Light-mediated synthesis of aliphatic anhydrides by Cu-catalyzed carbonylation of alkyl halides

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ABSTRACT: Acid anhydrides are valuable in the chemical industry for their role in synthesizing polymers, pharmaceuticals, and other commodities, but their syntheses often involve multiple steps with precious metal catalysts. The simplest anhydride, acetic anhydride, is currently produced by two Rh-catalyzed carbonylation reactions on bulk scale for its use in synthesizing products ranging from aspirin to cellulose acetate. Here, we report a light-mediated, Cu-catalyzed process for producing aliphatic, symmetric acid anhydrides directly by carbonylation of alkyl (pseudo-)halides in a single step without any precious metal additives. The transformation requires only simple Cu salts and abundant bases to generate a heterogeneous Cu photocatalyst in situ, maintains high efficiency and selectivity upon scale up, and operates by a radical mechanism with several beneficial features. This discovery will enable engineering of bulk processes for producing commodity anhydrides efficiently and sustainably.

Acid anhydrides, the dehydrated forms of carboxylic acids, are ubiquitous in chemical synthesis. Their precisely tuned electrophilicity makes them reactive as acylating reagents yet stable enough for convenient handling. Acetic anhydride (Ac₂O), the simplest acid anhydride, is produced on ~3 million tons/year scale due to its broad industrial applications. It is widely used in pharmaceutical industries, especially for synthesizing analgesics such as aspirin and paracetamol. It is crucial for synthesizing cellulose acetate, a biodegradable polymer extensively used in the food packaging and textile industries. Ac₂O is also vital in the wood industry, where its hydrophobicity is exploited for use as a rot-resistant coating. Thus, exploring convenient routes to synthesize commodity anhydrides has broad impact.

![Diagram showing established and new routes for anhydride synthesis](Diagram-Link)

**Figure 1.** Acid anhydride syntheses: (A) Established industrial routes to acetic anhydride; (B) Photocatalytic synthesis of aliphatic anhydrides reported here.

One strategy for accessing anhydrides is to expose carboxylic acids to dehydrating reagents such as phosgene, tosyl chloride, isocyanate, or thionyl chloride. However, the high reactivity and toxicity of those reagents limit their broad applicability. Two main industrial routes to Ac₂O have been implemented at bulk scale (Figure 1A). One is based on the long-known reaction of acetic acid and ketene, the latter of which is an unstable and toxic gas. The second is the Rh-catalyzed carbonylation of methyl acetate to synthesize Ac₂O, a process developed by Tennessee Eastman in 1983 that remains the dominant source of Ac₂O today. The methyl acetate used in the Tennessee Eastman process typically derives from esterification of acetic acid, which is itself synthesized by the Monsanto process for Rh-catalyzed carbonylation of methanol. The use of two Rh-catalyzed reactions and the need for isolation of two intermediates en route to Ac₂O limit the sustainability and efficiency of this synthetic route.

Although most carbonylation reactions in industry utilize precious metal catalysts, recently there has been significant research effort toward developing carbonylation reactions catalyzed by non-precious metals that operate by different mechanisms and therefore enable complementary reactivity to emerge. Our group has specialized in Cu-catalyzed carbonylation reactions, which allow carboxylative C-C and C-X coupling reactions of alkyl halides to occur via single electron transfer (SET) pathways involving alkyl and acyl radical intermediates. Here, we report a Cu-catalyzed carbonylation method to convert alkyl (pseudo-)halides to aliphatic acid anhydrides in a single step using inexpensive copper halide salts as catalysts. The reaction takes place under photoexcitation by blue LED light in the presence of the abundant base, K₂CO₃, and under mild CO pressure. This discovery provides an efficient and sustainable route to commodity acid anhydrides that avoids precious metal catalysts or intermediate isolation steps (Figure 1B).

Previous Cu-catalyzed carbonylation reactions involve nucleophilic coupling partners that generate electron-rich organocopper(I) intermediates with sufficient reducing potential to engage alkyl halides in SET activation. Here, we began our investigation by exposing 3-phenyl-1-iodopropane (1a) to Cu-catalyzed carbonylation conditions (CH₃CN, 6 atm CO, 2 equiv. K₂CO₃, 10 mol% IMesCuCl) without any coupling
partner (Table 1). No reaction was observed at 70°C (entry 1), presumably due to a lack of any intermediate capable of doing SET with 1a. We hypothesized that photoexcitation of the Cu catalyst would facilitate SET activation of 1a.26 Irradiating the reaction with blue LED light (390 nm) at room temperature resulted in 96% conversion to anhydride 2a (entry 2). Although Cu-catalyzed carboxylation reactions have produced carboxylic acid derivatives such as esters15, amides19,23, and other acyl-X compounds24,25, there is no precedent for anhydride formation. Under Pd-catalyzed carbonylation conditions, aryl halides can be converted to anhydrides using carboxylic nucleophiles.26 Similar results were observed with NaOH in place of K2CO3 (entry 3), but little to no 2a was observed when using alkoxide or amine bases (see Table S2). Next, we determined that the IMes ligand is not required, as quantitative conversion to 2a was observed when using simple cuprous halide salts such as CuCl or CuBr·SMє as catalysts without any added ligand (Table 1 entries 4-5, see also Table S1). On the other hand, no product was observed when Cu was omitted (Table 1 entry 6). For experimental convenience, we proceeded with CuBr·SMє as the catalyst. Similar results were obtained with 4 h rather than 8 h reaction time, but 8 h was used for subsequent experiments to ensure complete conversion of all substrates. Importantly, a 15-fold scale-up of the reaction (entry 7) with substrate 1a resulted in 87% conversion to 2a, with the trace impurities being unreacted 1a (6%), its corresponding alkyl bromide (5%), and the monocarboxylated ester product (2%).

