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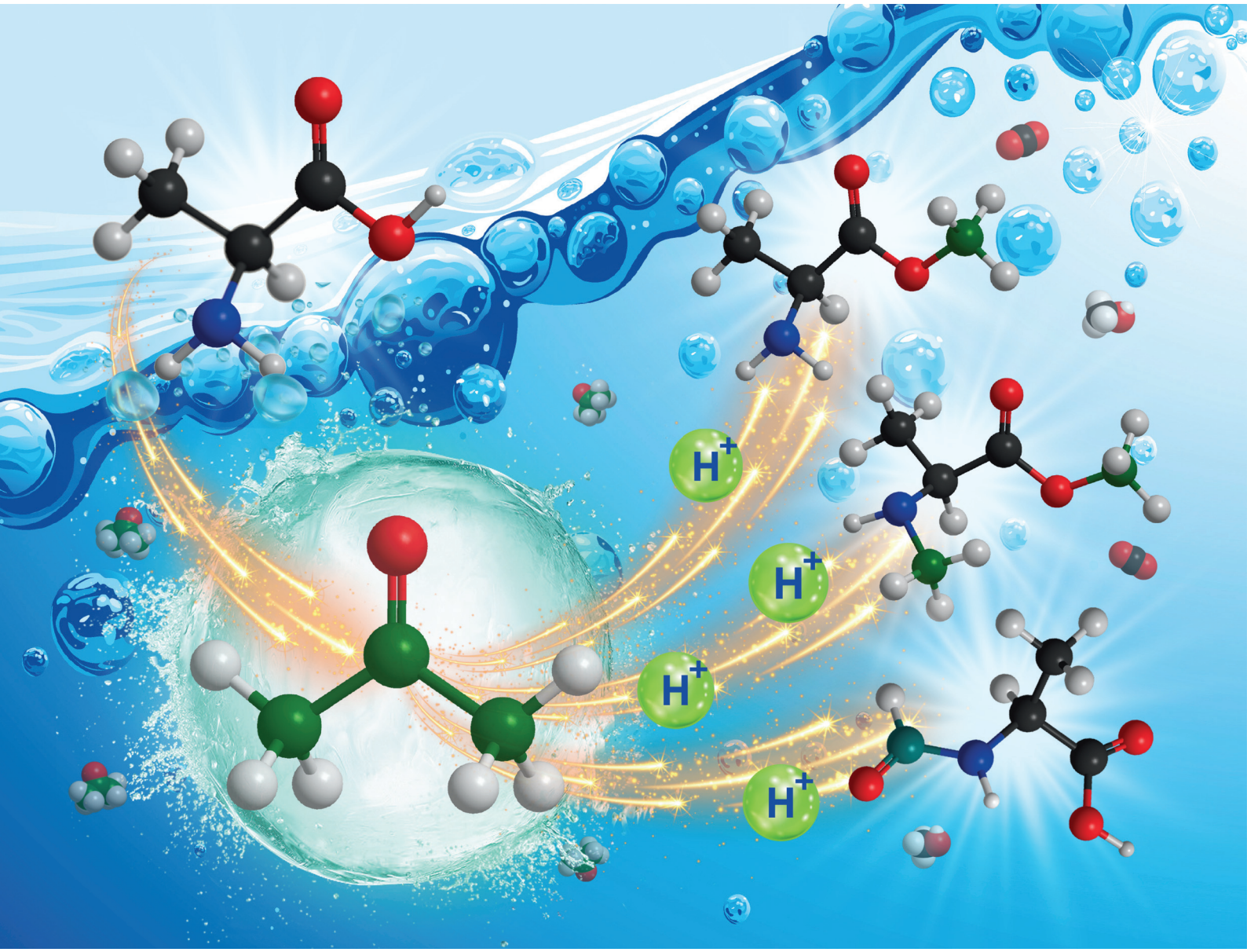

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A novel approach to amino acid synthesis: acid-assisted reactions with dimethyl carbonate for efficient *O*-methylated, *N*,*O*-methylated and *N*-formylated derivatives†

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A novel and efficient method for the modification of amino acids using a dimethyl carbonate (DMC) and acid system has been developed. *N*-Methylation, *N*,*O*-dimethylation, and *N*-formylation of various amino acids have been successfully achieved using this simple acid-assisted method (>99% conversions and >99% yields) and the modified amino acids were fully characterized using NMR spectroscopy. This method offers several advantages, including the use of a sustainable and cost-effective reagent, high selectivity, efficiency, eco-friendliness, broad applicability to a range of amino acids with different side chain functionalities, and being secure in the knowledge that there is no risk of racemization and epimerization. This study provides a new, sustainable, and practical approach for the modification of amino acids, which has potential applications in drug discovery and chemical biology.

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Introduction

Amino acids are fundamental components of proteins, and their modification has gained significant interest in a number of scientific sectors.[1] Amino acids and peptide-based drugs play a crucial role in the current landscape of the health industry.[2–5] Within the structures of modern pharmaceuticals, one frequently encounters residues of individual amino acids and their various chemical modifications. This underscores the pervasive influence and integral contribution of amino acids to the development and formulation of pharmaceutical compounds,[2,3,6,7] especially derivatives of amino acid methyl esters, *N*-methyl amino acid methyl esters, and *N*-formyl amino acid, which are important intermediates utilized in a variety of fields, including medical chemistry,[8–11] chiral auxiliary,[12–16] peptide synthesis,[17–20] and polymer materials.[21–23] The modification of amino acids is an important aspect of organic chemistry, with applications ranging from the synthesis of peptides and proteins to the development of pharmaceuticals and other high-value chemicals.[24–28] A key challenge in this area is the development of selective synthetic routes for the modification of specific functional groups within the amino acid molecule.

