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Chemoselective calcium-catalysed direct amidation of carboxylic esters†

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Unactivated carboxylic esters and primary amines undergo calcium-catalysed direct amide bond formation in excellent yields under homogeneous conditions in toluene. This green and mild reaction proceeds chemoselectively with esters, whereas related carboxylic acids and amides remain unreactive.

Many highly useful transformations in organic chemistry are catalysed by transition metals, such as Ru, Rh, Ir, Os, Pt, Pd, Au, Cu, and Fe.[1] Transition metal catalysis is no longer recognised as the most optimal method for generating organic compounds, mainly due to the increased toxicity, high cost and restricted accessibility of such catalysts. At present, however, basic transformations often lack greener variations employing benign and cheap catalysts. Calcium, as one of the cheapest, most abundant and most non-toxic metals, is a particularly attractive candidate that could replace widely used transition metals.[2] In the past decade, several calcium-catalysed reactions have been reported, most of them acting on alkenes, alcohols, or carbonyl-containing compounds.[3]

This work arises from our interest in developing novel catalytic amide bond formation reactions. Despite the ubiquitous presence of amides in nature, chemists' toolbox in making amides has remained more or less unchanged over the past decades. Synthetic methods still heavily rely on classical stoichiometric reactions between carboxylic acids and amines in the presence of diimide-based coupling reagents or transformations of acids into more reactive acyl chlorides, followed by reactions with amines.[4] The reactions between carboxylic acids or carboxylic esters and amines lead to corresponding amides at elevated temperatures (>140 °C) or under microwave conditions in the absence of any catalyst.[5] Catalytic variations of direct amide bond formations between commonly available carboxylic acids, esters or amides and amines have only recently been developed; these, however, generally require the presence of organocatalysts[6] or expensive and environmentally harmful transition metal catalysts.[7] Herein, we report the development of chemoselective calcium-catalysed amide bond formation between unactivated carboxylic esters and primary amines.

In order to develop a highly sustainable catalytic method for the formation of amides from readily available carboxylic esters and amines, we focused especially on the evaluation of cheap, non-toxic, and abundant metal salts as potential catalysts. Transition metals and rare earth metals have already been reported to catalyse direct amidation of esters into amides.[8] We reasoned that simple alkali metals and alkaline earth metals might possess good catalytic properties for direct amidation of carboxylic esters. Alkali metal salts were observed to act as poor catalysts for the model reaction between methyl butyrate and benzylamine to yield *N*-benzyl butyramide in anhydrous toluene at 110 °C in 4 hours; lithium, sodium, potassium, rubidium, and cesium salts afforded the amide in <40% conversions (Table 1).

Alkaline earth metal salts have shown superior ability over alkali metal salts to catalyse direct amidation of methyl butyrate. The conversions into the amide in the presence of $MgBr_2$ and MgI_2 were observed to be 21% and 89%, respectively, indicating that the nature of the anion has a substantial effect on the overall reaction (Table 1). Simple calcium salts catalysed direct amidation of methyl butyrate in excellent conversions. CaI_2, $CaBr_2$ and $Ca(OTf)_2$ all afforded the amide in 89–92% conversions under standard conditions. In contrast, sulfate, oxalate, chloride and carbonate salts of calcium only yielded <32% of the amide product. We attribute the observed significant differences in catalytic properties for these calcium salts to alterations in their solubilities in toluene at 110 °C. The reactions in the presence of 10 mol% of CaI_2, $CaBr_2$ or $Ca(OTf)_2$ were carried out under homogeneous conditions (*i.e.* no solid was observed in the reaction mixture), whereas $CaSO_4$, CaC_2O_4, $CaCl_2$ and $CaCO_3$ were only partially soluble or insoluble under the reaction conditions. In this regard, we also showed that lower CaI_2 catalyst load resulted in decreased conversions into

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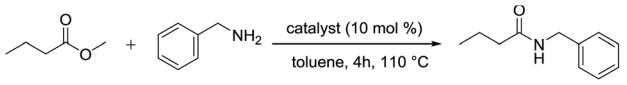
† Electronic supplementary information (ESI) available: Reaction optimisation, background reactions, characterisation of products. See DOI: 10.1039/c5ra18288c

Table 1 Screening of catalysts for amide bond formation[a]



Entry	Catalyst	Conversion[b]
1	LiI	40
2	NaCl	36
3	NaI	22
4	KI	11
5	RbCl	1
6	CsBr	3
7	$MgBr_2$	21
8	MgI_2	89
9	CaI_2	91
10	CaI_2[c]	92
11	$CaI_2 \cdot xH_2O$	92
12	$CaBr_2$	90
13	$Ca(OTf)_2$	89
14	$CaSO_4$	32
15	CaC_2O_4	11
16	$CaCl_2$	10
17	$CaCO_3$	2
18	$Ca(NTf)_2$	71
19	$Ca(NTf)_2/Bu_4NPF_6$	24
20	SrI_2	92
21	BaI_2	88
22	Et_4NI	14
23	HI	29
24	—	7

