Metal-, Photocatalyst-, and Light-Free Direct C-H Acylation and Carbamoylation of Heterocycles

Metal-, Photocatalyst- and Light-Free Direct C-H Acylation and Carbamoylation of Heterocycles

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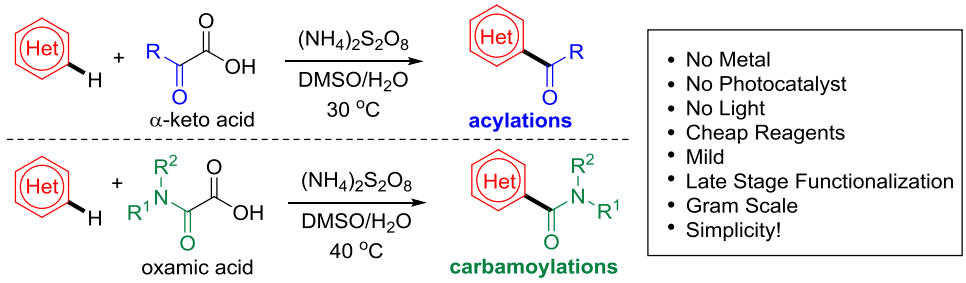
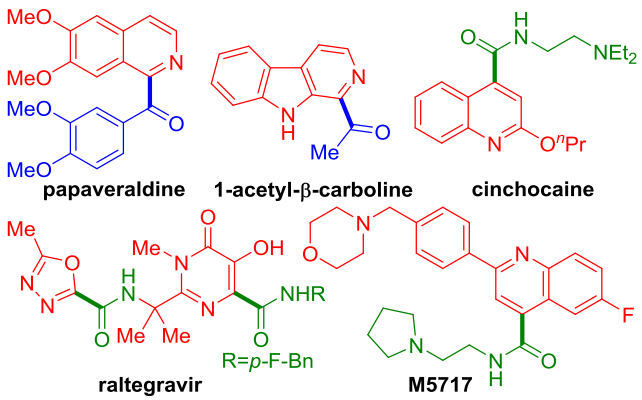


ABSTRACT: Direct C-H acylations and carbamoylations of heterocycles can now be readily achieved without requiring any conventional metal, photocatalyst, electrocatalysis or light activation, thus significantly improving on sustainability, costs, toxicity, waste and simplicity of the operational procedure. These mild conditions are also suitable for gram-scale reactions and late-stage functionalizations of complex molecules, including pharmaceuticals, *N*,*N*-ligands and light-sensitive molecules.

Minisci-type direct C-H functionalizations, involving the addition of carbon-centered radicals to basic heteroarenes, have recently seen a surge of interest due to their utility in mild, late-stage C-H functionalizations of pharmaceuticals, natural products and ligand scaffolds.[1] While much development has occurred with respect to Minisci-type alkylations in recent years,[1c] functionalizations with sp^2-C has been relatively less explored. Nevertheless, the ability to carry out mild, late-stage C-H acylation and carbamoylation of *N*-heterocycles in a cost-effective and facile manner would be of great interest, not least due to the many natural products[2] and pharmaceutical drugs containing these functionalities (Fig. 1). Significantly, amide functionalized *N*-heterocycles are widespread amongst pharmaceutical drugs, for example, antiretroviral raltegravir, local anaesthetic cinchocaine and anti-malarial candidate[3] M5717. The ability to rapidly C-H carbamoylate *N*-heterocycles has the potential to greatly expedite the synthesis of such drugs and analogues, as these would otherwise typically be made from more inefficient, conventional amide coupling methodologies,[4] which require prefunctionalization of the *N*-heteroaryls with carboxylic acid,[5] as well as waste-generating coupling reagents.

