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A facile, one-pot procedure for the conversion of aromatic aldehydes to esters, as well as thioesters and amides, *via* acyl hydrazide intermediates

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Herein we present an efficient method for the synthesis of esters from aromatic aldehyes *via* readily accessible acyl hydrazides. The developed reaction protocol is shown to be tolerant of a range of aromatic aldehydes, bearing various functionalities, as well as being amenable to the synthesis of thioesters and amides.

Esters are one of the most important functional moieties in organic synthesis. They are abundant in various polymers, natural products and pharmaceutical agents.[1] Classically, esters have been synthesised *via* the reaction of carboxylic acid derivatives (*e.g.* anhydrides, acyl halides and activated esters) with alcohols.[2] An alternative to this classical approach is the oxidative esterification of aldehydes *via* a hemiacetal intermediate (Figure 1a).[3] In this context, metal-mediated oxidative aldehyde esterifications have been investigated in great detail.[3] Effective conversion of aldehyde to ester has been achieved by the use of gold,[4] rhodium,[5] palladium[6] and iron[7] catalysts. Whilst successful, these protocols tend to suffer from limited substrate scope due to harsh reaction conditions, use of a stoichiometric amount of catalyst and the high cost of the procedures. However, over the last few decades, direct transition-metal-free aldehyde esterification protocols have been reported using oxidants such as iodine,[8] *N*-iodosuccinimide,[9] oxone,[10] pyridinium hydrobromide perbromide,[11] sodium hypochlorite,[12] and hydrogen peroxide.[13] Despite the obvious benefits provided by metal-free protocols, the developed methods suffer from issues of hemiacetal instability and most methods to date only provide access to methyl esters in an efficient manner. Thus, an intriguing alternative for the direct conversion of aldehydes to esters is that which does not proceed through a hemiacetal intermediate. Such protocols have been developed using *N*-heterocyclic carbene (NHC) methodologies (Figure 1b).[14] Nonetheless, these protocols remain, almost solely, limited to the use of primary alcohols, which are also employed in large excess.

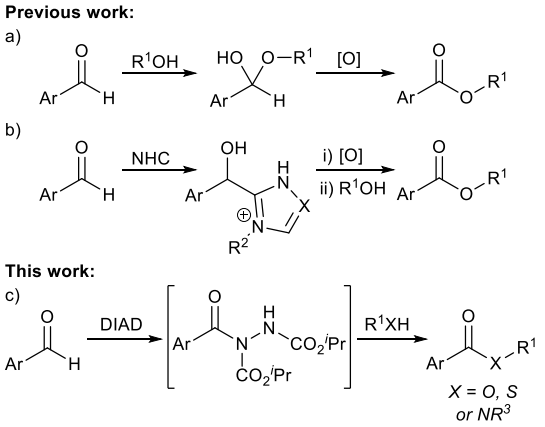

Figure 1 a-b) Classical methods for the direct conversion of aldehydes to esters and c) the novel strategy disclosed in this manuscript, which is also amenable to the synthesis of thioesters and amides.

Recently, a plethora of methods for the efficient and effective conversion of aldehydes to acyl hydrazides have been reported.[15-26] Moreover, the overall transformation has been shown to proceed under a wide range of reaction conditions, in a variety of solvents and with the aldehyde being employed as the limiting reagent. More recently, Chudasama, Caddick and co-workers have shown the formed acyl hydrazides to undergo reaction with Grignard reagents for the efficient synthesis of ketones.[19,21] With the acyl donor ability of acyl hydrazides in mind, we were intrigued by the possibility of using acyl hydrazides for the synthesis of esters. Moreover, with the stability of acyl hydrazides being well documented, we envisioned from the outset that such a development could be adapted to the one-pot conversion of aldehydes to esters *via* an *in situ* prepared acyl hydrazide intermediate (Figure 1c).

