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A New Strategy for the Construction of α-Amino Acid Esters via Decarboxylation

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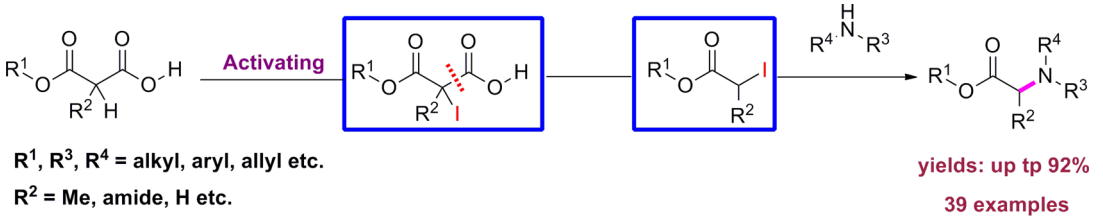
ABSTRACT



A new α-amino acid esters formation reaction has been developed via decarboxylation. The methodology is distinguished by its practical novelty in terms of the readily accessible starting materials, environmentally benign reaction conditions and waste streams, and wide substrate scope.

The carboxyl group is one of the most common functionalities in organic molecules and has a broad range of applications in synthetic chemistry because of its high activity and versatility.[1] Carboxyl groups effectively activate the C−H bonds of the sp^3 carbon atoms to which they are attached because of their strong electron-withdrawing effect, and the α-functionalization of carboxyl groups has been elegantly developed on the basis of this activation mechanism to provide access to α-substituted carboxylic acids.[2] For example, the Hell−Volhard−Zelinsky reaction,[3] which is one of the oldest reactions in organic chemistry, has been extensively used for the construction of α-halogenated carboxylic acids. Unfortunately, however, there are several limitations to this particular method, including the handling of a stoichiometric amount of a toxic halogenation reagent and the generation of halogen-containing waste. In addition, during the course of the past decade, transition metal catalyzed decarboxylative coupling reactions have been developed as powerful tools for the formation of carbon−carbon and carbon−heteroatom bonds. A variety of different research groups, including those of Goossen,[4] Myers,[5] and Tunge,[6]

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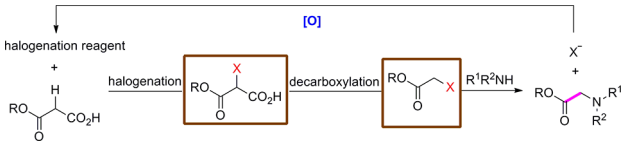
among others,[7] have recently published pioneering and systematic studies in this area.

Scheme 1. Our Design to Construct α-Amino Acid Esters



Herein, we describe the successful sequential combination of the α-halogenation and decarboxylation reactions of a series of malonates to generate the corresponding electrophilic α-halogenated esters, which were subsequently reacted with an amine to form the α-amino acid esters (Scheme 1).[8] To minimize the amount of halogenated waste generated by the process, the use of an oxidant was investigated to regenerate the halogenation reagent, with several different oxidants being evaluated. It is noteworthy that the decarboxylation of malonates has found widespread application in synthetic chemistry.[9] For the current work, it was envisaged that a consecutive halogenation and decarboxylation process would provide the basis for a new approach to the synthesis of α-amino acid esters. α-Amino acids themselves are important molecules in the chemical, biochemical, and material sciences.[10,11] Conventional routes to this ubiquitous class of molecules include the nucleophilic substitution of amines to α-halogenated esters.[12] Unfortunately, however, the involvement of a stoichiometric quantity of halide constitutes a noticeable limitation to this approach. Based on the general importance of α-amino acids and shortcomings in existing synthetic methodologies, we decided to develop an alternative synthetic strategy to provide facile access to this group of compounds.