Nevertheless, the original Minisci-type decarboxylative acylations and carbamoylations via α-keto acids and oxamic acids required stoichiometric silver reagents[6] and harsh conditions (e.g. H_2SO_4 and reflux), rendering them unsuited to late-stage functionalizations.[7] For this reason, photoredox catalysis,[8] iron catalysis,[9] electrocatalysis[10] and light-mediation[11] have very recently been used to render the acylation mild and silver-free.[12] For carbamoylations, few mild procedures existed until two photoredox-catalyzed methods were recently reported during the course of this study.[13,14] It would therefore be a significant progress if these mild, late-stage reactions could do away entirely with requiring metal, photocatalyst, electrocatalysis, light-irradiation and specialist equipment, as this would significantly improve on sustainability, costs, toxicity, energy, waste, simplicity of reaction setup and also allow for functionalizations of light-sensitive compounds. We herein present the first C-H acylation and carbamoylation of basic heterocycles under metal-, photocatalyst- and light-free conditions, and showcase its application in late-stage functionalization of medicinally relevant compounds, ligands and light-sensitive substrates.

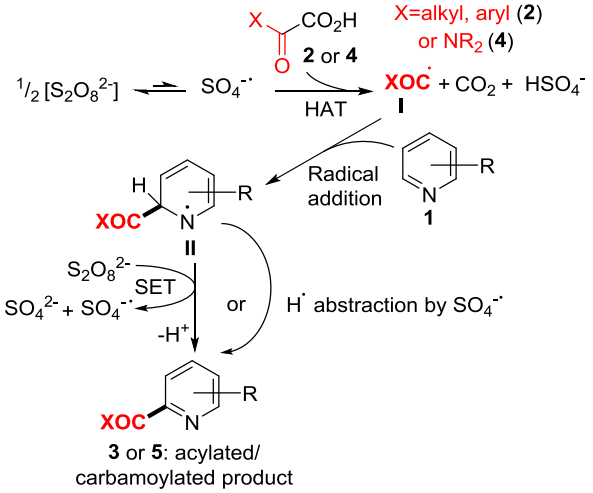
Figure 1. Acyl- and Amide-Functionalized *N*-Heterocycles in Natural Products and Pharmaceutical Drugs



Our proposed mechanism to achieve a mild yet metal-, photocatalyst- and light-free acylation/carbamoylation is shown in Scheme 1. We recently discovered that contrary to the accepted

convention, metal, photocatalyst and light are all not necessary for mild C-H *alkylations* of basic heteroarenes with alkylcarboxylic acids.[15] While Minisci-type reactions commence via the decomposition of persulfate $S_2O_8^{2-}$ to the sulfate radical anion $SO_4^{-\cdot}$, typically under metal-mediation, photolysis, photocatalysis or light activation,[1] we unexpectedly discovered that the use of DMSO as solvent under optimized conditions allows for uncatalyzed decomposition at mild temperatures (30 °C), achievable presumably because its rate is dependent on solvent.[16] Persulfate has been reported to decompose more readily in DMSO,[16b,17] and an added benefit is that DMSO is a more environmentally benign solvent,[18] compared the more commonly used MeCN. Thus, we postulated that under optimized DMSO conditions, the sulfate radical anion $SO_4^{-\cdot}$ can perform hydrogen atom transfer (HAT)[19,20] with readily available α-keto acid **2** or oxamic acid **4** to form the acyl or carbamoyl radical **I** respectively[21] alongside extrusion of CO_2.[22,23,24] Minisci-type radical addition to the *N*-heterocycle **1** followed by H radical abstraction by $SO_4^{-\cdot}$ or SET using persulfate should then furnish the desired acylated or carbamoylated products **3** and **5**.

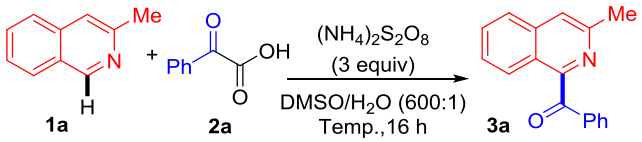
Scheme 1. Plausible Mechanism



With this proposal in hand, we commenced our investigations using 3-methyl isoquinoline **1a** and α-keto acid **2a**, using conditions originally developed for C-H alkylations.[15,25] To our delight, acylated **3a** was promisingly observed in moderate 45% yield (Table 1, Entry 1). The reaction also worked well at lower temperatures (22-30 °C, Entries 2-4), although 30 °C seemed optimum, as does 3 equiv oxidant $(NH_4)_2S_2O_8$ (Entry 2 vs. 3).