Our study began by optimising the reaction of acyl hydrazide **1a** with *n*-butanol **2a** (Table 1). Initially, the reaction was carried out under solvent-free conditions with 5 to 100 equivalents of alcohol and using caesium carbonate as base (Table 1, Entries 1-4). Complete conversion was observed

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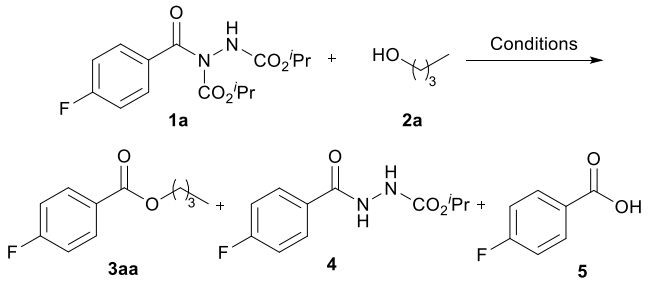
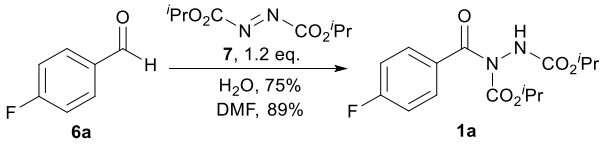
when the reaction was carried out in a vast excess of alcohol (100 eq.). However, it was clear that the solvent-free conditions would not be amenable to the synthesis of esters in high yields without employing a significant alcohol loading. As such, a solvent screen was carried out using 5 equivalents of *n*-butanol **2a** and caesium carbonate as base (Table 1, Entries 5-8). An excellent yield of ester **3aa** was observed in DMF. Moreover, high yield was retained on reducing alcohol equivalence from 5 through to 1.1. However reducing the equivalents of base or exchanging it for other common bases (*e.g.* NEt_3, DIPEA) reduced the yield dramatically, except for when potassium *tert*-butoxide was employed. The main side-products identified in the reaction protocol were hydrazide **4** and acid **5**. Hydrazide **4** is likely to have formed *via* attack of the alcohol at the carbamate carbonyl, whereas acid **5** is presumably derived from hydrolysis of hydrazide **1a** with residual water in the alcohol or solvent. We also highlight that the optimised conditions were not amenable to synthesis of esters when using aliphatic-based acyl hydrazides.



Entry	Solvent	Base[a]	Time/h	**2a**/eq	Conversion **1a**/%[b]	**3aa**/%[b]
1	-	Cs_2CO_3	16	100	100	95
2	-	Cs_2CO_3	16	50	80	70
3	-	Cs_2CO_3	16	10	55	44
4	-	Cs_2CO_3	16	5	30	21
5	NMP	Cs_2CO_3	16	5	95	88
6	DMF	Cs_2CO_3	16	5	100	94
7	THF	Cs_2CO_3	16	5	75	60
8	CH_2Cl_2	Cs_2CO_3	16	5	60	48
9	DMF	Cs_2CO_3	16	2.5	97	91
10	**DMF**	**Cs_2CO_3**	**16**	**1.1**	**94**	**87**
11	DMF	NEt_3	16	1.1	68	60
12	DMF	DIPEA	16	1.1	70	58
13	DMF	KO^tBu	16	1.1	95	82
14	DMF	Cs_2CO_3 (0.5 eq.)	16	1.1	60	47
15	DMF	Cs_2CO_3	12	1.1	85	71
16	DMF	Cs_2CO_3	6	1.1	51	42

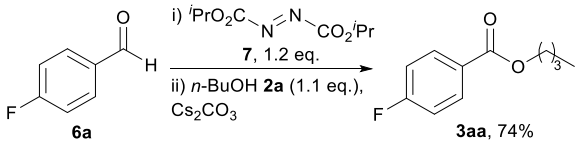
Table 1 Reaction of acyl hydrazide **1a** with alcohol **2a** under a range of conditions. [a] 1 eq. unless otherwise stated in parenthesis. [b] ^{1}H NMR yield of based on pentacholorobenzene as internal standard.

Having optimised the conditions for the conversion of an aromatic acyl hydrazide into an ester, we set about combining this work with the formation of acyl hydrazides from aldehydes in a single pot. Previously we have reported a highly efficient protocol for the conversion of aldehydes to acyl hydrazides using aerobic C-H activation, which proceeded successfully "on water".[21,22] However, in view of the fact that esterification proceeded most efficiently in DMF, we appraised the reaction of an aldehyde with an azodicarboxylate (for the formation of an acyl hydrazide) in this solvent. Gratifyingly, use of DMF as solvent actually improved the yield of the transformation from 75% to 89% (Scheme 1).