[a] Conditions: methyl butyrate (2.5 mmol), benzylamine (3.25 mmol), catalyst (0.25 mmol), anhydrous toluene (0.6 mL), 110 °C, 4 h. [b] Conversion determined by GC. [c] 99.999% pure CaI_2.

the amide, although the reaction proceeded very well even with 2 mol% of CaI_2 (see ESI†). $Ca(NTf)_2$, and in particular $Ca(NTf)_2/Bu_4NPF_6$ that is known to catalyse several transformations in organic chemistry,[2b] were found to be less active catalysts for our model amidation reaction.

In order to exclude any potential transition metal-catalysed amide bond formation,[9] we also used CaI_2 with the highest possible purity available (*i.e.* 99.999%); it afforded 92% amide, similar to the 99.95% pure CaI_2 that we use in standard reaction. This result confirms that the formation of the amide is calcium-catalysed. The reaction also proceeds very well with very cheap $CaI_2 \cdot xH_2O$ ($x = 4$–6), indicating that the presence of water does not affect the progress of the reaction. In addition, the CaI_2-catalysed amide bond formation proceeds in excellent conversions in normal toluene and other non-polar solvents under open-flask conditions (see ESI†).

Other toluene-soluble earth alkali metal salts, such as SrI_2 and BaI_2, also exhibited very efficient catalytic properties for the conversion of methyl butyrate into *N*-benzyl butyramide (92% and 88% conversion, respectively). The reaction in the presence of 10 mol% of Et_4NI or HI yielded <30% of the amide product, indicating that iodide itself does not act as a catalyst for amidation reaction. It is noteworthy that the model reaction in the absence of catalyst only yielded 7% of *N*-benzyl butyramide.

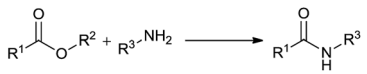
After screening of catalysts and optimisation of reaction conditions (Table 1, see ESI†), we used the most optimal reaction conditions for the synthesis of various amides (Table 2). Aliphatic methyl and ethyl esters reacted with benzylamine to afford the corresponding amides in excellent yields. Reactions with *para*-substituted methyl benzoates also proceeded well in 80–84% conversions; deactivated 4-methoxy derivative gave only 45% amide. CaI_2-catalysed amidation also worked well with other alkyl benzoates, including ethyl, benzyl and allyl (see ESI†). Ethyl hippurate, and Boc- and Cbz-protected glycine methyl esters yielded corresponding amides in quantitative 98–100% conversions. Cyclic γ-butyrolactone underwent amidation with ring-opening in 91% conversion at 50 °C. Amidation of enantiopure Boc-protected methyl esters of *R*- and *S*-alanine gave the amide products in 85–98% conversions; we observed a small degree (4–8%) of racemisation (see ESI†).

CaI_2-catalysed amidation of methyl butyrate also proceeds very efficiently with other primary amines. Reactions with substituted benzylamines, heteroaromatic amines and fully aliphatic amines afforded corresponding amides in 84–96% conversions (Table 2). All background reactions in the absence of CaI_2 provided only <20% of amides (see ESI†). Interestingly, secondary amines did not undergo CaI_2-catalysed direct amidation reaction. Methyl butyrate and methyl benzoate did not react with piperidine, morpholine or *N*-methylbenzylamine under standard conditions as well as at harsher conditions (20 hours at 140 °C in the presence of 20 mol% CaI_2). We observed that all reactions with secondary amines immediately furnished a large amount of insoluble material (likely an insoluble complex between CaI_2 and secondary amine).

Recent studies showed that unactivated carboxylic esters, acids and amides all undergo Cp_2ZrCl_2-catalysed amidation reactions under virtually the same experimental conditions (toluene or cyclohexane at 80–110 °C).[7i–k] We were pleased the CaI_2-catalysed direct amidation is highly chemoselective for carboxylic esters under our reaction conditions (Scheme 1). Unlike Cp_2ZrCl_2-mediated amidation, CaI_2 did not catalyse the reaction between carboxylic acids and amines. Not surprisingly and in accordance with previous report,[7i] butanoic acid underwent direct amide bond formation in the absence of CaI_2 in 64% conversion. The presence of CaI_2 even lowered the conversion to 30%, presumably by the chelation of carboxylic acid by calcium cation, thus making it inaccessible for amidation reaction. Similarly, CaI_2-catalysed and uncatalysed amidation of benzoic acid only afforded <10% of amide. Interestingly, a recent study demonstrates that carboxylic acids, unlike ester counterparts, undergo selective amidation under mild conditions in the presence of catalytic amounts of Cp_2HfCl_2.[7l]

We have not observed transamidation of butyramide with benzylamine in the presence of CaI_2 (Scheme 1). CaI_2-catalysed and uncatalysed background reactions only produced traces (1%) of the amide product. Similarly, reaction between benzamide and benzylamine afforded 22% and 21% of the *N*-benzyl benzamide product in the absence and presence of 10 mol% CaI_2, respectively, again demonstrating that amides do not undergo CaI_2-catalysed transamidation under our standard conditions.