The one drawback of the aforementioned C-H alkylation procedure is that 10 equiv of the alkylcarboxylic acid was required,[15] thus we were keen to significantly reduce the equiv of α-ketoacid **2** for C-H acylation. Initially, however, dropping the equiv of **2a** to 2 yielded poor results (Entry 5). Nevertheless, optimization of concentration of the reaction resulted in the largest improvement to yields (Entries 5-11) and to our delight, a concentration of 0.3 M allowed for a significant reduction in amount of **2a** to 2 equiv, producing our optimal conditions (Entry 10). Control reactions in commonly used solvents for Minisci, MeCN and MeCN/H_2O, resulted in poor conversions, as expected (Entries 12-13). The reaction can be carried out in air and non-degassed solvents, instead of under argon, albeit with a reduction in yield from 80% to 60% (Entries 10 vs. 14). Acylation works just as well in the dark (Entry 15), proving that the reaction is not light-mediated, while Entry 16 shows that the persulfate oxidant is necessary for reaction. It should be noted that unlike many Minisci-type procedures,[1] no acid additive is required to activate the heterocycle. Furthermore, the use of cheap inorganic $(NH_4)_2S_2O_8$ is much more cost-effective than recently adopted hypervalent iodine oxidants,[2,11a,13a] with the added benefit that any excess $(NH_4)_2S_2O_8$ is readily removed via an aqueous wash.

Table 1. Selected Optimization Studies

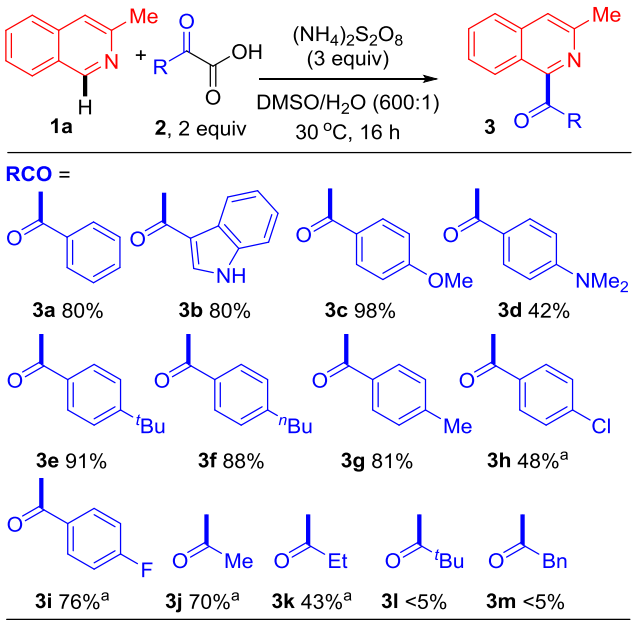


entry[a]	temp (°C)	**2a** equiv	M (mol/L)	notes	**1a** (%)[b]	**3a** (%)[b]
1	40	10	0.075	-	0	45
2	30	10	0.075	-	9	58
3	30	10	0.075	2 equiv ox.	51	35
4	22	10	0.075	-	55	45
5	30	2	0.075	-	31	25
6	30	5	0.15	-	6	76
7	30	3	0.15	-	7	80
8	30	5	0.3	-	6	78
9	30	3	0.3	-	10	74
10	**30**	**2**	**0.3**	-	**N/A**	**80**[c]
11	30	1	0.3	-	35	64
12	30	2	0.3	MeCN solvent	82	9
13	30	2	0.3	MeCN/H_2O 2:1 solvent	82	14
14	30	2	0.3	Air atm.[d]	31	60
15	30	2	0.3	In dark	16	76
16	30	2	0.3	No oxidant	84	0

[a]0.15 mmol **1a** in degassed solvent unless otherwise stated. [b]Determined by ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield. [d]And non-degassed solvent.

