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Nucleophilic Acyl Substitution via Aromatic Cation Activation of Carboxylic Acids: Rapid Generation of Acid Chlorides under Mild Conditions

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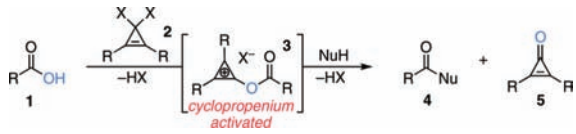
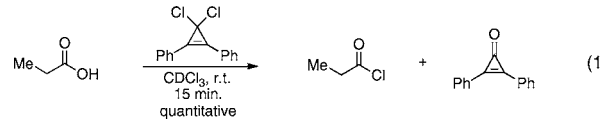
Recently, we developed a new strategy for the activation of alcohols toward nucleophilic substitution based on the facile formation of Breslow-type[1] cyclopropenium ethers.[2] Given the broad synthetic importance of carboxylic acid derivatives, we wondered whether our aromatic cation activation strategy might also be effective for facilitating nucleophilic acyl substitution (Scheme 1). Specifically, we hypothesized that treatment of a carboxylic acid **1** with a cyclopropene **2** bearing geminal leaving groups (X) would produce a cyclopropenium carboxylate intermediate **3**. Nucleophilic acyl substitution of this intermediate would then produce a carboxylic acid derivative **4** and cyclopropenone **5**. Although this design had close analogies to our previous work, it was unclear at the outset whether aromatic cation activation would be effective in the mechanistically distinct context of acyl substitution. However, if viable, it seemed clear that such a strategy would enable the design of powerful new acylation technologies using simple yet highly modifiable carbon-based reagents. In this Communication, we demonstrate the feasibility of achieving nucleophilic acyl substitution via aromatic cation activation, in the context of the rapid conversion of carboxylic acids to acid chlorides.

Scheme 1. Nucleophilic Acyl Substitution via Aromatic Cation Activation



Due to their strong electrophilicity, acid chlorides may be readily converted to virtually all other acyl derivatives and thus represent the most powerful means to achieve carboxylic acid functionalization. Although traditional methods of acid chloride formation using oxalyl chloride, thionyl chloride, or phosphorus chlorides have long been staples of synthetic chemistry,[3] the HCl generated with these procedures renders them incompatible with acid sensitive substrates. Accordingly, several methods have been developed that allow for acid chloride synthesis under nonacidic conditions.[4] However, many of these protocols are complicated by the use of undesirable reagents (e.g., PPh_3)[4a−d] or suffer from poor reaction rates.[4a,e] Indeed, very few acid chloride forming reagents offer high reactivity under nonacidic conditions,[4f,g] and those that do arguably lack broad structural and electronic versatility of the type desired for method development. As such, we were especially interested in the prospect of acid chloride formation via aromatic cation activation in the presence of amine base.

First, to investigate the possibility of aromatic cation activated nucleophilic acyl substitution, we examined the readily available 3,3-dichlorocyclopropene that had proven successful in our previous study.[2] Thus, propionic acid was treated with 1.2 equiv of 3,3-dichloro-1,2-diphenylcyclopropene[5] in $CDCl_3$ at ambient temperature. Within 15 min, we observed (^{1}H NMR, IR) quantitative conversion to propionyl chloride and 2,3-diphenylcyclopropenone (eq 1), demonstrating that cyclopropenium formation does in fact provide a potent means to activate carboxylic acids toward nucleophilic substitution.



To further probe this reactivity, we next examined the effect of cyclopropene structure on reaction rate. For this study we chose the conversion of pivalic acid to pivaloyl chloride, a transformation we reasoned would offer an observationally convenient (i.e., slower) reaction rate due to steric encumbrance (Chart 1a). Notably, in this case the diphenylcyclopropene reagent **A** was rather inefficient, providing only ~20% conversion after 60 min. On the other hand, replacing the cyclopropenyl phenyl groups with isopropyl substituents (reagent **C**) resulted in a significantly faster reaction rate, comparable to that observed using oxalyl chloride **E**. Since it is well-known that cyclopropenium ions bearing alkyl substituents possess higher pK_{R+} values than those with simple aryl groups,[6] it is worth stressing that in this case the *more stable* carbocation provided the faster rate of acyl substitution. We attribute this fact to the greater propensity for the dialkylcyclopropene to ionize, thereby accessing the key cyclopropenium carboxylate intermediate. This trend apparently has its limits, however, because the exceedingly stabilized bisguaiazulenyl cyclopropene **D**[7] resulted in only 13% conversion after 60 min. As expected, use of a mixed phenyl isopropyl cyclopropene **B** resulted in a rate of acid chloride formation approximately intermediate between that provided by **A** and **C**.

Satisfied that aromatic cation activation was a viable means of acid chloride production, we next decided to investigate the effect of an amine base additive. In fact, we found that the addition of an equivalent of Hünig's base significantly enhanced the rate of conversion (Chart 1b). Thus for example, using diisopropylcyclopropene **C** in the presence of 1 equiv of Hünig's base, formation of pivaloyl chloride was complete within 10 min, proceeding to 78% conversion.[8] Interestingly, the relative efficiencies of cyclopropenes **A** and **B** were now the reverse of those expected based on relative cyclopropenium ion stabilities. Although conversions with **A** and **B** were significantly lower than that observed with **C**, all three cyclopropenes performed better in the presence of base than did oxalyl chloride (**E**), the activity of which was significantly retarded by the presence of amine.

