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Acetic acid as a catalyst for the *N*-acylation of amines using esters as the acyl source†

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We report a cheap and simple method for the acetylation of a variety of amines using catalytic acetic acid and either ethyl acetate or butyl acetate as the acyl source. Catalyst loadings as low as 10 mol% afforded acetamide products in excellent yields at temperatures ranging from 80–120 °C. The methodology can also be successfully applied for the synthesis of a broad range of other amides, including the formation of formamides at 20 °C.

The amide bond is one of the most important functionalities in both industrial and medicinal chemistry. Traditional amidation methods involve the use of coupling reagents, however the production of stoichiometric by-products resulted in the ACS's Green Chemistry Institute Pharmaceutical Roundtable highlighting the need for a catalytic and waste-free synthesis of amides in 2005.[1] Extensive research has since been carried out by various groups, including our own, in order to develop more efficient methodologies.[2]

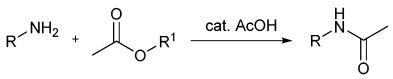
A particular area of interest for the group has involved the use of metal catalysts to form amides from a range of starting materials. Zirconocene dichloride, Cp_2ZrCl_2, has been identified as an efficient catalyst for the coupling of amines with both carboxylic acids[3] and amides,[4] whilst use of 10 mol% $Fe(NO_3)_3 \cdot 9H_2O$ has been shown to catalyse the addition of amines to nitriles.[5] Rana and Dutta have also reported the formation of amides from carboxylic esters, using 20 mol% InI_3 and an excess of the amine.[6] Other more recent catalysts that couple esters and amines include BEMP,[7] K_3PO_4,[8] $La(OTf)_3$,[9] NaOMe[10] and CaI_2.[11] In addition to metal catalysts, non-metal compounds have also been found to catalyse amidation reactions successfully, with boronic acids and related compounds the most common examples.[12]

As well as these general amidation methods there are also many protocols reported that are specific to the formation of acetamides. These amides have many applications and are important to the polymer, agrochemical and pharmaceutical industries.[13] However, the traditional methods used to synthesise acetamides usually involve the use of activated acylating agents, such as acetic anhydride and acetyl chloride. Although these reagents are cheap, their toxicity and hygroscopic nature make them less than ideal as acylating agents.[13a] Many procedures also use metal catalysts, both heterogeneous and homogeneous, which are often expensive and add further purification steps.[14]

Herein we describe a novel non-metal catalysed method for the acetylation of primary and secondary amines, as well as aniline derivatives. The lower reactivity of the acetate esters used in this new procedure make them a more desirable acylating agent compared with acid chlorides and acid anhydrides (Scheme 1).

It is well known that in polar solvents salt formation usually occurs upon mixing of amines and acids, thus disfavouring the amidation reaction.[15] However, previous studies, such as that by Brahmachari and co-workers,[14b] have shown that the presence of acetic acid does not result in reduced conversion from amine to amide. This is likely due to the relatively moderate pK_a value of acetic acid (12.3 in DMSO at 25 °C) compared with stronger acids such as H_2SO_4 (see ESI†). We hypothesised that the lower acidity of acetic acid results in the protonation/deprotonation equilibrium being pushed in favour of the free amine, thus allowing transfer of the acyl group.

With this rationale in mind, we theorised that acetic acid would be an appropriate catalyst to investigate (Table 1). The choice of organic acid also meant that the same product would be produced, irrespective of whether the acetyl group was transferred from the acetic acid or acetate ester. Initial experiments showed that quantitative conversion of our model substrate, 4-methylbenzylamine, into the acetamide product could be



Scheme 1 General reaction scheme for the *N*-acetylation of amines using catalytic acetic acid and an acetate ester as the acyl source.

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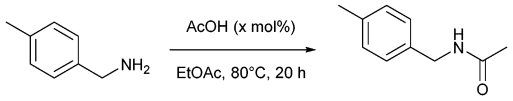
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterisation and copies of the ^1H and ^{13}C NMR spectra are provided. See DOI: 10.1039/c6cc09023k

Table 1 Optimisation of reaction conditions for the conversion of 4-methylbenzylamine into *N*-(4-methylbenzyl)acetamide



Entry[a]	AcOH (mol%)	EtOAc (mL)	Conversion[b] (%)
1	100	1	100
2	50	1	100
3	20	1	100
4	10	1	100
5	5	1	98
6	—	1	2
7[c]	10	1	96
8	10	0.5	100
9[d]	10	0.5	53
10	10	0.25	90

[a] All reactions were performed on a 1 mmol scale. [b] Conversions were determined by analysis of the ^{1}H NMR spectra. [c] The reaction was performed for 16 hours. [d] The reaction was performed at 60 °C.