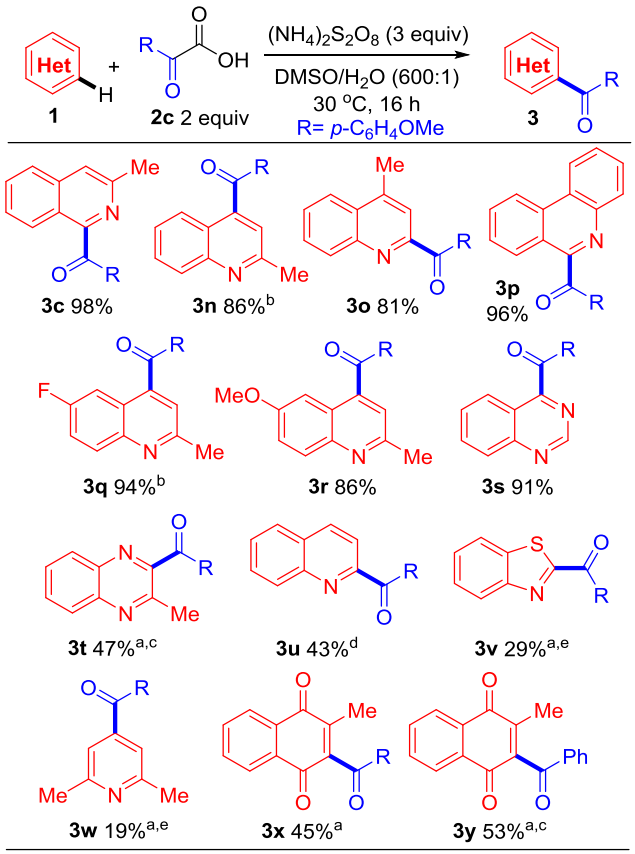
With optimized conditions in hand, a screen of α-keto acids **2** was carried out (Scheme 2). To our delight, the phenyl in **3a** can be replaced with a heterocycle (indole) in **3b** with no detriment in yield (80%). Aryl α-keto acid containing electron-donating *p*-OMe produced **3c** in an excellent 98% yield. *p*-NMe_2 substitution yielded a moderate 42% of **3d**, presumably due to competing SET on the dimethylamino group.[26] Alkyl-substitution on the aryl ring is well tolerated, yielding **3e**, **3f** and **3g** in excellent 91%, 88% and 81% respectively. Aryl α-keto acids with electron-withdrawing substituents on the aryl ring reacted more sluggishly at 30 °C (33% **3h** and trace **3i**), but yields improved drastically upon warming to 50 °C (48% **3h** and 76% **3i**). Thus, while both electron-rich and electron-poor aromatic α-keto acids are tolerated, the electron-rich ones react more readily, reflecting the increased nucleophilicity of the corresponding acyl radical.

Scheme 2. α-Keto Acid Scope for C-H Acylations



Isolated yields reported. [a]50 °C.

Scheme 3. Heteroarene Scope – C-H Acylation



Isolated yields reported unless otherwise stated. [a]50 °C. [b]Approx. 90% purity. [c]4 equiv oxidant. [d]Also isolated: 23% acylation at 4-position and 19% di-addition. [e]Determine by ^{1}H NMR analysis.

Alkyl α-keto acids are also successful acylating reagents, albeit reacting more sluggishly at 30 °C compared to their aryl counterparts (34% **3j**, see Sup. Info). Once again, warming to 50 °C improves the yield drastically (70% **3j**, 43% **3k**). In contrast, α-keto acids with ^{t}Bu or Bn do not react (<5% **3l** and **3m**), presumably because the corresponding ^{t}BuOC˙ and BnOC˙ radicals decarbonylate readily to the stabilized ^{t}Bu˙ and Bn˙ radicals.[27]

Next, the heteroarene scope was investigated (Scheme 3). 3-Methyl isoquinoline, 2-methylquinoline, lepidine and phenanthridine were directly acylated in good to excellent yields (81-98%, **3c**, **3n-p**). Both electron-withdrawing and electron-donating substituents are tolerated well on the quinoline ring (**3q** and **3r**). *N*-Heterocycles containing two nitrogen atoms are also tolerated, with quinazoline forming **3s** in excellent 91% yield and 2-methylquinoxaline forming **3t** in 47% yield. The 2-substituted **3u** is successfully formed from quinoline (43%), albeit 4-monosubstituted (23%) as well as the disubstituted products (19%) are also isolated. Conversely, benzothiazole and 2,6-lutidine reacted sluggishly even under more forcing conditions (29% **3v**, 19% **3w**).

