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Radical alkylation of C(sp^3)–H bonds with diacyl peroxides under catalyst-free conditions†

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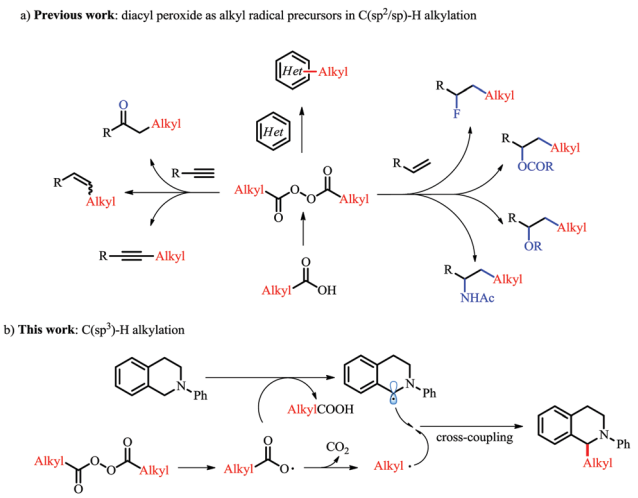
Herein, we describe a protocol for alkylation reactions of C(sp^3)–H bonds with diacyl peroxides by means of a process involving cross-coupling between an alkyl radical and an α-aminoalkyl radical. The mild, catalyst- and additive-free conditions make this protocol superior to previously reported C(sp^3)–H alkylation strategies. The protocol was applied to 1,2,3,4-tetrahydroisoquinolines and a tetrahydro-β-carboline derivative and could be carried out on a gram scale, indicating its utility for the alkylation of late-stage synthetic intermediates.

Alkyl groups in general, and alkyl groups bonded to sp^3 carbons in particular, play an important role in drug discovery because they can affect both the biological activity and the physical properties of a molecule.[1] Therefore, the development of new and better alkylation methods would be valuable to the pharmaceutical industry.

Several methods for transition-metal-catalyzed C(sp^3)–H alkylation have been reported,[2] but the need to use prefunctionalized starting materials makes these methods inefficient and costly. In recent years, photoredox catalysis has proved to be an efficient strategy to solve this problem, and a series of C(sp^3)–H alkylation reactions have been reported.[3] However, all of them require catalysts, and some require more than one catalyst or ligand. Thus there remains a need for economical, environmentally friendly methods for C(sp^3)–H alkylation.

We speculated that diacyl peroxides might be useful for this purpose. Diacyl peroxides can be obtained easily from carboxylic acids and are inexpensive, nontoxic, and environmentally friendly. Bao *et al.* carried out a series of methodological studies on these compounds (Scheme 1)[4] and found that when heated in the presence of a photo-catalyst or a metal ion, they can be used for C(sp)–H and C(sp^2)–H alkylation reactions, such as addition to alkenes (alkyl-esterification, alkyl-fluorination, alkyl-amination, and alkyl-etherification reactions),[4a–e] addition to electron-deficient (hetero)arenes,[4f–h] addition to alkynes, and other reactions.[4i–n] However, direct C(sp^3)–H alkylation reactions involving diacyl peroxides have not been reported.



Scheme 1 Alkylation with diacyl peroxides.

In this study of the use of alkyl diacyl peroxides for C(sp^3)–H alkylation, we began by carrying out reactions of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) and dilauroyl peroxide (**2a**) as model substrates (Table 1). When CuI was used as the catalyst, reaction of **1a** (0.2 M in MeCN) and **2a** (1 equiv.) at room temperature under argon afforded an 81% yield of alkylated product **3aa** (entry 1). Interestingly, the yield was higher (84%) in the absence of a catalyst (entry 6), which indicated that the acyloxy radicals generated by decomposition of the diacyl peroxide could oxidize *N*-phenyl-1,2,3,4-tetrahydroisoquinoline directly. Therefore, we focused on optimizing catalyst-free reaction conditions. Screening of several organic solvents revealed that MeCN gave the best results (entries 3, 4 and 6). Increasing or decreasing the amount of **2a** slightly decreased the yield (compare entries 5 and 6 with entry 2). Neither increasing nor decreasing the concentration of **1a** improved the yield (entries 7–9).