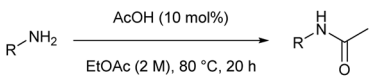
achieved using a stoichiometric amount of acetic acid in ethyl acetate at reflux (1 M) (Table 1, entry 1). Further investigations revealed that catalyst loadings as low as 10 mol% afforded the acetamide product in quantitative conversion (Table 1, entry 4), compared with only a 2% background rate (Table 1, entry 6). The fully optimised reaction conditions allowed the reaction to be performed in reduced ethyl acetate solvent (2 M) at 80 °C for 20 hours (Table 1, entry 8). We subsequently showed that the methodology could be applied to a range of primary amines, affording acetamide products in excellent yields (Table 2).

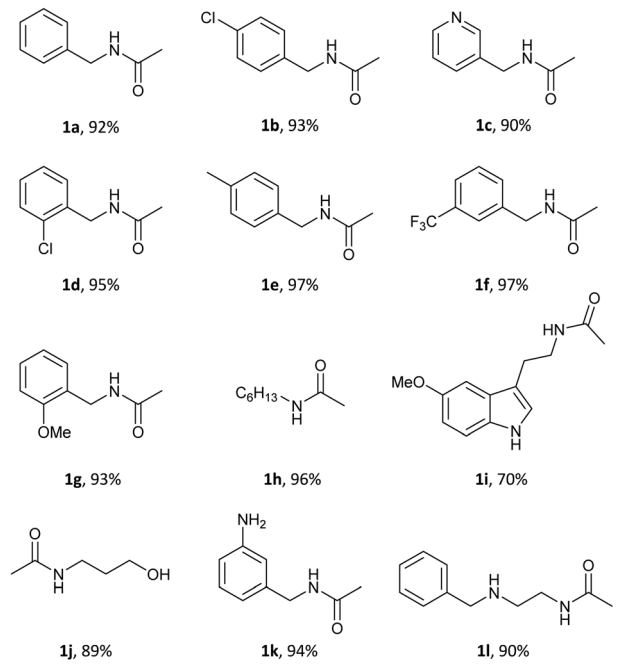
Secondary amines were then explored, however, due to their decreased nucleophilicity, harsher conditions were required to achieve good conversions. Using *N*-benzylmethylamine as the model substrate, the catalyst loading was firstly increased to 50 mol%. However, due to the poor conversion, it was decided to increase the catalyst loading further, although no significant increase in conversion was observed (see ESI†). Instead, we hypothesised that an increase in the reaction temperature, using butyl acetate as a higher-boiling solvent, would push the reaction further towards completion. Following optimisation, quantitative conversion was achieved using catalytic acetic acid (50 mol%) at 120 °C for 20 hours. A selection of tertiary acetamides was successfully synthesised from secondary amines using these reaction conditions (Table 3).

In addition, although our methodology is primarily focused on the *N*-acetylation of primary and secondary amines, it can also be applied to aniline derivatives. Significantly harsher conditions are required for this transformation, due to the lower nucleophilicity of anilines. The reaction is no longer catalytic, with 2.5 equivalents of acetic acid needed to achieve near quantitative conversion at 110 °C in 20 hours (Table 4).

We were pleased to find that the three sets of reaction conditions allowed the *N*-acetylation of a wide range of amines. The methodology is tolerant to a variety of functional groups, including halogens (**1b**, **1d** and **1f**), heterocycles (**1c**, **1i**, **2a** and **2c**), arenes (**1a**, **1b**, **1d–1g**, **1i**, **1k**, **1l**, **2a–2c**, **3a** and **3b**), alkenes (**2c**) and long alkyl chains (**1h**).

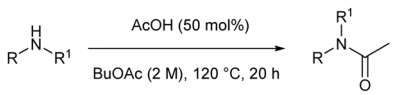
Table 2 *N*-Acetylation of primary amines using acetic acid as a catalyst and ethyl acetate as the acyl source[a]

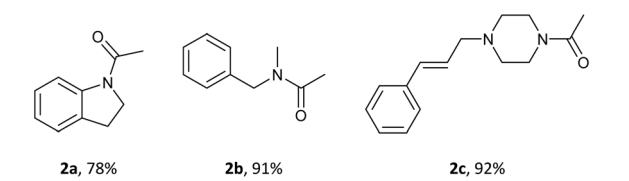




[a] Isolated yields.

Table 3 *N*-Acetylation of secondary amines using acetic acid as a catalyst and butyl acetate as the acyl source[a]



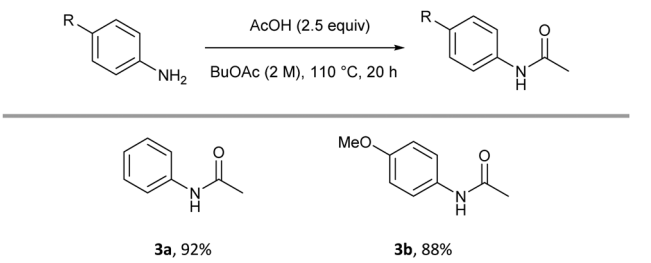


[a] Isolated yields.