Numerous reagents have been reported for the conversion of amino acids into amino acid methyl esters, including methanol/trimethylchlorosilane,[29] methanol/hydrochloric acid,[30] butanol/thionyl chloride,[31] dichloromethane/thionyl chloride,[32] dimethyl sulfate,[33,34] 2,2-dimethoxypropane/hydrochloric acid,[35] ion-exchange resins (amberlyst™-15),[36] and diazomethane.[37] Frequently, procedures require multiple complicated and potentially wasteful synthetic steps to achieve the desired product, such as *N*-protection, esterification, and deprotection. While some of these procedures are used regularly, they have several drawbacks, including arduous workups and harsh reaction conditions, as well as having safety and waste disposal issues.

N-Methylamino acids are one of the naturally occurring biologically active compounds,[38–40] such as cyclosporine,[41,42] dolastatins,[43–45] and didemnins,[46,47] which have fascinating therapeutic profiles. The inclusion of *N*-methylamino acids into physiologically active peptides have been shown to regulate backbone conformation and enhance pharmacological characteristics.[24,26,27] There have been a few studies on the synthesis of *N*-methyl amino acid methyl esters. The use of conventional methylating agents such as diazomethane,[9] methyl iodide,[48] and trimethyloxonium tetrafluoroborates[49] has limited interest in *N*-methyl amino acid methyl ester com-

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pounds due to reagent handling issues and their chronic health risks.[50–54]

In chemical synthesis and medicinal chemistry, *N*-formylation of amines is essential. Several medicinally active compounds are formed from formamides. *N*-Formyl protection is widely used in peptide synthesis because it can be easily deprotected without damaging peptide bonds and used as a precursor for isocyanide and formamidine synthesis.[55] Reported literature methods for the preparation of *N*-formyl amino acid derivatives use reagents such as anhydrous ammonium formate,[20] formyloxyacetoxyphenyl-methane,[56] acetic formic anhydride,[57] trimethylorthoformate,[58] triethylorthoformate,[59] *N*-(diethylcarbamoyl)-*N*-methoxyform-amide,[60] pivalaldehyde,[61] cyanomethylformate,[62] and formic acid/EDCI/glyceroacetonide-oxyma.[63] Most of these procedures involve the use of hazardous volatile organic solvents, particularly chlorinated hydrocarbons, which have presented a threat to the environment and human health.[64,65] Such procedures require multistep reactions that are extremely intricate, difficult to prepare, and require costly reagents, inert atmospheres and dry solvents, and use poisonous or unstable chemicals to yield a vast array of products.

These traditional procedures for methylation and formylation of amino acids rely on hazardous and costly chemicals, limiting their practical application in large-scale synthesis. Consequently, it is necessary to develop a novel, convenient, and simple approach for the modification of amino acids, which employs sustainable solvents/reagents and is cost effective. Dimethyl carbonate (DMC) is non-toxic and has found application as a solvent or reagent in agrochemicals, pharmaceuticals, polymers, solvents for coatings and adhesives, green oxidants, lithium-ion battery electrolytes and gasoline additives.[66–72] DMC has long been viewed as a sustainable alternative to highly toxic and hazardous reagents such as dimethyl sulphate and methyl halides, used for synthetic methylation reactions. Owing to its low toxicity and biodegradability, DMC has been utilized as a green solvent[73] and a green substitute for hazardous intermediates such as phosgene.[74,75] DMC can be commercially produced from waste carbon dioxide, making this a truly sustainable solvent and chemical.[76,77] The by-products of the methylation process are carbon dioxide and methanol, which are easily separated and can be recycled into the DMC synthesis process.[78] Previous research has shown that under acid-catalysed conditions, DMC is able to perform highly efficient carboxymethylation and methylation of amines.[79] Ji *et al.*[80] reported the use of DMC to *O*-methylate a few examples of *N*-Boc amino acids under basic conditions with moderate to high yields. Until now, no publication has studied amino acid modification with DMC under acidic conditions.

To the best of our knowledge, this work reports the first modification of amino acids with DMC under acidic conditions to date. Herein, a sustainable, single step, highly selective and high-yielding alternative method for the modification of *O*-methylation, *N*,*O*-dimethylation, and *N*-formylation of amino acids based on treatment with DMC in acid-assisted reactions is reported. In addition, these methods are facile and do not require a dry solvent or an inert atmosphere. Green chemistry metrics have been assessed and to better comprehend the reaction's selectivity, the reaction mechanism has been investigated.

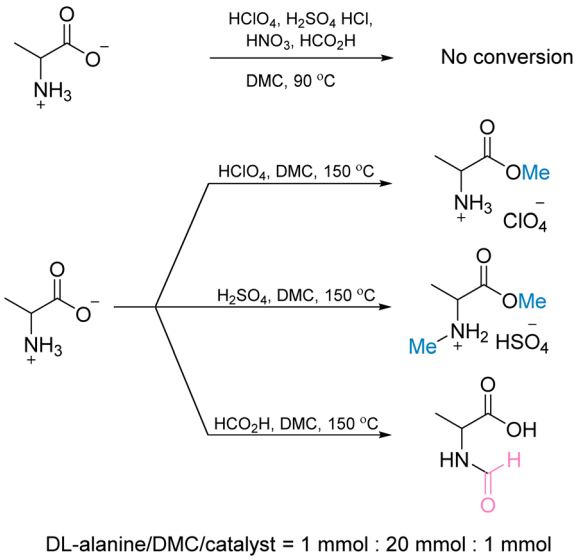
Results and discussion

Our initial studies focused on the selectivity of DMC modification of DL-alanine catalysed by homogenous systems. Various Brønsted acids (H_2SO_4, $HClO_4$, HCl, NHO_3, and formic acid) were investigated under reflux conditions (90 °C, 24 h) or in a high-pressure reactor (150 °C, 6 h). Under reflux conditions, DL-alanine is slightly soluble in DMC. Analysis by ^{1}H NMR reveals no product since only the characteristic signals of the starting material were detected. Thus, no reaction occurs under reflux conditions (Fig. S49–S53†). The solubility of DL-alanine is enhanced when the reaction is carried out in a high-pressure reactor (150 °C, 6 hours) and the crude product is a homogeneous phase, which agreed with the previously reported literature.[81] Under some conditions, more than 99% of DL-alanine was converted with excellent selectivity (>99%) into alanine methyl ester (Table 1, entry 6, and Scheme 1) with DMC acting as a reagent and *N*-formyl alanine (Table 1, entry 10, and Scheme 1), with DMC acting as a solvent. Although only 59.68% was converted into *N*-methyl alanine methyl ester, the selectivity was also high (>99%) (Table 1, entry 7, and Scheme 1).

