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Iodide as an Activating Agent for Acid Chlorides in Acylation Reactions

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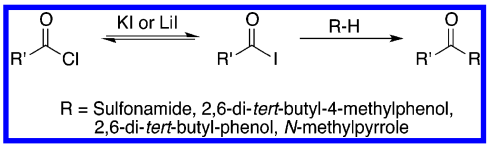
ABSTRACT



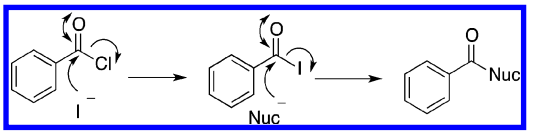
Acid chlorides can be activated using a simple iodide source to undergo nucleophilic attack from a variety of relatively weak nucleophiles. These include Friedel–Crafts acylation of *N*-methylpyrroles, *N*-acylation of sulfonamides, and acylation reactions of hindered phenol derivatives. The reaction is believed to proceed through a transient acid iodide intermediate.

The use of acid chlorides and activation of carboxylic acids have long been established as successful ways to acylate a wide variety of nucleophiles.[1] Activation is typically achieved using agents such as dicyclohexylcarbodiimide (DCC),[2] 1,1-carbonyldiimidazole (CDI),[3] or chlorotriazine.[4] However, the process usually requires a stoichiometric amount of these activating agents and the substrate scope does have limitations. The need continues for alternative approaches to the acylation of some problematic nucleophiles.

Herein we describe how an acid chloride can be activated by nucleophilic attack from iodide leading to *in situ* formation of the corresponding acid iodide which is more electrophilic than the acid chloride (Scheme 1). ^{13}C NMR spectroscopic studies show the formation of the acid iodide intermediate as well as evidence of its increased reactivity.

Although iodide has been widely used to enhance the reactivity of alkyl chlorides in S_N2 nucleophilic substitution reactions,[5] its application to acyl transfer reactions does not appear to have been reported.

Scheme 1. Possible Mechanism for Activation of Acid Chlorides To Allow Nucleophilic Attack from Poor Nucleophiles



N-Acylsulfonamides are typically synthesized by the activation of carboxylic acids using CDI or DCC and DMAP.[6] Other notable methods are the use of rhodium as a catalyst to access the nitrene intermediate[7] and the use

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of azides to activate sulfonamide.[8] We proceeded on the basis that lithium iodide could be used as an activating agent for acid chlorides. Lithium iodide showed some improvement over the background rate, but after a screen of iodide sources, sodium and potassium iodide showed the greatest enhancement of reactivity. Further optimization led to the discovery that the rate enhancement was completely suppressed in most common solvents except for anhydrous acetonitrile and anhydrous ethyl acetate, with the former proving to be the most effective. Finally, 60 mol % potassium iodide and a slight excess of acid chloride were required to drive the reaction to completion and a wide range of *N*-acylsulfonamides could now be isolated in excellent yields. It is interesting to note that increasing the concentration of potassium iodide led to a reduction in conversion into the *N*-acylsulfonamide product.

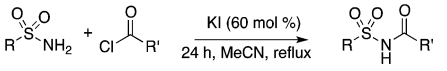
The reaction was extended to the synthesis of a range of *N*-acylsulfonamide products (Table 1). Both aliphatic and aromatic acid chlorides were found to be suitable substrates, as were aliphatic and aromatic sulfonamides. There was some partial racemization in the formation of the chiral product in entry 12, Table 1. However, as the product was not racemic, this suggests that the reaction did not proceed wholly via a ketene intermediate.