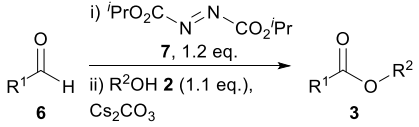
Scheme 1 Reaction of aldehyde **6a** with azodicarboxylate **7** (1.2 eq.) "on water" and in DMF.

We next appraised whether a one-pot conversion of aldehyde **6a** to ester **3aa** was feasible. To do this, the aldehyde and azodicarboxylate were reacted in DMF at 21 °C for 24 h, followed by addition of alcohol and caesium carbonate and incubation at 21 °C for 16 h; reaction times were optimised by ^{19}F NMR studies. To our delight, after this two-step procedure, flash column chromatography afforded the desired ester in 74% isolated yield.‡ Notably, a one-pot procedure where all reagents were combined from the start was also successful, albeit in a lower overall yield of 54%.



Scheme 2 One-pot conversion of aldehyde **6a** to ester **3aa**.‡

With optimised conditions in hand we took the opportunity to investigate the applicability of our protocol for the formation of various esters (Table 2). A range of aromatic aldehydes (**6a-f**) and alcohols (**2a-h**) were appraised under the developed reaction conditions.



Entry	Aldehyde **6**, R^1 =	Alcohol, R^2 =	Yield/%
1	**6a**	**2a**	74, **3aa**
2	**6b**	**2a**	72, **3ba**
3	**6c**	**2a**	71, **3ca**
4	**6d**	**2a**	72, **3da**
5	**6e**	**2a**	67, **3ea**

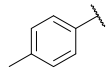
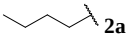
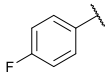
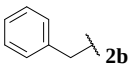
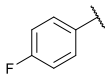
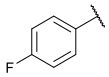
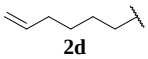
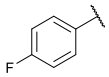
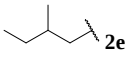
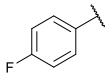
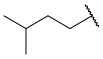
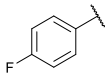
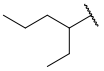
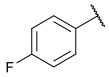
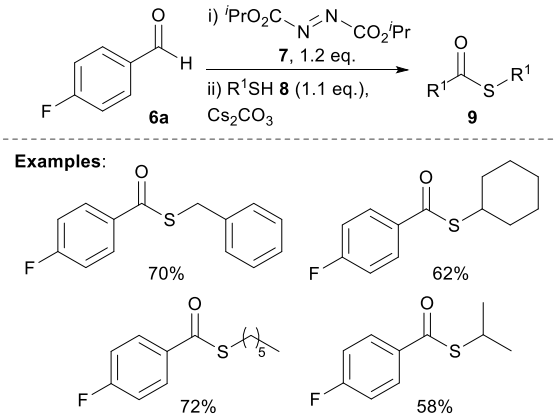
6	 **6f**	 **2a**	72, **3fa**
7	 **6a**	 **2b**	76, **3ab**
8	 **6a**	 **2c**	52, **3ac**
9	 **6a**	 **2d**	70, **3ad**
10	 **6a**	 **2e**	76, **3ae**
11	 **6a**	 **2f**	72, **3af**
12	 **6a**	 **2g**	68, **3ag**
13	 **6a**	 **2h**	76, **3ah**

Table 2 One-pot reaction of aldehydes **6** with alcohols **2** for the formation of esters **3**.