We have found that this method can be employed for the rapid and mild conversion of carboxylic acids to amides, via the intermediacy of acid chlorides (Table 1). For these experiments, 1,1-dichloro-2,3-diisopropylcyclopropene **C** was prepared *in situ*

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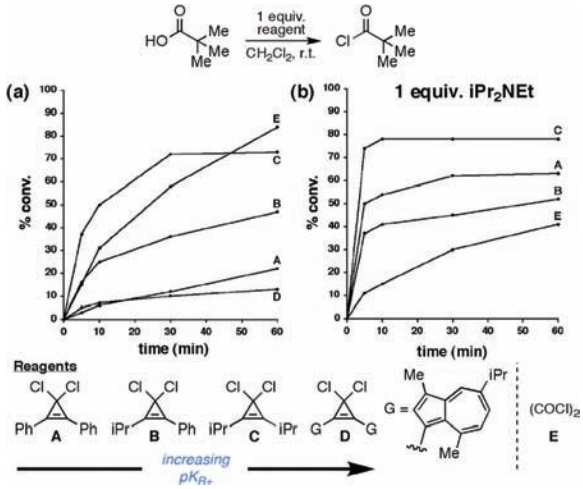
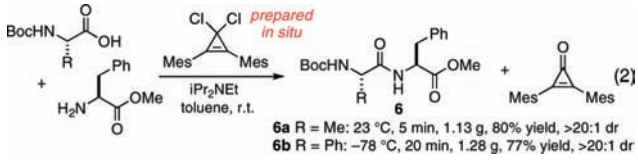
Chart 1. Rate Comparison for Acid Chloride Formation[a]



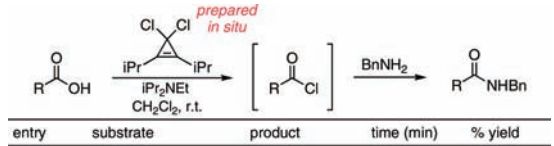
[a] Reactions were run by the addition of a solution of pivalic acid without (a) or with (b) *i*Pr_2NEt to a solution of 3,3-dichlorocyclopropenes **A**−**D** in CH_2Cl_2. Timed aliquots were quenched with excess (5 equiv) benzylamine, and % conversions were determined by ^{1}H NMR analysis of *N*-benzylpivalamide compared to Bn_2O as an internal standard.

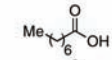
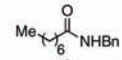
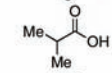
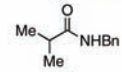
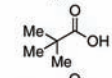
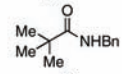
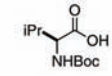
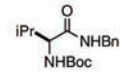
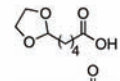
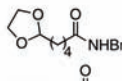
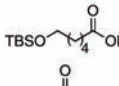
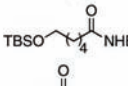
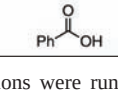
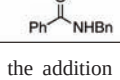
by the treatment of a solution of 2,3-diisopropylcyclopropenone with oxalyl chloride for 10 min. Subsequently, a mixture of carboxylic acid and Hünig's base was introduced to the flask, followed by, after the indicated time, benzylamine. Using this procedure, amide formation was found to occur readily for aliphatic carboxylic acids of varying steric profiles (entries 1−3). Most notably, the mildness of this procedure enabled acid chloride/amide formation with substrates bearing acid-sensitive functionality, including an *N*-Boc amino group (entry 4). We are aware of only one other (low-yielding) example of the preparation of an *N*-Boc amino acid chloride.[4d] Other potentially acid labile functional groups such as a glycol acetal (entry 5) and a silyl ether (entry 6) were also compatible with this method. In contrast to the other substrates we investigated, the reaction efficiency with benzoic acid was relatively poor (entry 7). We hypothesize that this low conversion may be due to the electron deficiency of the benzylic carboxylate group, which would weaken its ability to participate in cyclopropenium carboxylate formation. Importantly, diisopropylcyclopropenone could be recovered from the reaction mixture and reused in every case.



Finally, we have leveraged our activation strategy to achieve cyclopropenium-mediated peptide couplings (eq 2). These couplings, which utilized commercially available 2,3-dimesitylcyclopropenone as the cyclopropene precursor, were conducted on a preparative scale (>1 g product), were complete within 5 min at ambient temperature or 20 min at −78 °C, and furnished the *N*-Boc dipeptides **6a** and **b** in 80% and 77% yields respectively without any observed stereochemical erosion.

Table 1. Substrate Scope Studies for Amidation[a]



entry	substrate	product	time (min)	% yield
1			2	97
2			5	86
3			10	78
4			5	79
5			5	94
6			5	92
7			20	44

[a] Reactions were run by the addition of a solution of the carboxylic acid and *i*Pr_2NEt to a solution of 3,3-dichloro-1,2-diisopropylcyclopropene in CH_2Cl_2, followed by the addition of benzylamine.

In conclusion, we have demonstrated the effectiveness of aromatic cation activation for nucleophilic acyl substitution. The compatibility of this method with amine base offers rapid access to acid chlorides, including with acid sensitive substrates, using readily available, electronically tunable, and easily recyclable carbon-based reagents. The possibility of extending nucleophilic acyl substitution via aromatic cation activation to include other nucleophiles is the subject of current study in our laboratory.

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Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) A reviewer has suggested that this less than complete conversion may be the result of an equilibrium between acid chloride and cyclopropenium carboxylate. However, when pivaloyl chloride was treated with an equivalent of 2,3-diisopropylcyclopropenone, no change was observed, nor was the subsequent yield of *N*-benzylpivalamide diminished.

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