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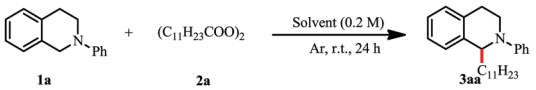
Table 1 Optimization of reaction conditions[a]



1a 2a 3aa

Entry	Variation from conditions shown above	Yield[b] (%)
1[c]	CuI as catalyst	81
2	None	91
3[c]	MeOH as solvent	76
4[c]	EtOH as solvent	36
5	1.5 equiv. of **2a**	89
6	1.0 equiv. of **2a**	84
7	0.4 M **1a** in MeCN	90
8	0.1 M **1a** in MeCN	81
9	0.05 M **1a** in MeCN	47

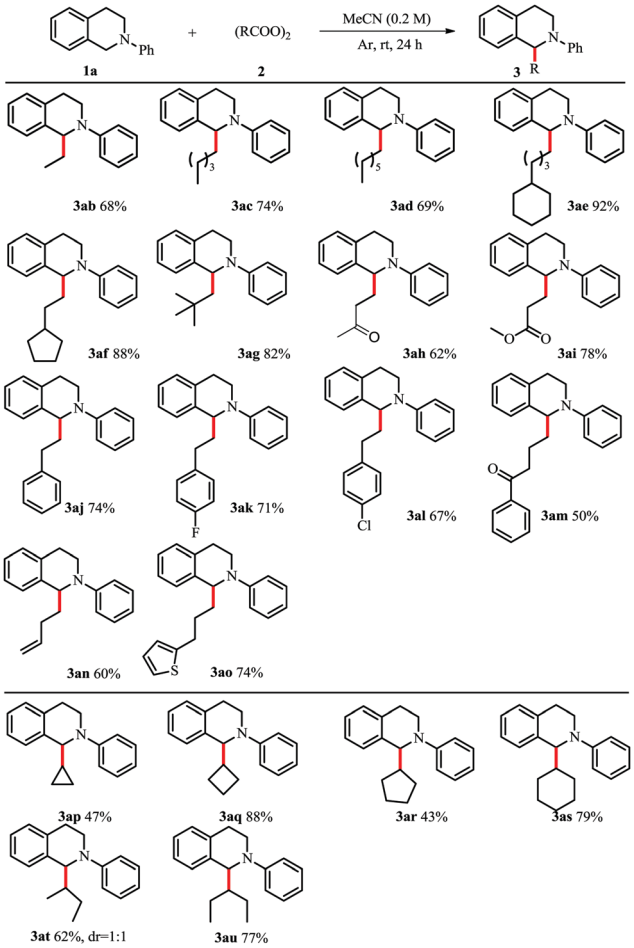
[a] Reaction conditions, unless otherwise noted: **1a** (0.2 mmol) and **2a** (0.22 mmol) in MeCN (1 mL) were stirred in an 8 mL bottle at rt under Ar for 24 h. [b] Isolated yields are given. [c] **2a** was used in 1 equiv.

Next we explored the substrate scope of the reaction with respect to the diacyl peroxide by using the optimized conditions to carry out reactions of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) with a variety of diacyl peroxides **2** (Table 2), which were synthesized from the corresponding carboxylic acids. We obtained good to moderate yields of products **3ab–3ad** from peroxides with unsubstituted linear alkyl chains. In addition, diacyl peroxides with hexyl, cyclopentyl, *tert*-butyl, keto, and ester groups in the chain also afforded good to excellent yields of the desired products (**3ae–3ai**). Peroxides bearing aryl groups were satisfactory, affording **3aj–3am**, as were peroxides containing a alkene or a thiophene moiety (**3an–3ao**).