Table 1. Examination of selected reaction parameters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation(s)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70°C, no hr</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>NaOH instead of K2CO3</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>CuCl instead of IMesCuCl</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>CuBr·SMє instead of IMesCuCl</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>No catalyst</td>
<td>&lt;5</td>
</tr>
<tr>
<td>7</td>
<td>CuBr·SMє catalyst, 15x scaleup</td>
<td>87</td>
</tr>
</tbody>
</table>

*IMes = N,N'-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.

Reactions were performed on 0.1-mmol scale unless otherwise noted; yields determined by 1H NMR using CH2Br2 as an internal standard.

With the optimized conditions, we examined the generality of the reaction towards different alkyl iodides (Figure 2A). Primary alkyl iodides with tethered aromatic rings provided moderate to excellent yields, with no significant impact from aromatic substituents (1a-1d). Aliphatic, primary alkyl iodides (1e-1g) were equally effective. Bulkier primary alkyl iodides (1h-1l) were successfully converted to the desired products, but with slightly lower yields. Both cyclic and acyclic secondary alkyl iodides (1j-1m) smoothly produced the corresponding products with moderate to good yields. Heterocyclic 4-iodotetrahydropyran (1n) was also tolerated under the reaction conditions. It should be noted that the yields for a few of the aforementioned substrates were reduced during the workup process due to product volatility. A beneficial feature of the reaction is that the anhydride is typically produced in high purity, such that isolation involves simply filtering the crude product mixture and removing volatiles under reduced pressure. In experiments with methyl iodide as the substrate at 15x scale, we successfully detected 78% conversion to Ac2O (Figure 2A inset). Thus, we envision that an industrial-scale synthesis of Ac2O would be feasible under such mild and economical reaction conditions with appropriate reaction engineering.

Next, we focused on alkyl electrophiles that are more abundant than iodides (Figure 2B). The alkyl bromide variant of 1a was found to be inert toward the transformation. However, the desired products were obtained with high yields when NaI was used as an additive to generate alkyl iodide in situ (Finkelson conditions)27 with primary alkyl bromides (3a-3g), except for attenuated yield with bulky 3h. Tertiary alkyl bromides and benzyl bromide were unsuccessful in delivering the corresponding anhydrides with or without NaI (see Supplementary Information). Taking inspiration from the Monsanto process, which uses alcohol as the alkyl source, we decided to test protected alcohols in our reaction. To our delight, various alkyl tosylates (3i-3k) were successfully converted into the related anhydrides in nearly quantitative yields with NaI additive. Both these conditions and the Monsanto and Tennessee Eastman processes require iodide additives to generate active electrophiles in situ, although the current method requires alkyl tosylate rather than free alcohols.

Having established the broad scope of the reaction, we turned our attention to the mechanism. Based on our initial experiments, we had already established that Cu(I) (pre-)catalyst and photoradiation were required for the reaction to proceed (Table 1, entries 1 and 6). Furthermore, although K2CO3 could donate either CO or CO2 to the product in principle, this possibility was ruled out due to high yield obtained with NaOH in place of K2CO3 (Table 1, entry 3). Thus, we propose that the anhydride products incorporate two CO gas molecules plus an oxygen atom from the base. Noticing that solids typically precipitated from solution during the reaction, we next interrogated whether the transformation proceeds by homogeneous or heterogeneous catalysis using a filtration test28 (Figure 3A, reaction i). Reactant 1a was consumed quantitatively under optimized conditions at 4.5 h reaction time. Stopping the reaction at 1 h provided 51% consumption of 1a. Filtering the reaction mixture at 1 h and then allowing it to further proceed to 4.5 h gave only 55% consumption of 1a. Since reaction progress effectively halts upon filtration of the reaction mixture, we concluded that an in-situ generated heterogeneous catalyst material is responsible for mediating the observed transformation. A solid material was also found to form by exposing a 1:10 mixture of CuBr·SMє and K2CO3 (no alkyl iodide) to the photochemical reaction conditions. XPS analysis of the solid precipitate indicated the presence of Cu0 (see Supporting Information), and so a working hypothesis is that Cu nanoparticles are the active catalysts under operating conditions29.