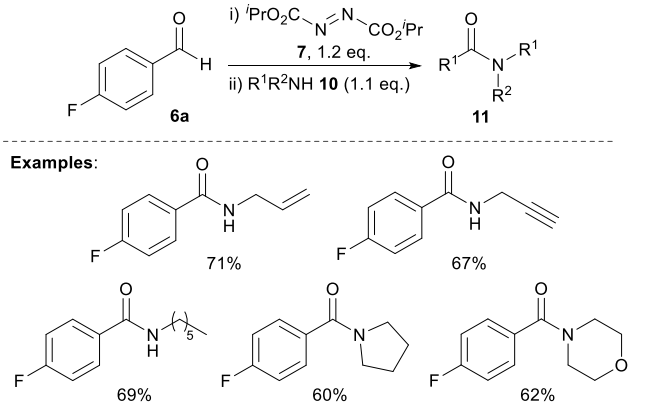
To our delight, the reaction was tolerant of various functional groups on the aromatic aldehyde motif, *e.g.* nitro, halo, trifluoromethyl, cyano and methyl functionalities (Table 2, Entries 1-6), on reaction with *n*-butanol **2a**. Excellent and consistent yields were observed across the series, 67-76%. Moving to the tolerance of the alcohol reagent, alcohols bearing a range of functional groups (*e.g.* alkene, alkyne, aromatic) were appraised, as well as secondary alcohol **2g**. Gratifyingly, the optimised reaction conditions, on reaction with aldehyde **6a**, afforded esters in generally good yields (Table 2, Entries 7-13). Perhaps as expected, due to its reduced nucleophilicity, the only modest yield was observed upon use of phenol **2c**.

The reaction protocol was also shown to be amenable to the synthesis of thioesters. Application of the optimised reaction conditions for the synthesis of esters to the formation of thioesters afforded various thioesters in good yields (Scheme 3). Gratifyingly, primary, secondary and benzylic thiols were all tolerated under the reaction conditions. This was particularly pleasing as sulfur-containing motifs are present in a large number of natural products, biologically active molecules, and materials.[27] Traditional methods for the construction of thioesters tend to be limited to the reaction of acyl bromides or chlorides with thiol derivatives.[28] This suffers from limitations in terms of the instability and moisture-sensitivity of acyl bromides/chlorides. Thus, the method presented is a mild and efficient alternative to traditional methods, and moreover, may proceed *via* conversion from an aromatic aldehyde in a simple one-pot procedure.



Scheme 3 One-pot conversion of aldehyde **6a** to thioesters **9** using azodicarboxylate **7** and thiols **8**.

Finally, the developed reaction conditions were trialled for the formation of amides. To do this, aldehyde **6a** was reacted with DIAD followed by the addition of a collection of primary and secondary amines in the absence of caesium carbonate. To our delight, good yields were observed across the series (Scheme 4). Previously, it has been shown that aliphatic-based acyl hydrazides undergo efficient amide formation when using primary amines but the yields were significantly reduced on application of secondary amines due to nucleophilic attack of the amine at the carbamate carbonyl (*i.e.* to form compounds of the form of hydrazide **4**).[21] In this case however, when using aromatic aldehydes, and thus in turn aromatic hydrazides, no sharp decrease in yield was observed (*ca.* 10% reduction). This discrepancy is likely to be due to the aromatic acyl hydrazide residing in a different conformation to an aliphatic analogue, potentially due to the steric clash of the aromatic group and the carbamate α- to the amide carbonyl group. The developed procedure is of appreciable significance as amides are of high value, particularly in the pharmaceutical industry.[29] They are typically prepared *via* highly reactive acyl derivatives or from carboxylic acids using one of several possible coupling reagents.[30] Whilst amides may be prepared from aldehydes, this typically involves the use of undesirable metals.[31] Thus, the detailed protocol provides an appealingly, simple and orthogonal route for amide preparation from aromatic aldehydes with tolerance of primary and secondary amines.



Scheme 4 One-pot conversion of aldehyde **6a** to amides **11** using azodicarboxylate **7** and amines **10**.

Conclusions

In conclusion, we have shown readily accessed acyl hydrazides to be suitable candidates for the synthesis of esters, thioesters and amides. Moreover, one-pot transformations from aromatic aldehydes to esters, thioesters and amides have been established with various aromatic aldehydes, alcohols, thiols and amines being tolerated under the mild reaction conditions.

Acknowledgements

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‡ 74% yield refers to the reaction being carried out on a 0.5 mmol scale of aldehyde. The reaction was also successful on a 5.0 mmol scale of aldehyde with the ester being isolated in 68% yield (see ESI for further details).