Table 1 Optimization of the reaction conditions[a]

Entry	Brønsted acid	Temp (°C)	Time (h)	Conversion[b] (%)	Selectivity[b] (%)
1	$HClO_4$	90	24	—	—
2	H_2SO_4	90	24	—	—
3	HCl	90	24	—	—
4	HNO_3	90	24	—	—
5	HCO_2H	90	24	—	—
6	$HClO_4$	150	6	>99	>99 (*O*-methylation)
7	H_2SO_4	150	6	59.68	>99 (*N*,*O*-dimethylation)
8	HCl	150	6	>99	—
9	HNO_3	150	6	>99	—
10	HCO_2H	150	6	>99	>99 (*N*-formylation)

[a] Conditions: DL-alanine (1 mmol), Brønsted acid (1 mmol), DMC (1 mmol). [b] Calculated by ^{1}H NMR and structure confirmed by HMBC.



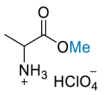
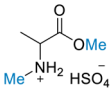
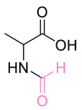
Scheme 1 The selectivity of DMC catalysed by Brønsted acids of DL-alanine.

HMBC method was used to confirm the structure of the reaction products (ESI†). Thus, highlighting the function of DMC at elevated temperatures (>150 °C) in the presence of H_2SO_4 and $HClO_4$ as methylating agents is consistent with the previous research,[82] while a combination of formic acid and DMC functions as a formylating agent.

Nonetheless, HCl and HNO_3 exhibited non-selective conversion under the same conditions, the products of which cannot be identified based on the ^{1}H NMR spectra, (Fig. S54 and S55†). According to the literature, a mixture of HCl and H_2O can induce the decomposition of amino acids,[83] whereas HNO_3 can be decomposed under high-temperature conditions to form NO_2,[84,85] which can cause amino acid damage.[86] In addition, heterogeneous acid systems ($FeCl_3$, $AlCl_3$, H_2SO_4–SiO_2 and $HClO_4$–SiO_2) were employed for methylation or carboxymethylation but were unsuccessful due to the lack of selectivity towards the product. This is in contrast with previous results for the methylation and carboxymethylation of amines, which provided positive results with these heterogeneous acids.[79] The ^{1}H NMR spectra of the DMC reactions of amino acids involving $AlCl_3$, H_2SO_4–SiO_2, and $HClO_4$–SiO_2 as acid indicate the presence of unidentified products, whereas $FeCl_3$ results in a significantly low conversion (Fig. S56–S59†).

Furthermore, we attempt to enhance the production of *N*-methyl alanine methyl ester by adjusting the ratio of DMC to 20, 40, and 80 equiv., respectively (Table 2). When stoichiometric through to 40 equiv. of DMC is used, excellent conversion and yield of more than 99% are observed (ESI†). However, for $HClO_4$ and formic acid systems, increasing DMC loading results in a decrease in conversion. It was discovered that the conversion and yield of the reaction may be affected by the type of acid catalyst and the DMC-to-acid ratio. Both formic acid and $HClO_4$ are monoprotic acids, demonstrating that 1 equiv. acid : 20 equiv. DMC allowed significant conversions

Table 2 Optimization of DMC loading[a]

Entry	Brønsted acid	Product	%Conversion (%selectivity)[b] (DMC mmol) 20	40	80
1	$HClO_4$		>99 (>99)	79.38 (>99)	53.70 (>99)
2	H_2SO_4		59.68 (>99)	>99 (>99)	73.04 (>99)
3	HCO_2H		>99 (>99)	92.44 (>99)	85.59 (>99)

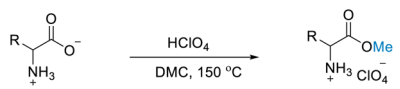
[a] Conditions: DL-alanine (1 mmol), Brønsted acid (1 mmol), 150 °C, 6 h. [b] Calculated by ^{1}H NMR and structure confirmed by HMBC.

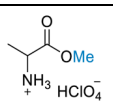
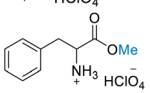
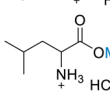
(>99%). In contrast, H_2SO_4 is a diprotic acid with a high quantitative yield of 1 equiv. acid : 40 equiv. DMC (Table 2).