Monomethyl malonate **1a** and *N*-methylaniline **2a** were selected as model substrates to evaluate our strategy. We recently developed an interest in green oxidation reactions using tetrabutylammonium iodide (TBAI) as a catalyst and *tert*-butyl hydroperoxide (TBHP) as a primary oxidant.[13c–g] It was envisaged that the use of the TBAI/TBHP system would address several key issues associated with our strategy, including (1) the in situ generation of hypoiodite or iodine from TBAI and the subsequent iodination of monomethyl malonate **1a**; (2) the decarboxylation to generate methyl iodoacetate; and (3) the nucleophilic substitution of *N*-methylaniline **2a** to methyl iodoacetate to deliver the desired α-amino acid esters. Following a period of extensive screening, it was established that the reaction of **1a** and **2a** in the presence of 20 mol % TBAI, 2.2 equiv of TBHP, and 2.0 equiv of NaOAc in a mixture of H_2O and MeCN at 90 °C for 8 h furnished the desired product **3a** in a high yield (84%). Pleasingly, the stoichiometric addition of a halide was therefore not required for this novel α-amino acid ester forming reaction. Furthermore, in contrast to the transition metal catalyzed versions of this particular transformation,[4–7] this metal-free strategy had the advantage of not being sensitive to moisture.

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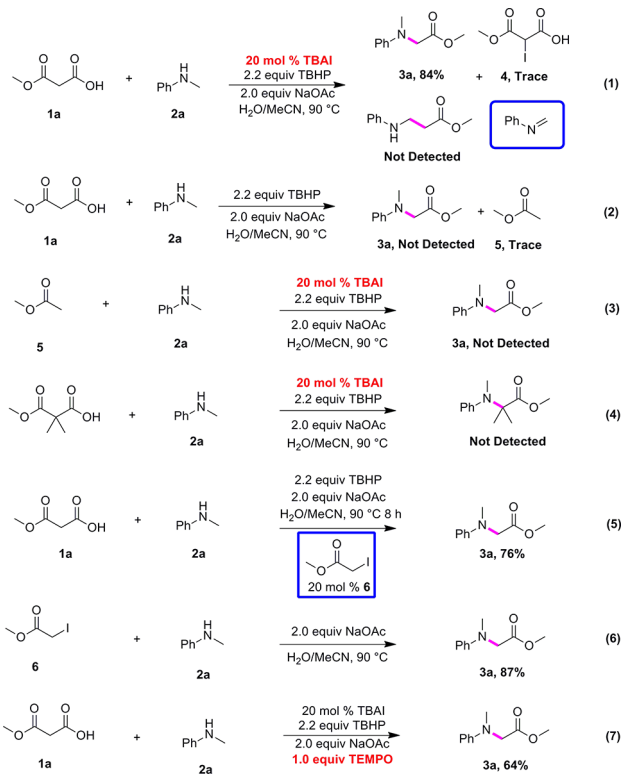

As well as the desired amino acid product **3a**, a small amount of the α-iodinated acid **4** was also obtained as a byproduct in the model reaction. Notably, no *β*-amino acid ester was observed, which indicated the addition of enolate to imine was not involved in this reaction (eq 1). Only a trace amount of methyl acetate **5** was detected when the reaction was conducted in the absence of TBAI (eq 2), suggesting the iodination event promoted the subsequent decarboxylation process. It is noteworthy that no product **3a** was observed when methyl acetate **5** was reacted with *N*-methylaniline **2a** in place of monomethyl malonate **1a**, which indicated that the iodination of methyl acetate **5** was not involved in the catalytic cycle (eq 3). Not surprisingly, none of the corresponding product was detected when monomethyl 2,2-dimethylmalonate was used as the reaction partner (eq 4). Further control experiments were carried out to elucidate the detailed mechanism of this reaction. The use of methyl iodoacetate **6** as a catalyst resulted in the desired product **3a** in good yield (eq 5). As expected, product **3a** was isolated in 87% yield via the direct nucleophilic substitution of amine **2a** to methyl iodoacetate **6** (eq 6). On the basis of these results, it was concluded that the decarboxylation reaction in the current reaction occurred following the initial halogenation of the monomethyl malonate **1a**, which is in sharp contrast with the mechanism of the Hunsdiecker (decarboxylative halogenation) reaction.[14] When TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), a well-known radical-trapping reagent, was added to the reaction, product **3a** was isolated in good 64% yield (eq 7), thus suggesting that this α-amino acid esters formation reaction was not a radical process.

