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Unnatural α-Amino Acid Synthesized through α-Alkylation of Glycine Derivatives by Diacyl Peroxides

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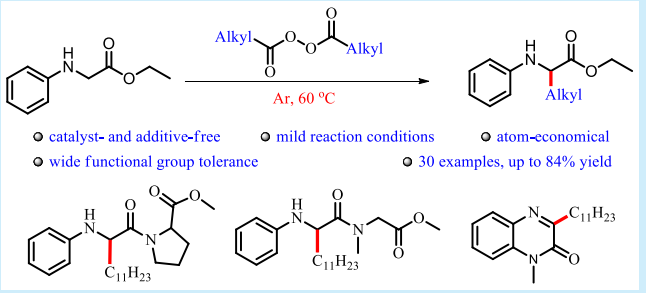
ABSTRACT: We have developed a protocol for catalyst- and additive-free α-alkylation reactions of glycine derivatives with diacyl peroxides, which proceed by a pathway involving addition of alkyl radicals to imine intermediates. The diacyl peroxide substrate acts as both alkylation agent and oxidizing agent, which means it is atom-economical. It was applied to various glycine derivatives, dipeptides, and a 3,4-dihydroquinoxalin-2(1*H*)-one derivative and could be carried out on a gram scale, indicating its utility for late-stage functionalization.



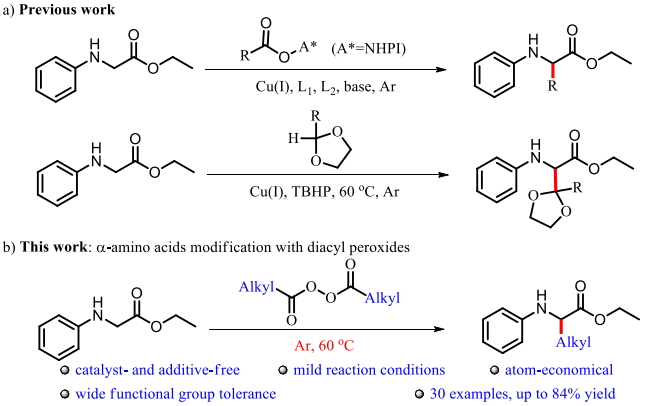
Unnatural α-amino acids have been used for various purposes, including asymmetric synthesis and the modification of bioactive peptides to enhance their biochemical and pharmacokinetic properties.[1] Therefore, increasing attention has been paid to the development of methods for site-specific chemical modification of peptides and natural amino acids. Transition-metal catalysis is one such method, but most of the uses reported to date involve side-chain modification and require Pd catalysts and halide-derived coupling partners and are thus expensive and environmentally unfriendly.[2] In recent years, several investigators have reported strategies that utilize photoredox catalysis and inexpensive metal catalysts for structural modification of amino acids.[3]

One potentially straightforward method for synthesizing unnatural α-amino acids is α-C(sp^3)−H alkylation of α-amino acids. However, only a few examples have been reported,[4] including those by Segundo and Correa, Xu and Wang et al. (Scheme 1a),[4e,f,g] and all of these examples require catalysts and additives. Therefore, an economical, metal-free method for modification of α-amino acids remains to be developed.

We speculated that diacyl peroxides might be useful for this purpose. Diacyl peroxides are inexpensive and environmentally friendly and have been used as alkylation reagents for a variety of substrates.[5] In fact, we previously showed that diacyl peroxides can be used in direct C(sp^3)−H alkylation reactions.[5o] Inspired by this previous work, we have now explored the modification of α-amino acids with diacyl peroxides.

We began by carrying out reactions of ethyl 2-(phenylamino) acetate (**1a**) as a model substrate and dilauroyl peroxide (**2a**) as the alkylation reagent (Table 1). Screening of several organic solvents indicated that both MeCN and dioxane were suitable (entries 2, 3, and 5). A reaction temperature of 60 °C was found to favor the formation of

Scheme 1. Modification of α-Amino Acids



desired product **3aa** (entries 4−7). Varying the amount of **2a** or the concentration of **1a** did not substantially increase the yield of **3aa** (compare entry 6 with entries 8−11). Notably, a 65% yield was obtained when the reaction was carried out under air instead of under argon (entry 12), which suggests that the reaction involved the addition of an alkyl radical to an imine.