In addition to the dilution effect, pressure may also influence the reaction's conversion and yield. Increasing the DMC ratio leads to increases in the pressure of the hydrothermal reactor. During the reaction, an increase in pressure decreased the rate of conversion, due to an increase the viscosity of the reaction mixture, thus restricting molecular mobility, both of which inhibit mass transfer.[87,88]

Table 3 presents the results of reacting DL-alanine, DL-phenylalanine, DL-leucine, and DL-methionine with $HClO_4$ in stoichiometric amounts of 20, 40, and 80 equiv. of DMC in a high-pressure reactor. In the case of DL-alanine, DL-phenylalanine, and DL-leucine, 20 equiv. of DMC with relation to the

Table 3 Reaction conditions for the synthesis of amino acid methyl esters (*O*-methylation)[a]



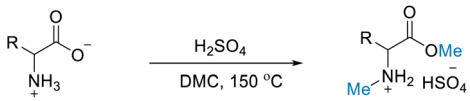
Entry	Substrate	Product	%Conversion (%selectivity)[b] (DMC mmol) 20	40	80
1	DL-Alanine		>99 (>99)	79.38 (>99)	53.70 (>99)
2	DL-Phenylalanine		>99 (>99)	80.15 (>99)	49.26 (>99)
3	DL-Leucine		>99 (>99)	87.71 (>99)	53.70 (>99)
4	DL-Methionine	Decomposition	—	—	—

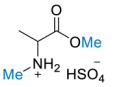
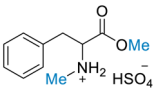
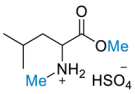
[a] Conditions: amino acid (1 mmol), $HClO_4$ (1 mmol), 150 °C, 6 h. [b] Calculated by ^{1}H NMR and structure confirmed by HMBC.

amino acid displayed more than 99% conversion, >99% selectivity to *O*-methylation with no evidence of competitive side reactions such as *N*-methylation. When an excess loading of DMC (20 equiv.) was used, the ^{1}H-NMR spectra revealed a significant decrease in conversion (ESI†). These results may be attributable to the low concentration of amino acids and $HClO_4$. The ^{1}H and ^{13}C NMR spectra revealed the addition of a singlet methoxy proton for ester –CO_2Me of amino acids in the range of δ_H 3.75 to 3.82 ppm and a methoxy carbon in the range of δ_C 51.70 to 53.45 ppm. In addition, the HMBC spectra also exhibited correlations between the –OMe group and the carbonyl of the amino acid, confirming that the products were amino acid methyl ester derivatives (ESI†). Selective *O*-methylation of amino acids by nucleophilic substitution on DMC at temperatures up to 150 °C is consistent with previously reported literature.[75] Ji and co-workers[80] investigated the use of DMC as a methylating agent for two amino acids, including isoleucine and phenylalanine, under basic conditions with a moderate to high yield (83% and 68%, respectively). Their approach demonstrates various limitations, including the need for *N*-protection with Boc, reaction under an inert atmosphere, long reaction times (18 h), multiple workup steps, chromatographic separation, and the use of an additional solvent (DMSO) despite the use of 20 equiv. of DMC. As such, this current procedure provides a highly efficient single step reaction, which is significantly easier, more convenient and potentially selective than previous methods for producing DL-alanine, DL-phenylalanine, and DL-leucine methyl ester with an excellent yield (>99%), little work up, no column purification, using non-toxic compounds without the use of volatile chlorinated hydrocarbons, and with reduced chemical wastes.[29,31–34,37,89,90] Unfortunately, these DMC conditions were not successful for the reaction of DL-methionine. Under our conditions, decomposition of methionine appears to take place as evidenced by a strong smell upon opening the reactor (under ventilation) and by the disappearance of the SMe chemical shift in ^{1}H NMR (Fig. S60†). Furthermore, the preparative-scale reaction was successfully conducted using 12 mmol of DL-alanine, representing a 12-fold increase. This resulted in an impressive 88.21% conversion with a product selectivity exceeding 99%. Thereby demonstrating the potential applicability of this method at a preparative scale.

Subsequently, H_2SO_4 mediated reactions of DMC with different amino acids were investigated. It was discovered that, except for methionine (which decomposed, Fig. S61†),[91,92] almost all amino acids were selective for *N*,*O*-dimethylation, resulting in good to high conversion and yields of *N*-methyl amino acid methyl esters (Table 4). Comparing ^{1}H and ^{13}C NMR spectra of the product and substrate demonstrated the presence of one methoxy and one methyl ammonium proton signals within the range of δ_H 3.60–3.82 ppm, as well as one methoxy and one methyl ammonium carbons within the range of δ_C 52.90–55.03 ppm, respectively. HMBC demonstrated correlation of one methoxy group to carbonyl carbon and the methine proton (H-2) of amino acids to methylammonium carbon. This confirmed the structure of the product (ESI†).

Table 4 Reaction conditions for the synthesis of *N*-methyl amino acid methyl esters (*N*,*O*-methylation)[a]



Entry	Substrate	Product	%Conversion (%selectivity)[b] (DMC mmol) 20	40	80
1	DL-Alanine		59.68 (>99)	>99 (>99)	73.04 (>99)
2	DL-Phenylalanine		50.00 (>99)	>99 (>99)	68.15 (>99)
3	DL-Leucine		53.92 (>99)	>99 (>99)	71.26 (>99)
4	DL-Methionine	Decomposition	—	—	—

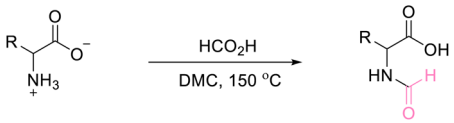
[a] Conditions: amino acid (1 mmol), H_2SO_4 (1 mmol), 150 °C, 6h. [b] Calculated by ^{1}H NMR and structure confirmed by HMBC.