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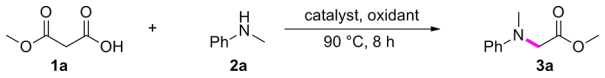
Table 1. Investigations on the Active Species[a]

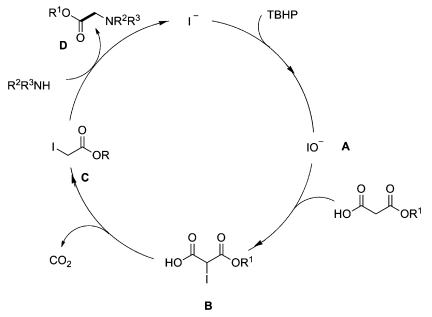


entry	catalyst	oxidant	base	yield[b]
1	I_2	TBHP	NaOAc	73
2	I_2 (1.2 equiv)	–	NaOAc	13
3	NIS	TBHP	NaOAc	72
4	IBr	TBHP	NaOAc	72
5	$PhI(OAc)_2$	TBHP	NaOAc	N.D.[c]
6	IBX	TBHP	NaOAc	N.D.

[a] 1.0 mmol of **1a**, 0.5 mmol of **2a**, 1.0 mmol of NaOAc, 20 mol % of catalyst, 2.2 equiv of TBHP, 1.0 mL of MeCN, and 1.0 mL of H_2O. [b] Isolated yield. [c] Not detected.

The use of iodine as a catalyst provided the product **3a** in 73% yield (Table 1, entry 1). However, only a small amount of product **3a** was observed when stoichiometric iodine was used in the absence of TBHP (Table 1, entry 2). The use of catalytic iodine(I) reagents provided the desired product **3a** in good yields (Table 1, entries 3 and 4). In sharp contrast, the use of hypervalent iodine reagents halted the transformation (Table 1, entries 5 and 6). Hypoiodite, which was generated in situ from iodide in the presence of TBHP, was the active species in this transformation and became the preferred choice for the reaction. Relative to the well documented use of hypervalent iodine,[15] the use of hypoiodite has attracted much less attention,[16] likely because of its poor stability.

Scheme 2. Proposed Catalytic Cycle



Based upon the results described above and in the literature, a plausible catalytic cycle was proposed for the transformation, as depicted in Scheme 2. The key features of this cycle include (i) the in situ generation of hypoiodite[17] **A** from iodide in the presence of TBHP; (ii) the iodination of malonate to give the intermediate **B**;[18]

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(17) See ref 13f and 13g.

(iii) the decarboxylation of **B** to form iodoacetate **C**, and (iv) the nucleophilic substitution of amine to **C** releasing the desired amino acid ester **D** and iodide.

With the optimized conditions in hand, we proceeded to explore the general scope of the reaction and investigated the use of a variety of different amines (Figure 1). Aryl amines (products **3b**–**m** and **3r**–**v**) and alkyl amines (products **3n**–**q**) both performed well in the reaction, providing the desired amino acid esters in moderate to high yields. It is noteworthy that primary anilines were also well tolerated under the reaction conditions and transformed into the desired products **3r**–**v** when reacted with monomethyl malonate **1a**.