The reaction conditions also appear to be general for a variety of *N*-aryl tetrahydroisoquinolines **1** (Table 3). Substrates with an *N*-phenyl ring bearing several kind of groups, such as fluorine, bromine, methyl, tertiary butyl and methoxy group, gave corresponding alkylation products **3ca–3ga** in excellent yields. Furthermore, substituent in different positions of the *N*-phenyl do not affect the reaction (**3ga–3ia**). The substituent on the benzene ring of the tetrahydroisoquinoline moiety could also be varied, as demonstrated by the selective alkylation of **1b** in 88% yield (**3ba**). In addition, substrates with a naphthalene or biphenyl group on the nitrogen were also suitable, affording **3ja** and **3ka**, respectively. Meanwhile, we also use diphenylbenzylamine and isochroman as substrates. To our depressed, none of them got desire products which mean that nitrogen atoms and cyclic substrate are necessary.

To explore the reaction mechanism, we performed several control experiments. When a radical inhibitor (TEMPO, 1,1-diphenylethylene or BHT) was present in reaction mixture containing **1a** and **2a**,[5] only a trace of alkylation product **3aa** was observed, and radical coupling products **3la** and **3ma** were detected by high-resolution mass spectrometry (Scheme 2a). A radical clock reaction of **1a** and diacyl peroxide **2v** produced cyclization product **3av** in a 45% isolated yield (Scheme 2b).[6] Taken together, these results indicate that the reaction proceeded *via* a radical mechanism. To rule out the possibility of free radical addition, we synthesized substrate **1h** and allowed it to react with **2a** (Scheme 2c),[7] the fact that alkylation product **3aa** was not observed under these conditions confirmed that the reaction proceeded *via* cross-coupling of two different radicals.

Table 2 Substrate scope with respect to the diacyl peroxide[a]

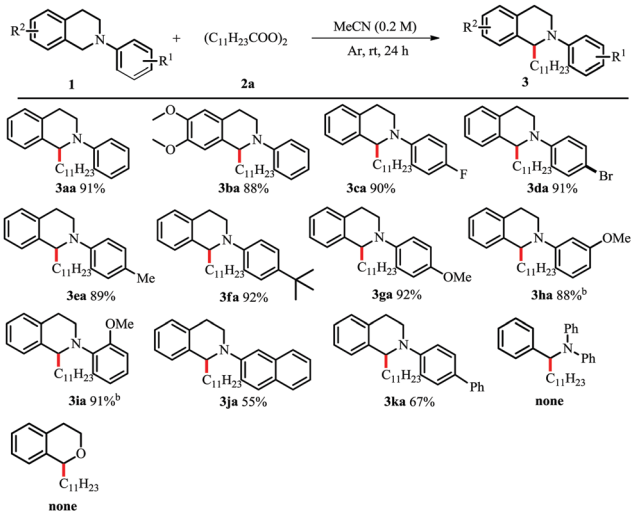


[a] Reaction conditions, unless otherwise noted: **1a** (0.2 mmol) and **2** (0.22 mmol) in MeCN (1 mL) were stirred in an 8 mL bottle at rt under Ar for 24 h.

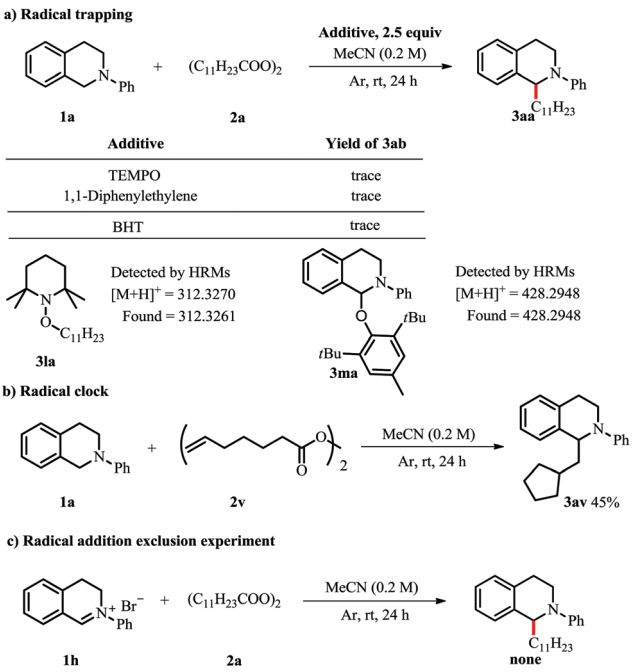
On the basis of these experiments, we propose the mechanism outlined in Scheme 3. Under argon, acyloxy radicals, alkyl radicals **A**, and CO_2 are readily formed by means of thermal homolytic dissociation of oxygen–oxygen bonds in acylperoxides followed by radical decarboxylation. A hydrogen abstraction between acyloxy radicals and *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) generates α-aminoalkyl radical cation **C** and corresponding carboxylic acid **B**.[8] Finally, selective cross-coupling of radicals **A** and **C** generates product **3aa**. It is worth noting that we cannot rule out the possibility of SET oxidation between **1a** and acyloxy radicals.

