): 3308, 2960, 1715, 1659, 1518 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.92 (br s, 1 H), 8.45 (d, *J* = 8.4 Hz, 1 H), 7.29–7.10 (m, 8 H), 5.04 (br s, 1 H), 4.51 (br s, 1 H), 3.70–3.69 (m, 4 H), 3.20 (t, *J* = 6 Hz, 2 H), 2.67–2.61 (m, 4 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 155.1, 140.9, 136.5, 132.9, 129.4, 128.8, 127.0, 125.7, 124.1, 120.6, 119.3, 67.4, 52.3, 38.5, 28.3.

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{32}N_3O_4$: 426.2317; found: 426.2433.

tert-Butyl [4-(Azidocarbonyl)phenyl]carbamate (16b)

The title compound was prepared following the general procedure for nucleophilic acyl substitution, from the corresponding benzoic anhydride and sodium azide; white solid; yield: 206 mg (79%); mp 124–127 °C.

IR (neat): 3344, 2138, 1728, 1670 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.93 (m, 2 H), 7.46 (d, *J* = 7.2 Hz, 2 H), 6.79 (br s, 1 H), 1.52 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 152.0, 144.1, 131.0, 124.8, 117.4, 81.5, 28.2.

MS (APCI): *m*/*z* = 133.1 $[M – (Boc + N_2)]^+$.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609564.

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