With the optimized conditions in hand (Table 1, entry 1), we examined the substrate scope of the reaction with respect to the α-amino acid derivative by testing various *N*-aryl α-amino

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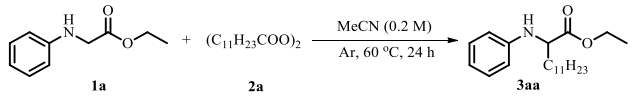
Table 1. Optimization of Reaction Conditions[a]

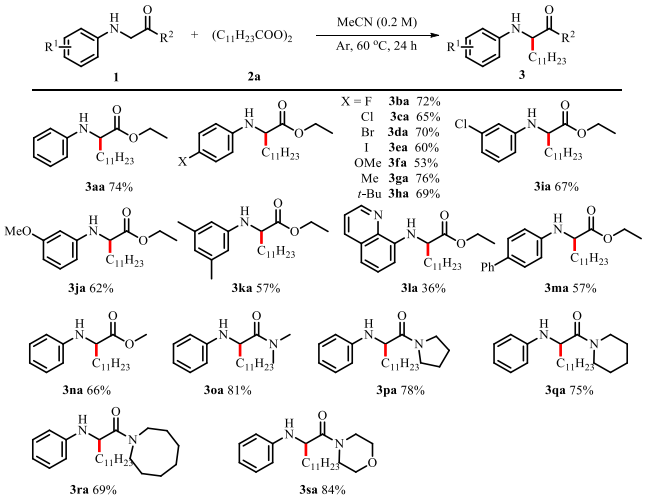


entry	temp (°C)	equiv	solvent	yield[b] (%)
1	60	1.5	MeCN	74
2	40	1	acetone	32
3	40	1	dioxane	37
4	rt	1	MeCN	N.R.[d]
5	40	1	MeCN	36
6	60	1	MeCN	63
7	80	1	MeCN	57
8	60	2	MeCN	52
9	60	1.5	0.4 M **1a** in MeCN	76
10	60	1.5	0.1 M **1a** in MeCN	53
11	60	1.5	0.05 M **1a** in MeCN	50
12[c]	60	1.5	MeCN	65

[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol) and **2a** (0.3 mmol) in MeCN (1 mL) were stirred in an 8 mL vial at 60 °C under Ar for 24 h. [b]Isolated yields are given. [c]Under air condition. [d]N.R.= no reaction.

acid esters and amides in reactions with **2a** (Scheme 2). To our delight, *N*-phenyl α-amino acid esters with either an electron-

Scheme 2. Substrate Scope with Respect to the α-Amino Acid Derivative[a]

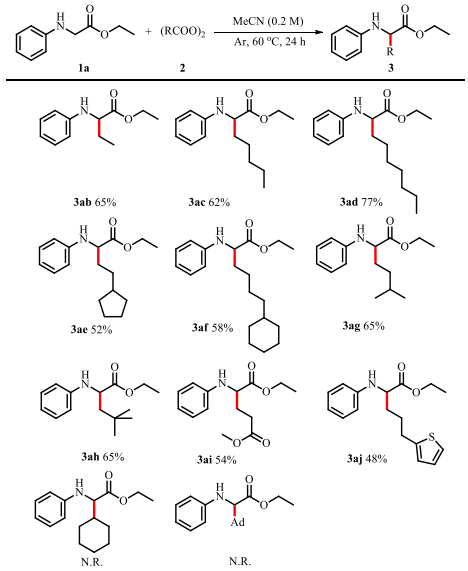


[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol) and **2** (0.3 mmol) in MeCN (1 mL) were stirred in an 8 mL vial at rt under Ar for 24 h.

withdrawing or an electron-donating substituent in the *para* position of the benzene ring (**3ba**–**3ha**) proved to be viable substrates. Furthermore, substrates with a substituent at other sites on the benzene ring, with multiple substituents, and with other aromatic rings (**3ia**–**3ma**) were also suitable. In addition to ethyl and methyl esters, amides were also acceptable substrates (**3aa**, **3na**–**3sa**), suggesting that the reaction could be used to modify short peptides.

We also investigated the scope with respect to the diacyl peroxide (Scheme 3). Reactions of **1a** with peroxides **2** bearing unsubstituted linear alkyl chains gave good to moderate yields of the corresponding products (**3aa**–**3ad**). In addition, peroxides with an alkyl chain bearing a cyclopentyl, cyclohexyl,

Scheme 3. Substrate Scope with Respect to the Diacyl Peroxide[a]

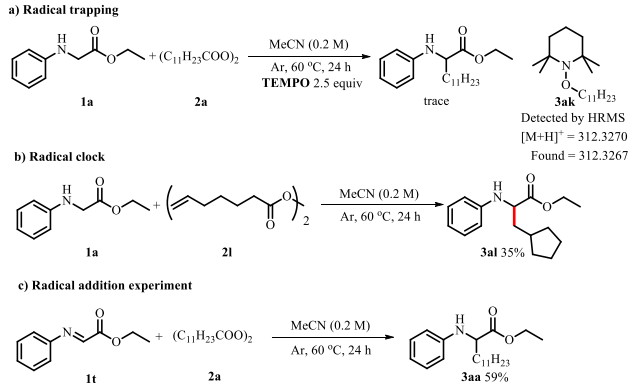


[a]Reaction conditions, unless otherwise noted: **1a** (0.2 mmol) and **2** (0.3 mmol) in MeCN (1 mL) were stirred in an 8 mL vial at rt under Ar for 24 h.

or *tert*-butyl group; an ester group; and even a thiophene group were also viable substrates, giving the desired products (**3ae**–**3aj**) in good yields. However, peroxides bearing a secondary or tertiary alkyl group were unsuitable. We attributed this result to the fact that the corresponding secondary and tertiary acyloxy radicals could readily undergo decarboxylation rather than oxidizing amino acid **1a**.