To verify that organic radical intermediates are involved in the reaction, we exposed cyclopropylmethyl iodide (1o) to the reaction conditions and obtained anhydride 2o in which both alkyl groups were ring-opened (Figure 3A, reaction ii). To test whether the reaction proceeds via an ester intermediate akin to the Tennessee Eastman process, we tested the viability of 3-phenylpropyl 4-phenylbutanoate (4) and obtained no evidence for ester carboxylation to yield 2a (reaction iii). On the other
hand, 4-phenylbutanoyl iodide (5) was found to be a viable intermediate, converting to \(2a\) with high efficiency under the optimized catalytic conditions. Further investigations indicated that conversion of 5 to \(2a\) did not require CO gas, Cu catalyst, or photoirradiation (reaction iv).

\[
\begin{align*}
&\text{CO (6 atm)} \\
&\text{CuBr \cdot SMg (10 mol\%)} \\
&K_2CO_3 (2.0 \text{ equiv}) \\
&\text{hv (390 nm)} \\
&\text{CH}_2CN, 8-12 \text{ h} \\
\end{align*}
\]

Figure 2. Substrate scope studies: (A) Scope in alkyl iodides; (B) Scope in alkyl bromides and tosylates in the presence of NaI additive. Reactions were conducted on 0.1-mmol scale unless otherwise indicated. Yields were determined by \(^1\)H NMR integration against an internal standard (CH\(_2\)Br) after silica gel filtration to remove inorganic catalysts and byproducts. \(^4\)Reaction time = 2 h. \(^5\)Estimated yield due to volatility.

A common mechanism for obtaining the key acyl iodide intermediate from an alkyl iodide reactant is atom transfer carbonylation (ATC), a radical chain process. However, our catalytic results are inconsistent with an ATC mechanism. Most importantly, ATC chemistry is efficient for secondary and especially tertiary alkyl halides but sluggish and unselective for primary alkyl and methyl halides, a pattern that has been attributed to the unfavorable thermodynamics of the halogen atom transfer step. By contrast, the reaction reported here proceeds well for primary alkyl and methyl halides, less efficiently for secondary alkyl halides, and not at all for tertiary alkyl halides. Thus, we can rule out ATC and instead propose a Cu-centered mechanism for alkyl iodide carbonylation (Figure 3B). The heterogeneous Cu catalyst A absorbs a photon to produce excited-state A*, which is likely to be sufficiently reducing to engage the alkyl halide in SET, producing iodine-adsorbed intermediate B and free alkyl radical C. Upon carbonylation, acyl radical D is formed. Rebound of D with B produces intermediate E with acyl and iodine group co-adsorbed on the catalyst surface. Subsequent C-I coupling regenerates A after desorption of acyl iodide F. Related mechanisms for light-mediated, Pd-catalyzed acyl halide formation have been proposed by Arndtens and, albeit with a homogeneous rather than heterogeneous catalyst. Next, as demonstrated in our metal-free dark reaction (Figure 3A, reaction iv), reaction of F with K\(_2\)CO\(_3\) with concomitant decarboxylation will form carboxylate G, which finally undergoes condensation with F to yield the anhydride product.
It is interesting to note that, in the absence of base, no acyl iodide formation is observed and only alkyl iodide is recovered (see Table S2). From this, we can conclude that acyl iodide formation is reversible under the photocatalytic conditions and driven forward by reaction with carboxylate G.

**Figure 3.** Mechanistic studies: (A) Experimental results probing the catalytic mechanism; (B) A plausible mechanism.

In addition to enabling carbonylation of primary alkyl and methyl halides in the absence of precious metals, a critical feature of the photocatalytic Cu conditions is the mild temperature at which the reaction proceeds. Carboxylate intermediate G is expected to react directly with the alkyl iodide partner to form an ester byproduct at slightly elevated temperatures. Thus, the high anhydride selectivity is enabled by the light-mediated conditions that access reactivity at ambient temperature. We expect that replacement of K$_2$CO$_3$ with other weak nucleophiles will provide access to other acyl pseudohalide products, and such explorations are currently underway.

**ASSOCIATED CONTENT**

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

Experimental procedures & spectral data (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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**REFERENCES**


\[ \text{R} - \text{X} + \text{Cu} + \text{K}_2\text{CO}_3 \rightarrow \text{R} - \text{O} - \text{R} \]

\( \text{R} = 1^\circ \text{ or } 2^\circ \text{ alkyl} \)

\( \text{X} = \text{Br}, \text{I}, \text{OTs} \)

\( \text{Ac}_2\text{O}: \text{R} = \text{Me} \)