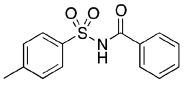
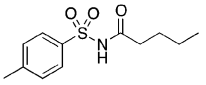
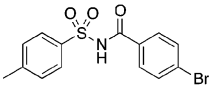
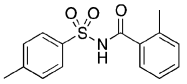
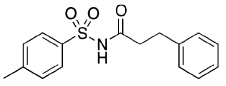
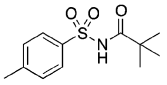
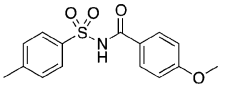
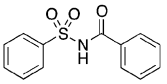
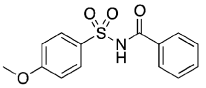
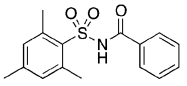
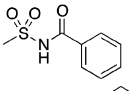
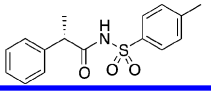
Although large amounts of iodide were needed in order to achieve a significantly beneficial rate enhancement, this method offers clear advantages to a process where the highly reactive acid iodide is isolated prior to use.

Next, we considered whether previous Friedel–Crafts acylations of pyrroles carried out within the group could also be improved.[9] We discovered that the additive lithium iodide enhanced the reactivity of acid chlorides in these reactions. Optimization of the process led to the discovery that the use of lithium iodide in the presence of an acid chloride in anhydrous ethyl acetate enhanced the Friedel–Crafts acylation of *N*-methylpyrroles. The reaction with benzoyl chloride could be completed within 1 h with the reduced yield, relative to conversion, owing to difficulty in purification.[10] Table 2 summarizes the substrate scope of this reaction.

We then continued to consider other nucleophiles that potassium or lithium iodide might improve the acylation of, and the formation of esters from hindered phenol derivatives was investigated.[11] 2,6-Di-*tert*-butyl-4-methylphenol (BHT) was chosen, and it was found that with 2.4 equiv of acid chloride and 1.2 equiv of potassium iodide the ester product could be produced in excellent yield (Table 3, entries 1 and 2).[2] By contrast when 2,6-di-*tert*-butylphenol was reacted with benzoyl chloride, the major product was the Friedel–Crafts *C*-acylation of the *para*-position over the formation of the ester, with the steric hindrance seemingly influencing the formation of the ketone (Table 3, entries 3 and 4).[12]

Table 1. Scope of Acylation of Sulfonamides[a]



entry	product	yield (%)[b]
1		89
2		88
3		67
4		92
5		91
6		80
7		97
8		96
9		83
10		73
11		83[c]
12		54[d] (80% e.e.)

[a] Reactions were performed on a 3 mmol scale using 3.6 mmol of acyl chloride in 3 mL of MeCN. [b] Isolated yields after column chromatography. [c] Isolated after recrystallization ($EtOH/H_2O$). [d] Isolated by prep. HPLC.

In order to understand the possible mechanisms for the activation of the acid chloride, several ^{13}C NMR experiments were carried out. From the literature, it is known that the ^{13}C carbonyl shift in benzoyl iodide occurs at 159.6 ppm, which is comparable with a shift of 168.6 ppm for benzoyl chloride.[3b] We were able to run the experiments within the NMR tube in CD_3CN at 70 °C therefore simulating the reaction conditions as closely as possible. The first NMR experiment was to investigate whether the acid iodide intermediate could be observed with the heating of benzoyl chloride and potassium iodide in the absence

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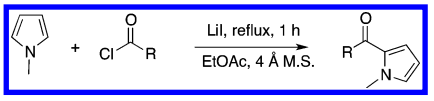
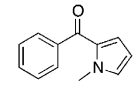
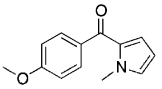
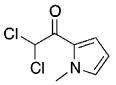
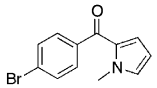
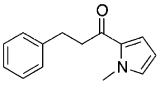
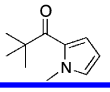
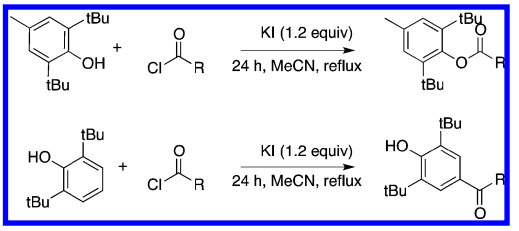
Table 2. Scope of Acylation of *N*-Methylpyrrole[a]