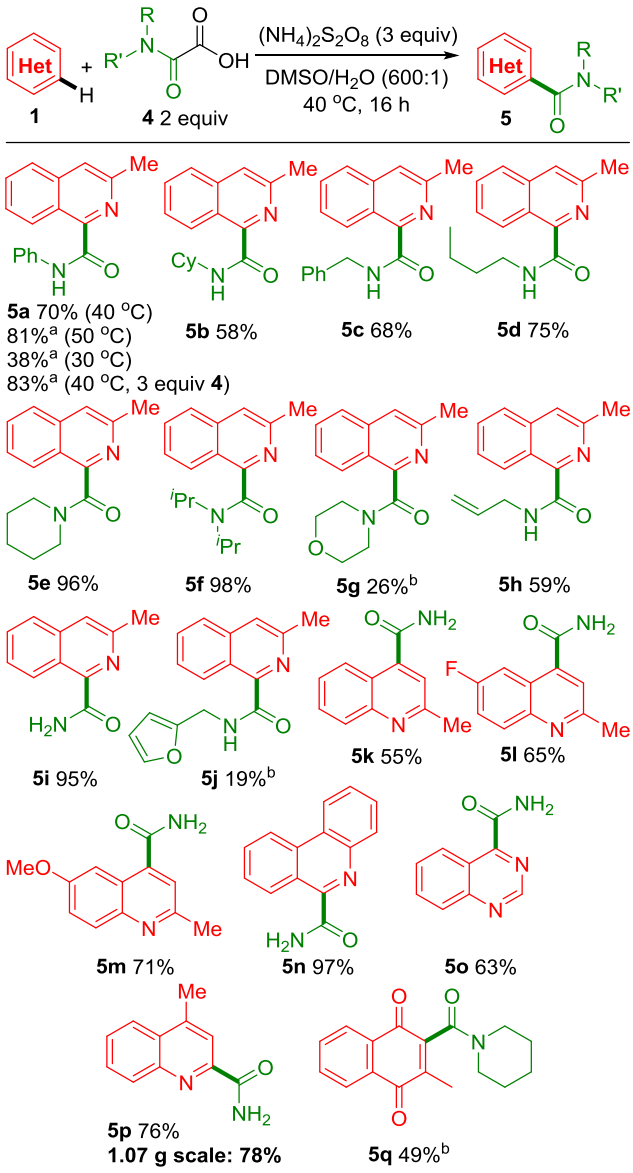
Pleasingly, acylated quinones **3x** and **3y**, which have been studied as potential anti-malarials,[28] can also be readily accessed (45% **3x**, 53% **3y**). The quinone substrates decompose under light irradiation[15] (see Sup. Info) and would therefore not be tolerated as well under photocatalysis or light-mediated procedures.

Following successful acylation, we turned our attention to carbamoylations (Scheme 4). The carbamoyl radical precursor, oxamic acids **4**, are either commercially available or easily synthesized from the corresponding amines without the need for column chromatography (see Sup. Info). Initial studies on model substrate 3-methyl isoquinoline **1a** and phenyl-substituted oxamic acid **4a** showed that higher temperatures and equiv of **4** has a positive effect on the yield of **5a** (Scheme 4). Nevertheless, in order to keep the initial general conditions as mild as possible, 40 °C and 2 equiv of **4** was chosen for the general substrate scope screen shown in Scheme 4. In general, oxamic acids containing secondary amides provided moderate to good yields of product (58-75%, **5a-5d**). The benzyl group (**5c,** 68%) is tolerated in carbamoylations, unlike its acylation counterpart (**3m**). Oxamic acids bearing tertiary amides provided up to excellent yields of **5e-5f** (96-98%), although the morpholine substituted **5g** did not perform as well (26%). Pleasingly, the alkene functionality is surprisingly tolerated (**5h**, 59%) as is unprotected oxamic acid (**5i**, 95%). The furan functionality, however, causes a drop in yield (**5j**, 19%).