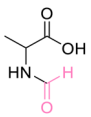
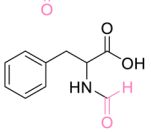
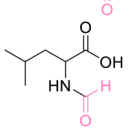
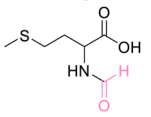
Dimethylation in the reaction may be caused by the dissociation of H_2SO_4, which may contribute to the formation of two hydrogen ions or protons (H^+) in the reaction. Diprotic H_2SO_4 with 40 equiv. of DMC, a double stoichiometric loading in comparison to $HClO_4$, resulted in excellent conversions and yields. De Marco *et al.*[49] reported the preparation of *N*-methyl amino acid methyl esters through the *N*-methylation of *N*-arylsulfonyl amino acid methyl esters of four amino acids (alanine, valine, isoleucine, and phenylalanine) using diazomethane and trimethyloxonium tetrafluoroborate as methylating agents in the presence of an organic base. When using *N*-nosyl-protected amino acids, the diazomethane reactions gave quantitative yields, but if using less reactive *N*-protecting groups, low yields were reported. Although their reactions using both methylating agents produced high-yields at room temperature, they have several limitations, including the need for an *N*-protecting group, the use of explosive and toxic diazomethane, a toxic solvent (dichloromethane), the need for purifying and drying solvents, the use of flame-dried glassware, and reactions under an inert atmosphere (dry N_2), plus multiple workup steps. The current methodology presented in this work offers significant advantages that are superior to those of the previously published methods for preparing *N*-methyl amino acid methyl esters.

Finally, the optimal conditions for *N*-formylation with various amino acids were determined. All amino acids were investigated in stoichiometric loading of formic acid and 20 equiv. of DMC which acted as solvent and potentially as a promotor but not as reagent. All reactions produced *N*-formyl amino acid in considerable yields (>99%) as shown in Table 5.

The NMR spectra of the reactions exhibited singlet proton additions in the range of δ_H 8.08–8.14 ppm for aldehyde and

Table 5 Reaction conditions for the synthesis of *N*-formyl amino (*N*-formylation)[a]



Entry	Substrate	Product	%Conversion (%selectivity)[b] (DMC mmol) 20	40	80
1	DL-Alanine		>99 (>99)	92.44 (>99)	86.59 (>99)
2	DL-Phenylalanine		>99 (>99)	88.97 (>99)	79.29 (>99)
3	DL-Leucine		>99 (>99)	92.68 (>99)	86.34 (>99)
4	DL-Methionine		>99 (>99)	87.40 (>99)	82.45 (>99)

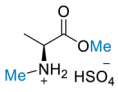
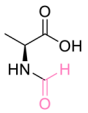
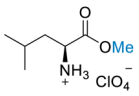
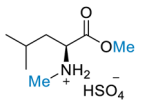
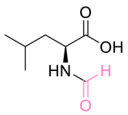
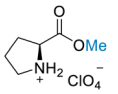
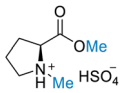
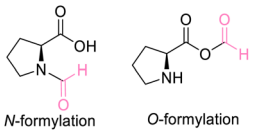
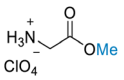
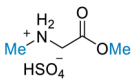
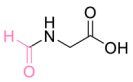
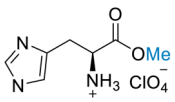
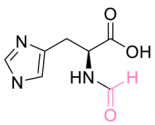
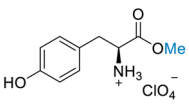
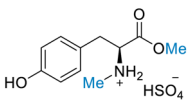
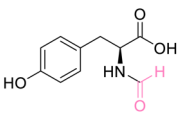
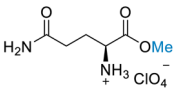
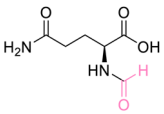
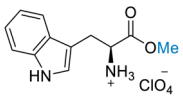
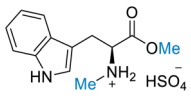
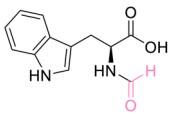
[a] Conditions: amino acid (1 mmol), HCO_2H (1 mmol), 150 °C, 6h. [b] Calculated by ^1H NMR and structure confirmed by HMBC.

carbonyl carbon additions in the range of δ_C 162.03–162.36 ppm for the *N*-formyl group. The lone pair of the amino groups may delocalize to the aldehyde carbon to form an ammonium ion, resulting in a proton deshielding effect at H-2 of amino acids (δ_H 4.50 to 4.50 ppm). In addition, the HMBC spectra of all products revealed correlations between H-2 of amino acids and both carboxyl and formyl group as well as the aldehyde proton of formyl group exhibiting a correlation with C-2 of amino acids. Hence, NMR data helps to identify the product as *N*-formyl amino acid derivatives (ESI†). Due to the stability of methionine in weak acids such as formic acid, there is no decomposition of methionine, like in the case of $HClO_4$ and H_2SO_4. It is vital to highlight that this method did not result in *O*-formylation side products. A recent study describes the *N*-formylation of amino acids using formyloxyacetoxy-phenylmethane (FAPM) as the *N*-formylating reagent. Six different amino acids were treated for 16 hours with 3 equiv. FAPM (an initial charge of 1.5 equiv. and a second addition of 1.5 equiv. after 8 h), resulting in 71–89% conversion to their corresponding formamides.[56] This method has the limitations of requiring the preparation and use of a formylating agent in considerable volumes, a prolonged reaction time, and the necessity for an extraction and purification procedure. Therefore, the current method in this work can be viewed as an efficient approach for the synthesis of *N*-formylation amino acid esters in a single step reaction, resulting in a higher yield than those previously reported.[20,56,57,60–63]