To test the pharmaceutical applicability of the methodology, we decided to synthesise the hormone and sleep disorder drug, melatonin, from 5-methoxytryptamine. To our delight, we were able to apply the primary amine conditions and isolate the target molecule in good yield (**1i**).

The chemoselectivity of the methodology was also investigated by applying the protocol to bifunctional amines (**1j–1l**). The methodology is able to selectively acetylate an amino group over an alcohol; negligible *O*-acetylation was observed when 3-amino-1-propanol was subjected to the reaction conditions to afford **1j**. In addition, when both an aromatic and benzyl amine are present

Table 4 *N*-Acetylation of aniline derivatives using acetic acid as a catalyst and butyl acetate as the acyl source[a]



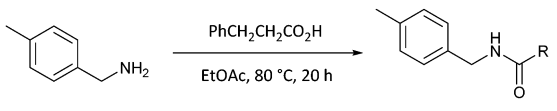
[a] Isolated yields.

in a substrate, the latter is selectively acetylated (**1k**). Finally, the protocol is able to distinguish between primary and secondary amines, operating only on the first functionality; for example, when *N*-benzylethylenediamine was employed only acetamide **1l** was obtained.

The scalability of the reaction was assessed by performing the *N*-acetylation of benzylamine on a 67 mmol scale. Quantitative conversion into *N*-benzylacetamide was achieved after 22 hours and the product isolated in 92% yield (9.2 g) after aqueous work-up.

To investigate the reaction mechanism, we firstly decided to explore the origin of the acetyl group which is subsequently transferred to the amine. Experiments were conducted using 4methylbenzylamine in which the acetic acid was replaced with a structurally similar organic acid, 3-phenylpropionic acid (Table 5). Using ethyl acetate (1 M) as the solvent and a stoichiometric amount of 3-phenylpropionic acid, we found that the majority of the resulting mixture contained acetamide product **4a**, with only a small proportion of **4b** present (Table 5, entry 1). As the amount of acid used in the reaction decreased, the product ratio (**4a** : **4b**), as expected, moved even further towards quantitative conversion into **4a** (Table 5, entries 2–5). Meanwhile, if the amount of ethyl acetate was reduced, the ratio decreased (Table 5, entries 6–8). However, even if the amine, acid and ester are reacted in an equimolar ratio,

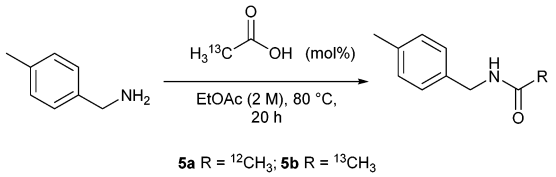
Table 5 Investigations into the transfer of the acetyl group



4a R = Me; **4b** R = CH_2CH_2Ph

Entry[a]	Acid (mol%)	EtOAc (mL)	Conversion into **4a** and **4b**[b] (%)	**4a** : **4b**[b]
1	100	1	100	95 : 5
2	50	1	100	96 : 4
3	20	1	100	97 : 3
4	10	1	100	98 : 2
5	5	1	97	99 : 1
6	100	0.5	100	93 : 7
7	100	0.25	97	91 : 9
8	100	0.098 (1 mmol)	62	84 : 16

[a] All reactions were performed on a 1 mmol scale. [b] Conversions and product ratios were determined by analysis of the ^{1}H NMR spectra.



5a R = $^{12}CH_3$; **5b** R = $^{13}CH_3$

Scheme 2 ^{13}C-Labelling study investigating the incorporation of acetic acid.

the major product remains **4a** (Table 5, entry 8). This therefore suggests that the acetyl moiety of the acetamides synthesised using our methodology largely originates from the acetate ester and not the acetic acid.

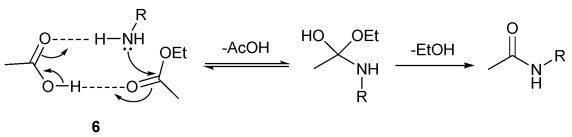
Further investigations were subsequently undertaken using ^{13}C-methyl-labelled acetic acid as the catalyst (Scheme 2). Two experiments were performed in which our model substrate, 4-methylbenzylamine, was reacted with catalyst loadings of 10 mol% and 50 mol% to give products **5a** and **5b**. Quantitative ^{13}C NMR studies showed minimal incorporation of acetic acid into the final product, with 0.5% and 3.0% incorporation respectively. These results were further confirmed through analysis of the acetyl group satellites in the ^{1}H NMR spectra for each experiment (see ESI†).