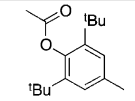
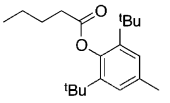
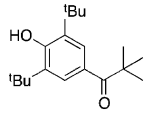
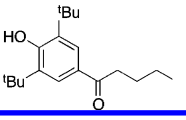


entry	product	yield (%)[b]
1		68 (100)
2		58 (100)
3		73 (100)
4		61 (100)
5[c]		50 (100)
6[d]		40 (100)

[a] Reactions were performed on a 1 mmol scale using 1.3 mmol of *N*-methylpyrrole in 1 mL of EtOAc. [b] Isolated yields after column chromatography; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra. [c] 4 h reaction time. [d] 20 h reaction time.

Table 3. Scope of Acylation of BHT[a]



entry	product	yield (%)[b]
1		95
2		97
3		58
4		97

[a] Reactions were performed on a 3 mmol scale using 7.2 mmol of acyl chloride in 3 mL of MeCN. [b] Isolated yields after column chromatography.

of any additional nucleophile. We were pleased to see a peak at 159.6 ppm appear within 2 h, and this peak remained stable at a relative (to the peak at 168.6 ppm) integration of ~20% implying that this is the approximate equilibrium amount of acid iodide present. In order to determine if the acid iodide formation caused the increase in reactivity or whether the Lewis acidity of the potassium was enhancing the reactivity, another experiment was carried out. When tetrabutylammonium iodide was used as the iodide source, analysis of the ^{13}C NMR spectra revealed that no acid iodide was formed *in situ*, with only benzoyl chloride being detected. We therefore assume that the potassium is necessary for the formation of the acid iodide. However, the use of other potassium salts (KCl or KBr) in the formation of *N*-acylsulfonamides produced much reduced conversions indicating that the reaction was not occurring via a purely Lewis acid mechanism.

In order to test the relative reactivity of the acid halides, 20 mol % benzylamine was added to the NMR tube after the PhCOCl/PhCOI equilibrium had been reached. We were pleased to observe that the acid iodide immediately disappeared and that the acid chloride peak remained present, implying that the acid iodide reacted preferentially with the nucleophilic benzylamine.

A subsequent NMR experiment involved the addition of *p*-toluenesulfonamide and 1.2 equiv of benzoyl chloride to 60 mol % KI in CD_3CN; the reaction was followed by ^{13}C NMR, and spectra were taken every 20 min for 24 h. The formation of the *N*-acylsulfonamide product could be readily followed, but no acid iodide was observed during this time. After 24 h, all of the *p*-toluenesulfonamide had been consumed and the presence of acid iodide was then observed to reach its equilibrium position after an additional 3 h.

It seems reasonable to conclude that the rate-determining step is the slow formation of acid iodide by reaction of acid chloride with the iodide source. Although iodide is an excellent nucleophile in S_N2 reactions, this is not the case for addition to the carbonyl group. The difference has been attributed to the hard nature of an sp^2 carbonyl carbon compared with the relatively soft nature of the sp^3 carbon; therefore soft nucleophiles such as iodide are more effective at soft carbon sites.[4,13]

Given the greater electronegativity of chlorine over iodine, it is not necessarily obvious why the acid iodide is inherently more reactive.[14] We suggest that the acid iodide is more reactive due to its greater polarizability and to the fact that the lone pairs on the iodine are less able to overlap with $\pi^*_{C=O}$.

In conclusion, we have developed a synthetically useful approach to activating acid chlorides via a proposed *in situ* acid iodide intermediate, using readily available potassium

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or lithium iodide. Thus, poor nucleophiles can be acylated in good to excellent yields, sometimes using a substoichiometric amount of group I iodide.

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Supporting Information Available. Experimental details, optimization reactions, characterizations, ^{13}C NMR experiments, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.