An investigation of a broader substrate scope and assessment of the limitations of the process including both the risk of racemization and epimerization were undertaken. Various functionalised amino acids, along with enantiopure substrates, dipeptides, and tripeptides were investigated using the optimal conditions as outlined in Table 6. In instances where amino acids lacked additional functional groups (L-alanine, L-leucine, L-proline, and glycine), utilizing 20 equivalents of DMC relative to the amino acid in $HClO_4$-assisted conditions resulted in more than 99% conversion, with a selectivity exceeding 99% toward *O*-methylation (Table 6, entries 1–4). Similarly, amino acids featuring functional groups like L-histidine and L-tyrosine displayed comparable conversions and selectivity under the same conditions (Table 6, entries 5 and 6). However, L-glutamine and L-tryptophan exhibited lower conversions of 77.5% and 50%, respectively, while still maintaining over 99% selectivity to *O*-methylation (Table 6, entries 7 and 8). The lack of interference from these functional groups in $HClO_4$-assisted conditions might be attributed to the delocalization of their lone pair electrons into aromatic rings. Conversely, amino acids with specific functional groups such as L-lysine, D-serine, and the dipeptide aspartame did not exhibit selectivity for *O*-methylation under the tested conditions and was attributed to the interference of their free lone pair electrons, resulting in the formation of unselective products (Table 6, entries 9, 10 and 12). Unfortunately, the DMC conditions were not effective for the reaction involving sulfur-containing amino acids like L-cystine and L-glutathione. Additionally, under the specified conditions, the decomposition of L-cystine and L-glutathione were observed, evident from a strong smell upon opening the reactor (under ventilation) (Table 6, entries 11 and 13). In addition, optical rotation experiments have substantiated that the specific rotation of the compounds remained unchanged throughout the successful reactions, as indicated in Table S6.† This observation underscores that our established conditions effectively mitigate the risk of racemization and epimerization during these reactions.

Reactions in the presence of H_2SO_4 and formic acid, were consistent with the outcomes of $HClO_4$-assisted conditions (Table 6). Amino acids without additional functional groups (L-alanine, L-leucine, L-proline, and glycine) exhibited remarkable performance. Employing 40 equivalents of DMC relative to the amino acid in H_2SO_4 or 20 equivalents of DMC relative to the amino acid formic acid conditions yielded conversions surpassing 99%, with selectivity exceeding 99% toward *N*,*O*-dimethylation, except for proline, which achieved a 64.9% conversion and >99% selectivity in H_2SO_4 conditions, or *N*-formylation, except for proline, which attained >99% conversion and 50% selectivity in formic acid conditions (Table 6, entries 1–4). Similarly, amino acids with functional groups such as L-histidine and L-tyrosine demonstrated comparable conversions and selectivity under the same conditions (Table 6, entries 5 and 6). An exception was noted for L-histidine in H_2SO_4 conditions, where an unknown solid formed, potentially contributing to the generation of two

Table 6 The investigation of the broader and limitation applicability of the process

Entry	Substrate	$HClO_4$ conditions[a]		H_2SO_4 conditions[b]		HCO_2H conditions[c]	
1	L-Alanine						
		>99% conversion	>99% selectivity	>99% conversion	>99% selectivity	>99% conversion	>99% selectivity
2	L-Leucine						
		>99% conversion	>99% selectivity	>99% conversion	>99% selectivity	>99% conversion	>99% selectivity
3	L-Proline						
		>99% conversion	>99% selectivity	65% conversion	>99% selectivity	>99% conversion	50% selectivity for *N*-formylation 50% selectivity for *O*-formylation
4	Glycine						
		>99% conversion	>99% selectivity	>99% conversion	>99% selectivity	>99% conversion	>99% selectivity
5	L-Histidine			Unknown solid			
		>99% conversion	>99% selectivity	>99% conversion	No selectivity	>99% conversion	>99% selectivity
6	L-Tyrosine						
		>99% conversion	>99% selectivity	>99% conversion	>99% selectivity	>99% conversion	>99% selectivity
7	L-Glutamine			Unknown liquid			
		78% conversion	>99% selectivity	>99% conversion	No selectivity	>99% conversion	50% selectivity
8	L-Tryptophan						
		50% conversion	>99% selectivity	50% conversion	>99% selectivity	>99% conversion	>99% selectivity
9	L-Lysine	>99% conversion	No selectivity	>99% conversion	No selectivity	>99% conversion	No selectivity
10	D-Serine	>99% conversion	No selectivity	>99% conversion	No selectivity	>99% conversion	No selectivity
11	L-Cystine	Decomposition		Decomposition		Decomposition	
12	Aspartame	>99% conversion	No selectivity	>99% conversion	No selectivity	>99% conversion	No selectivity
13	L-Glutathione	Decomposition		Decomposition		Decomposition	

[a] Conditions: amino acid (1 mmol), $HClO_4$ (1 mmol), DMC (20 mmol), 150 °C, 6 h. [b] Conditions: amino acid (1 mmol), H_2SO_4 (1 mmol), DMC (40 mmol), 150 °C, 6 h. [c] Conditions: amino acid (1 mmol), HCO_2H (1 mmol), DMC (20 mmol), 150 °C, 6 h.

hydrogen ions (H^+) or protons from H_2SO_4 in the reaction. This solid likely a result of protonation of one nitrogen atom of the imidazole side chain, leading to salt formation (Table 6, entry 5). L-Tryptophan exhibited >99% conversions with >99% selectivity to *N*-formylation in formic acid conditions, while displaying 50% conversion with >99% selectivity to *N*,*O*-dimethylation in H_2SO_4 conditions (Table 6, entry 8). In the case of L-glutamine, it exhibited low selectivity (50%) for *N*-formylation in formic acid conditions and was unsuccessful for *N*,*O*-dimethylation in H_2SO_4 conditions (Table 6, entry 7). Other functionalised amino acids, including L-lysine, D-serine, the dipeptide aspartame, and sulfur-containing amino acids (L-cystine and L-glutathione), presented high conversions but were unselective to desired products, these results were comparable to the outcomes under $HClO_4$ conditions (Table 6, entries 9–13). Intriguingly, despite these varied conditions, the