We believe that the role of the acid catalyst is not simply that of a proton transfer reagent. When H_2SO_4 is used as the acid catalyst, no conversion is observed, presumably due to the formation of the HSO_4^-/RNH_3^+ salt (see ESI†). However, RNH_3^+ is a stronger acid ($pK_a \approx 10$) than acetic acid ($pK_a \approx 12$) and therefore if the reaction mechanism solely involved proton transfer, a higher conversion would be expected with the protonated amine present compared with acetic acid.

However, this is not the case, leading us to believe that the reaction mechanism proceeds through a transition state involving acetic acid rather than just a proton (**6**), similar to that proposed by Whiting *et al.* in 2011 (Scheme 3).[16] Further mechanistic studies are to be performed in the future.

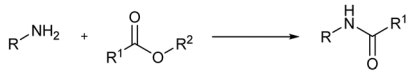
In addition to the *N*-acetylation work described, the scope of the ester component was also explored (Table 6). A variety of methyl and ethyl esters were reacted with benzylamine to produce a range of secondary amides. Ethyl propionate and related substrates were successfully transformed into their corresponding amide products using 2 equivalents of the ester and 10 mol% acetic acid (**7a–7c**).

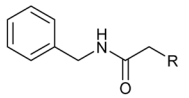
Remarkably, the transformation of ethyl trifluoroacetate (1 equiv.) into **7f–7h** was achieved at room temperature (25 °C) with no acid catalyst present. Pleasingly, the reaction of ethyl trifluoroacetate with (*R*)-(+)-α-methylbenzylamine proceeded with retention of stereochemistry (**7h**), as determined by chiral HPLC analysis (see ESI†).



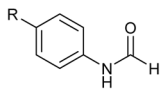
Scheme 3 Plausible mechanism for the *N*-acetylation of amines using acetic acid as a catalyst and ethyl acetate as the acyl source.

Table 6 Conversion of a variety of methyl and ethyl esters into amides[a]

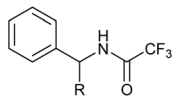




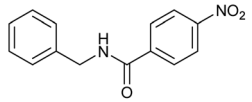
7a R = CH_3, 92%[b]
7b R = Ph, 93%[b]
7c R = CN, 94%[b]



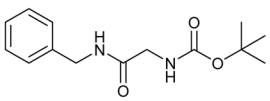
7d R = H, 94%[c]
7e R = OMe, 92%[c]



7f R = H, 100%[d,e]
7g R = Me, 100%[d]
7h R = (*R*)-Me, 100%[d], > 99% *ee*[f]



7i, 60%[g]



7j, 97%[e,h]

[a] Isolated yields. [b] Reaction conditions: ethyl ester (2 equiv.), AcOH (10 mol%), 110 °C, 20 h. [c] Reaction conditions: ethyl formate (2 M), AcOH or formic acid (50 mol%), 20 °C, 16 h. [d] Reaction conditions: ethyl trifluoroacetate (1 equiv.), no catalyst, 25 °C, 20 h. [e] Can also be performed in toluene (2 M). [f] As determined by chiral HPLC analysis. [g] Reaction conditions: methyl 4-nitrobenzoate (1 equiv.), AcOH (10 mol%), 150 °C, 20 h. [h] Reaction conditions: Boc-Gly-OMe (1 equiv.), AcOH (10 mol%), 110 °C, 20 h.

Furthermore, although the unsubstituted methyl benzoate proved relatively unreactive under the reaction conditions (see ESI†), the electron-deficient 4-nitro derivative was successfully converted into **7i** using 10 mol% acetic acid. However, a high reaction temperature of 150 °C was required in order to afford the product in good yield. An increased catalyst loading was not employed as this resulted in the production of a larger proportion of the acetamide side product.

Pleasingly, the methodology was shown to tolerate amino acid esters. For example, amide **7j** was afforded in excellent yield, with negligible deprotection of the Boc protecting group by the acetic acid catalyst. The protocol was also extended to *N*-formylations; aniline and *p*-anisidine were converted into products **7d** and **7e** respectively, using ethyl formate as the solvent and either formic acid or acetic acid as the catalyst (50 mol%).

In summary, we have identified acetic acid as an effective catalyst for the *N*-acetylation of amines, using either ethyl acetate or butyl acetate as the acyl source. The methodology has been shown to transform a wide variety of amines into their acetamide products in excellent yields. The methodology can also be applied to other esters, including formates, electron-deficient benzoates and amino acid esters, in order to synthesise higher amides.

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