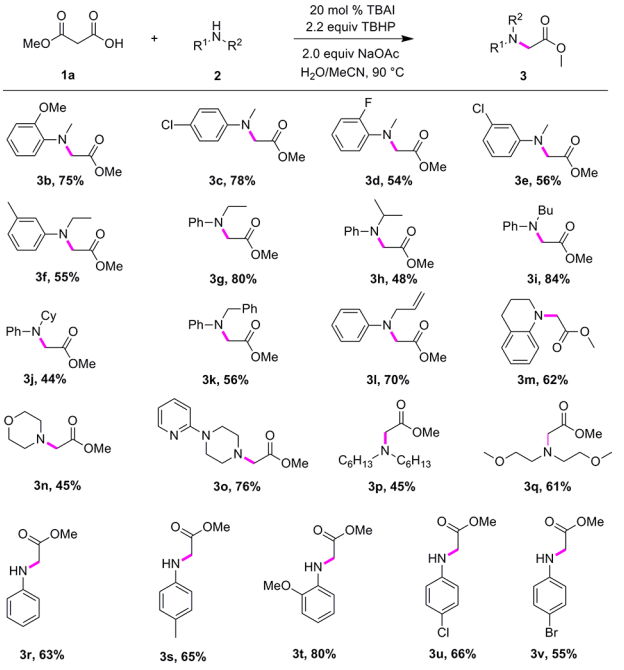

Figure 1. Scope of amines. Reaction conditions: 1.0 mmol of **1a**, 0.5 mmol of **2**, 1.0 mmol of NaOAc, 20 mol % of TBAI, 2.2 equiv of TBHP, 1.0 mL of MeCN, and 1.0 mL of H_2O at 90 °C for 8 h.

The scope of the current reaction was further expanded to a variety of malonates **1** (Figure 2). Both aryl (product **7k**) and alkyl malonates reacted smoothly under the optimized conditions to afford the corresponding products. Most notably, α-substituted malonates could also be subjected to the reaction conditions to afford the desired products in moderate yields (products **7l**–**p**), thus uncovering the potential of this methodology to prepare synthetically useful amino acid derivatives.

To highlight the overall utility of this methodology, we have designed one synthetic application for drug discovery.

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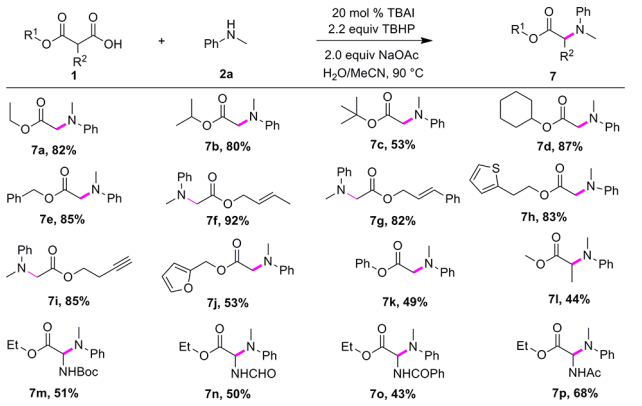
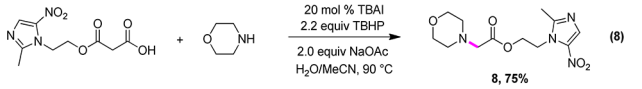


Figure 2. Scope of malonates. Reaction conditions: 1.0 mmol of **1**, 0.5 mmol of **2a**, 1.0 mmol of NaOAc, 20 mol % of TBAI, 2.2 equiv of TBHP, 1.0 mL of MeCN, and 1.0 mL of H_2O at 90 °C for 8 h.

Compound **8**, a potential prodrug of metronidazole with improved aqueous solubility and therapeutic efficacy,[19] was constructed in good yield under the optimized conditions (eq 8). In sharp contrast to previous approaches for the synthesis of this molecule, the key advantage of our method is that this transformation is not sensitive to moisture and does not require the stoichiometric addition of toxic halide reagents.



In summary, a novel method for the construction of α-amino acid esters has been developed, involving sequential iodination, decarboxylation, and nucleophilic substitution reactions. This work is of considerable interest in terms of the readily accessible starting materials, environmentally benign reaction conditions and waste streams, and wide substrate scope. Further investigations focused on the use of nucleophiles other than amines and an asymmetric version of the transformation are currently underway in our laboratory.

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Supporting Information Available. Experimental details, ^1H, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.