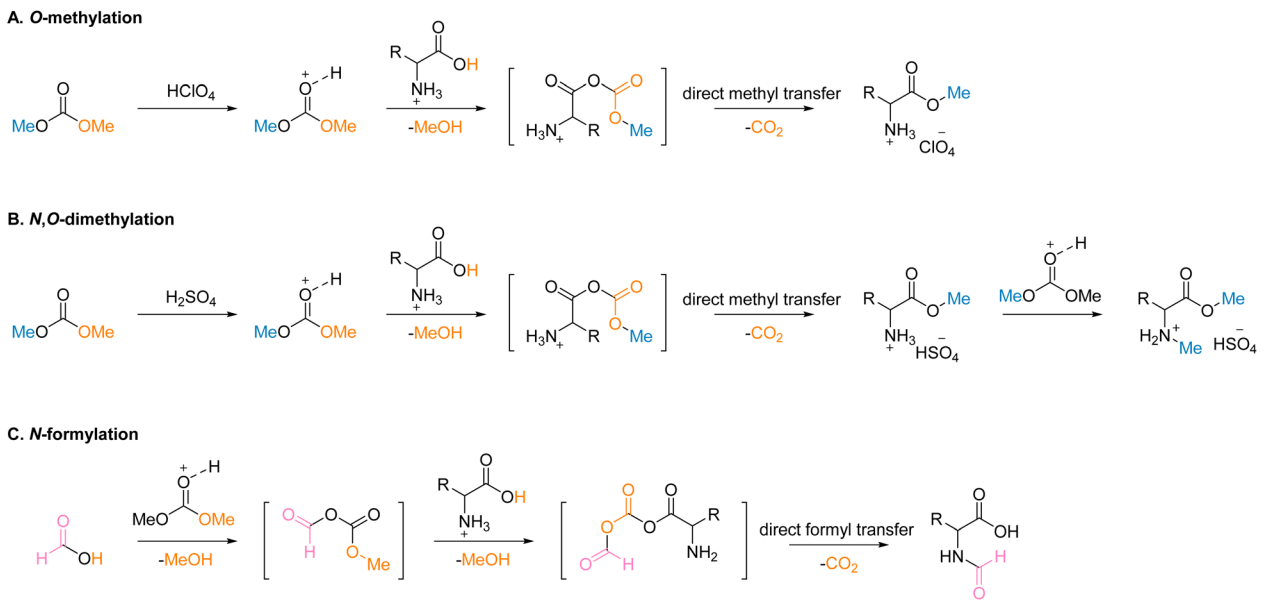
prevention of racemization and epimerization risks during the reactions remained consistent (Table S6†).

The comparison of the qualitative and quantitative green metrics[93–95] between the current reactions [A ($HClO_4$–DMC, *O*-methylation), B (H_2SO_4–DMC, *N*,*O*-dimethylation), and C (HCO_2H–DMC, *N*-formylation)] and recent literature methods [A′ ($KHCO_3$–DMC, *O*-methylation),[80] B′ (DIPEA–Me_3OBF_4, *N*-methylation),[49] and C′ (FAPM, *N*-formylation)[56]] (Table 7, see ESI† for details) clearly shows the advantages of the current methods over previous methods except for the high-temperature reaction. The previous processes necessitate workup and/or chromatographic processes that consume a considerable amount of solvent, some of which are hazardous, resulting in a high process mass intensity (PMI), *E*-factor, solvent intensity (SI), and water intensity (WI). In the current procedures, high conversion and yield, no workup, no chromatographic process, and the use of a green solvent/reagent (DMC) result in significantly improved PMI, *E*-factor, SI, and WI compared to earlier studies. Although this study demonstrates solvent elimination by evaporation, acid removal would

Table 7 Green metrics for the current and previous modification of phenylalanine

Criterion	A	B	C	A′	B′	C′
Qualitative green metrics						
Type of reaction	Stoichiometric	Stoichiometric	Stoichiometric	Catalytic	Stoichiometric	Stoichiometric
Reactor	Batch	Batch	Batch	Batch	Batch	Batch
Temperature (°C)	150	150	150	90	Room temperature	Room temperature
Workup	No	No	No	Extraction	Extraction	Extraction
Chromatography	No	No	No	Column chromatography	No	No
Solvent	Dimethyl carbonate	Dimethyl carbonate	Dimethyl carbonate	Dimethyl sulfoxide Water Ethyl acetate Hexane	Dichloromethane	Water Dichloromethane Ethyl acetate Petroleum ether
Quantitative green metrics						
Conversion (%)	>99	>99	>99	n.a.	n.a.	n.a.
Yield (%)	>99	>99	>99	68	Quantitative	86
PMI reaction	11.54	20.02	10.42	39.83	261.39	33.39
PMI workup	0	0	0	2,261.67	1,103.88	518.37
PMI total	11.54	20.02	10.42	2,301.53	1,365.27	551.76
E factor	10.54	19.02	9.42	2,300.53	1,364.27	550.76
SI	9.55	17.72	6.07	1,596.03	1,362.14	542.47
WI	0	0	0	444.44	716.50	208.43

A: $HClO_4$ (*O*-methylation); B: H_2SO_4 (*N*,*O*-dimethylation); C HCO_2H (*N*-formylation); A′: $KHCO_3$ (*O*-methylation);[80] B′: DIPEA–Me_3OBF_4 (*N*-methylation);[49] C′: FAPM (formylation);[56] n.a.: not available; colour code: green (preferred); yellow (acceptable), and red (undesirable).



Scheme 2 Propose mechanisms of A. monomethylation, B. demethylation, and C. formylation.

require a minimal additional washing procedure. As such, the methods developed in this current work are preferred for organic chemists and industrial applications.

The mechanism of the reactions was proposed to better comprehend the high selectivity observed. The basis of the proposed mechanism for the esterification of a carboxylic acid with DMC was obtained from isotope-labelling experiments.[80] For the monomethylation reaction employing monoprotic acid, $HClO_4$ (Scheme 2A), acid-activated DMC reacts with the substance to generate carbonic carboxylic anhydride. The *O*-methylation product is then formed by the direct transfer of a methyl group from DMC to the carboxylate oxygen.