To demonstrate the utility of our protocol for late-stage functionalization, we carried out a gram-scale (5.0 mmol) reaction between tetrahydroisoquinoline **1d** and **2a** (Scheme 4a), which afforded target product **3da** in 82% yield. In addition, tetrahydro-β-carboline derivative **1n** could be used as a substrate (Scheme 4b); its reaction with **2a** afforded desired alkylation product **3na** in an acceptable yield (63%).

Table 3 Substrate scope with respect to the Michael acceptor[a]

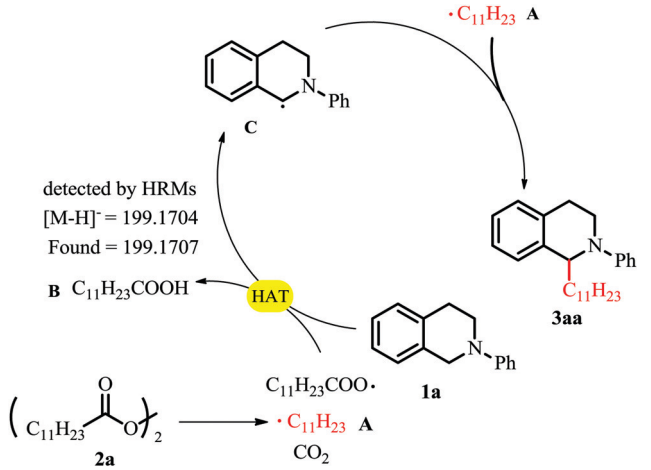


[a] Reaction conditions, unless otherwise noted: **1** (0.2 mmol) and **2a** (0.22 mmol) in MeCN (1 mL) were stirred in an 8 mL bottle at rt under Ar for 24 h. [b] MeCN : DCM = 9 : 1 was used as the solvent.

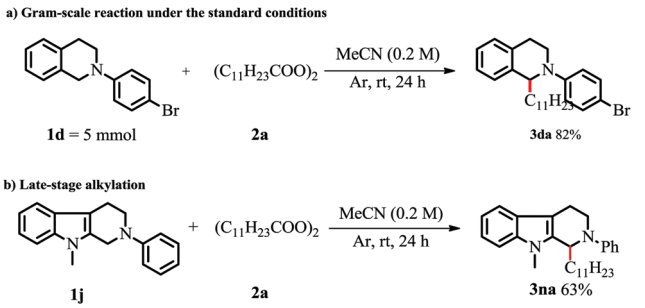


Scheme 2 Mechanistic experiments.

In summary, we have developed the first protocol for alkylation of C(sp^3)–H bonds with diacyl peroxides. The mild reaction proceeds at room temperature without the need for a catalyst or any additives and is therefore atom-economical and environmentally friendly. Various 1,2,3,4-tetrahydroisoquinolines and a tetrahydro-β-carboline derivative were suitable substrates. Mechanistic studies showed that the reaction proceeds *via* cross-coupling between an alkyl radical and an α-aminoalkyl radical. The mild, catalyst- and additive-free conditions make this protocol superior to previously reported C(sp^3)–H alkylation strategies.



Scheme 3 Mechanistic experiments.



Scheme 4 Demonstration of synthetic utility.

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Conflicts of interest

There are no conflicts to declare.

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