Table 2 Scope of the calcium-catalysed amidation of carboxylic esters[a]



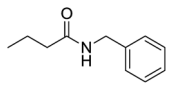
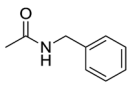
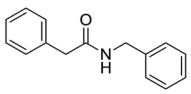
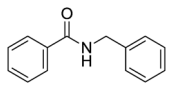
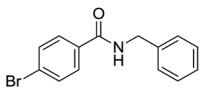
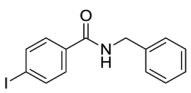
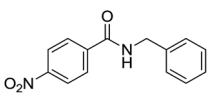
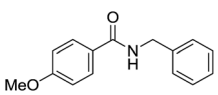
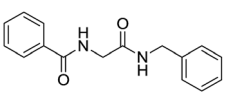
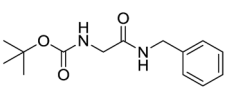
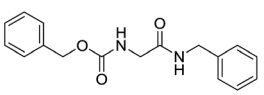
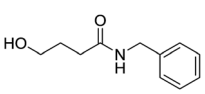
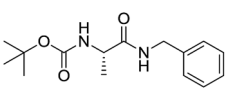
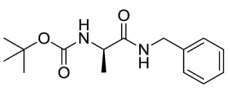
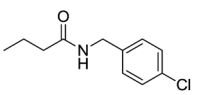
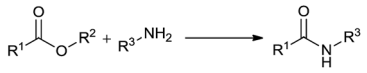
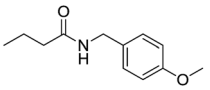
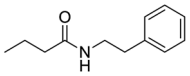
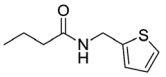
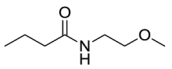
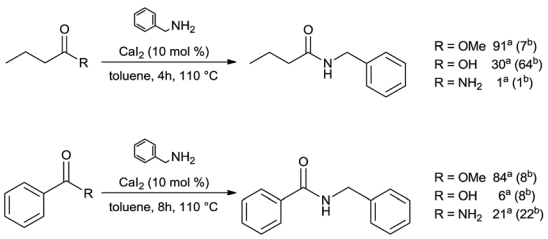
Entry	Amide	Conversion (yield)
1		91[b] (89)[c]
2		90 (86)
3		94 (68)
4		84 (79)
5		82 (64)
6		80 (77)
7		83 (80)
8		45 (38)
9		85 (82)
10		100 (67)
11		100 (88)
12		91 (85)[d]
13		98 (90)[e]
14		85 (82)[f]
15		94 (78)

Table 2 (*Contd.*)



Entry	Amide	Conversion (yield)
16		96 (89)
17		92 (70)
18		84 (75)
19		85 (66)

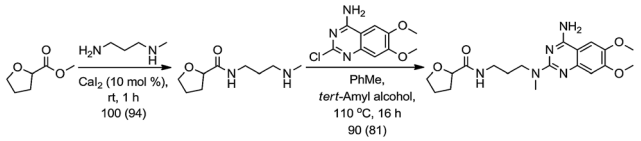
[a] Conditions: carboxylic ester (2.5 mmol), amine (3.25 mmol), CaI_2 (0.25 mmol), anhydrous toluene (0.6 mL), 110 °C, 4 h for aliphatic esters, 8 h for aromatic esters. [b] Determined by GC. [c] Isolated yield. [d] 50 °C, 2 h. [e] 96% ee. [f] 92% ee.



Scheme 1 Calcium-catalysed[a] and uncatalysed[b] amidation of aliphatic and aromatic carboxylic esters, acids and amides;[a,b] conversion (%) determined by GC.

We next applied the newly developed reaction for the rapid synthesis of alfuzosin, an antagonist of the alpha-1 adrenergic receptor. The first-step CaI_2-catalysed reaction between the methyl ester of tetrahydro-2-furanoic acid and *N*-methyl 1,3-diaminopropane proceeded quantitatively (100%) at 25 °C, whereas uncatalysed reaction afforded only 10% of amide (Scheme 2).

In conclusion, we have developed calcium-catalysed amide bond formation reaction between carboxylic esters and primary amines. The reaction is chemoselective for unactivated carboxylic esters over related carboxylic acids and amides, and



Scheme 2 CaI_2-catalysed synthesis of alfuzosin. Conversion (isolated yield).

for primary amines over secondary amines. This study demonstrates the ability of cheap and non-toxic alkaline earth metals to catalyse an important transformation in organic chemistry.

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