In the case of diprotic acid, H_2SO_4 (Scheme 2B), subsequent *N*-methylation of the *O*-methylation product from the same pathway in Scheme 2A with another acid-activated DMC to yield the *N*,*O*-dimethylation product. DMC is suspected to be involved in the formylation reaction with the use of formic acid. When water was substituted for DMC as the solvent in a chemical reaction, conversion was poor (Fig. S62†).

It is hypothesized that DMC participates catalytically in the formylation reaction. ^{1}H NMR of the reaction mixture containing only formic acid and DMC (1 mmol : 20 mmol) indicates disappearance of the hydroxyl proton of formic acid (Fig. S63–S65†), due to the formation of a formic acid and DMC species, as presented in Scheme 2A to generate carbonic formic anhydride. To corroborate the formation of this formic acid and DMC species, a 1 : 1 ratio of formic acid and DMC was used, and the ^{1}H NMR reveals the presence of methanol in the reaction mixture, confirming that DMC reforms (Fig. S66†). The substrate then reacts with one side of carbonic formic anhydride, followed by formyl group transfer to the nitrogen of the substrate to yield an *N*-formylation product (Scheme 2C). DMC serves as the linker to transfer the methyl or formyl groups to the substrate, consequently enhancing the selectivity of the product.

Conclusions

A novel, efficient, and eco-friendly strategy for the synthesis of amino acid derivatives using an acid assisted approach with dimethyl carbonate as a green methylating agent has been investigated. The application of simple acid systems, including perchloric acid, sulfuric acid, and formic acid demonstrated significant promise for selective modification of amino acids. The reactions achieved excellent yields and high selectivity for the synthesis of amino acid methyl esters, *N*-methylated amino acid methyl esters, and *N*-formylated amino acids. This approach offers several advantages over traditional methods, including reduced toxicity, lower cost, reduced chemical waste, fewer synthetic steps, excellent yields of the desired products in high purity, and mitigate the risk of racemization and epimerization. Furthermore, this efficient single step reaction used a sustainable solvent, readily available acid reagents/reactants, simple reaction setup, and the products were easily isolated from the solvent by removal under reduced pressure, however, removing acid would necessitate a minimally additional washing procedure. Overall, the results demonstrate the importance of acid selection and reaction optimization for achieving high yields and selectivity in the synthesis of amino acid derivatives. These findings will contribute to the development of sustainable and efficient synthesis of amino acid derivatives, important building blocks for the synthesis of biologically active compounds.

Experimental

Materials

DL-Alanine >99%, DL-phenylalanine >99%, DL-leucine >99%, DL-methionine >99%, chloroform-d ($CDCl_3$, >99.8% D), methanol-d_4 (CD_3OD, >99.68%), dimethylsulfoxide dimethyl carbonate (DMC) >99% and anhydrous sodium sulphate >99% were purchased from Sigma-Aldrich. Formic acid (AR grade) 98%, acetic acid (AR grade) >99.8%, sulphuric acid 98% and perchloric acid 70% were purchased from Qrec. Ethyl acetate (AR grade) >99.8%, methanol (AR grade) >99.8%, ethanol (AR grade) >99.8% and 4 Å molecular sieves (4–8 mesh) were purchased from RCI labscan.

General experimental procedure for reaction of amino acids with dimethyl carbonate at 90 °C

In a 50 mL round-bottom flask, dimethyl carbonate DMC (20, 40, or 80 mmol) and stoichiometric acid catalysts (1.00 mmol) such as 1.685 mL for 20 mmol DMC and 88, 54, and 39 μL for 1 mmol of $HClO_4$, H_2SO_4, and formic acid, respectively, were added (H_2SO_4, $HClO_4$, HCl, HNO_3, and HCO_2H). 1 mmol of each amino acid (DL-alanine, DL-phenylalanine, DL-leucine, and DL-methionine, represented by 89.1 mg of alanine) was then added to the solution mixture 30 minutes later. 24 hours were used for heating the solution at 90 °C under reflux. Once the reaction was complete, the mixture was cooled to room temperature. With reduced pressure, the solution solvent was removed to provide the crude product for NMR analysis. ^{1}H and ^{13}C-NMR were used to compute conversion (%) and selectivity (%).

General experimental procedure for reaction of amino acids with dimethyl carbonate at 150 °C

In a 25 mL hydrothermal reactor, dimethyl carbonate DMC (20, 40, or 80 mmol) and stoichiometric acid catalysts (1.00 mmol) such as 1.685 mL for 20 mmol DMC and 88, 54, and 39 μL for 1 mmol of $HClO_4$, H_2SO_4, and formic acid, respectively, were added (H_2SO_4, $HClO_4$, HCl, HNO_3, and HCO_2H). 1 mmol of each amino acid (DL-alanine, DL-phenylalanine, DL-leucine, and DL-methionine, represented by 89.1 mg of alanine) was then added to the solution mixture 30 minutes later. The solution was heated in an oven at 150 °C for 6 h. After the reaction was completed, the reaction was allowed to cool in the oven until 50 °C. With reduced pressure, the solution solvent was removed to provide the crude product

for NMR analysis. ^{1}H and ^{13}C-NMR were used to compute conversion (%) and selectivity (%).

^{1}H and ^{13}CNMR analysis

The structural was determined by based on the analysis ^{1}H and ^{13}CNMR spectra, which were recorded in $CDCl_3$, and CD_3OD as solvents on a Bruker 400 spectrometer using the residue of those solvents as the internal standards (16 scans for ^{1}H NMR analysis, and 256 scans for ^{13}C NMR analysis). The NMR signals were reported in terms of chemical shift as delta values are in pm, and *J* values are in Hz. The HMBC technique was used confirm structures.

Conflicts of interest

There are no conflicts to declare.

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