The carbamoylation procedure is also applicable to a wide range of heterocycles. 2-Methylquinoline, including ones with electron-withdrawing and –donating groups all react well (**5k-m**, 55-71%) as do phenanthridine (**5n**, 97%), quinazoline (**5o**, 63%) and lepidine (**5p**, 76%). The light-sensitive menadione quinone substrate also carbamoylates smoothly to form **5q** in 49% yield.

Gratifyingly, a 7.5 mmol scale reaction using lepidine (**5p** 78%, Scheme 4) demonstrates that the reaction is scalable to gram-scale without detriment to the yield.

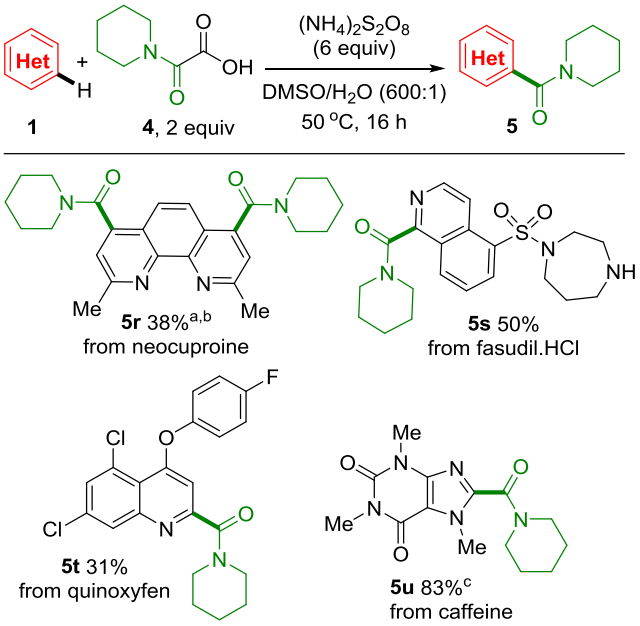
Scheme 4. Direct C-H Carbamoylations



Isolated yields reported unless otherwise stated. [a]Determined by ^{1}H NMR analysis. [b]50 °C.

Finally, Scheme 5 showcases the application of this procedure to late-stage C-H functionalization of *N*,*N*-ligands and medicinally/agrochemically relevant compounds. Typical *N*,*N*-ligand 2,9-dimethyl-1,10-phenanthroline (neocuproine), belonging to a ligand class which has been extensively applied in transition metal catalysis, supramolecular chemistry and materials science[29] was dicarbamoylated to produce **5r** in 38% yield. In the case of biologically relevant pharmaceuticals and agrochemicals, the well-known rho-kinase inhibitor and vasodilator, fasudil,[30] was successfully functionalized in 50% yield (**5s**) while antifungal agrochemical quinoxyfen[31] reacted more sluggishly at 31% yield (**5t**). To our delight, caffeine was successfully carbamoylated in a high 83% yield (**5u**) once the solvent concentration was adjusted to account for the lower solubility of caffeine.

Scheme 5. Late-stage C-H Functionalization



0.3 M and isolated yields reported unless otherwise stated. [a]4 Equiv **4**. [b]Monocarbamoylated product also isolated in 12% yield. [c]0.15 M as caffeine had solubility issues at 0.3 M.

In conclusion, we have developed the first direct C-H acylation and carbamoylation of basic heterocycles under metal-, photocatalyst- and light-free conditions. These sustainable conditions constitute a significant advance on cost, toxicity, waste and simplicity of operational procedure. We also demonstrate that the mild protocol can be applied to gram-scale reactions, as well as late-stage, direct C-H functionalizations of pharmaceutically/agrochemically relevant compounds and commonly used *N*-*N*-ligands.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization studies, all experimental details, characterization, copies of NMR data. (PDF)

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(20) In cases where the *N*-heterocycle is basic enough to deprotonate **2** or **4**, an alternative mechanism involving sulfate radical anion mediated SET from the corresponding carboxylate, followed by decarboxylation to form **I** is also possible. Nevertheless, successful reactions with insufficiently basic substrates such as quinones and caffeine implies that deprotonation of **2** or **4** is not strictly necessary.

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