Control experiments provided information about the possible mechanism of the reaction. First, when 2.5 equiv of TEMPO was added to the mixture as a radical trap,[6] the desired reaction was completely suppressed, and alkylated TEMPO product **3ak** was detected (Scheme 4a). When a

Scheme 4. Control Experiments



diacyl peroxide bearing an alkenyl moiety (**2l**) was used as a substrate, cyclization product **3al** was obtained in a 35% isolated yield (Scheme 4b).[7] These two observations imply that the reaction proceeded via a radical mechanism. Finally, in the reaction of **2a** with imine **1t** (Scheme 4c),[4e] α-alkylation product **3aa** was obtained in 59% yield. This result suggests that **1t** was an intermediate and that the reaction proceeded via a free-radical addition.

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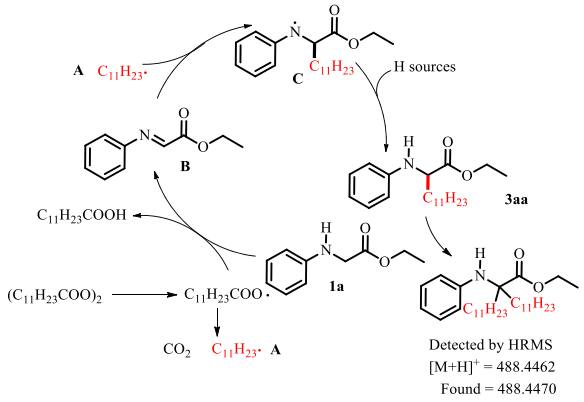
On the basis of the above-described results, a mechanistic pathway is proposed in Scheme 5 for the reaction of **1a** and **2a**.

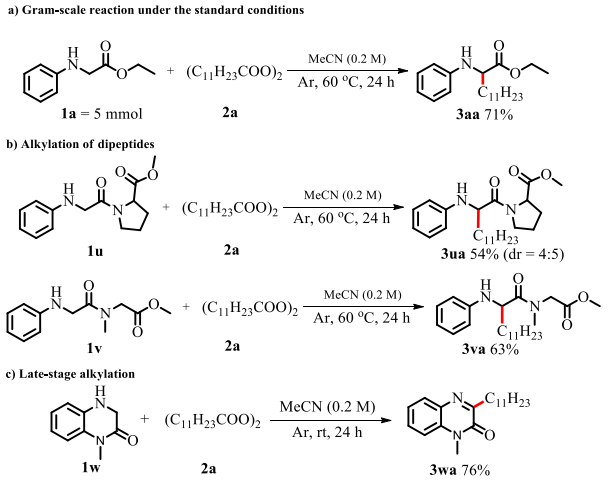
Scheme 5. Proposed Mechanism



Upon heating of the reaction mixture, homolysis of the diacyl peroxide produces an acyloxy radical, which undergoes decarboxylation to produce alkyl radical **A** and CO_2. Imine intermediate **B** is formed by oxidation of **1a** by the acyloxy radical. Then a free-radical addition reaction between **A** and **B** generates radical intermediate **C**. Finally, hydrogen abstraction by **C** generates product **3aa**. Note that high-resolution mass spectrometry revealed traces of a byproduct generated by the addition of a second alkyl radical.

We also explored the synthetic utility of our protocol. First, we carried out a gram-scale (5.0 mmol) reaction between **1a** and **2a**, which afforded target product **3aa** in 71% yield (Scheme 6a). In addition, reactions of dipeptides **1u** and **1v**

Scheme 6. Demonstration of Synthetic Utility



gave acceptable yields of desired alkylation products **3ua** and **3va**, respectively (Scheme 6b). In addition, the protocol could be utilized to modify a 3,4-dihydroquinoxalin-2(1*H*)-one (Scheme 6c). It is worth noting that after the free-radical addition reaction, further oxidation and aromatization afforded a quinoxalin-2(1*H*)-one compound. However, there still a limitation that this protocol can be only used on glycine derivatives and *N*-substituted peptides (see SI for more details).

In summary, because diacyl peroxides can serve as both alkylation agents and oxidizing agents, we were able to develop a catalyst- and additive-free protocol for α-alkylation of glycine derivatives. Various glycine esters, amides, dipeptides, and a 3,4-dihydroquinoxalin-2(1*H*)-one derivative were suitable substrates. Control experiments indicated that the mechanism involves a free-radical addition reaction between an alkyl radical and an imine intermediate. This protocol has the advantages of being metal- and additive-free and atom-economical.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01574.

- General Information; Preparation of Substrates; Investigation of the Key Reaction Parameters; Investigation of the Mechanism; Experimental Procedures and Product Characterization; References; NMR Spectra (PDF)

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Notes

The authors declare no competing financial interest.

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