



New insights into the old reaction between acryloyl chlorides and pyridine



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ABSTRACT

Direct acylation reactions of alcohols with acid chlorides in the presence of pyridine leads to the formation of unexpected pyridinium derivatives as major products. Although this phenomenon was briefly reported several decades ago, a detailed structure elucidation of the intermediates and ionic products was missing. In this study, the formed pyridinium products are structurally characterized and the underlying reaction mechanism is discussed. The addition of reactants in the order acryloyl chloride–R–OH–pyridine yields a structure **P1**, which was tentatively proposed before. However, if the order of reactant addition was changed, that is, R–OH was added to a mixture of acryloyl chloride and pyridine, two new types of pyridinium derivatives (**P2** and **P3**) were observed. Their formation implies the unprecedented β -addition of pyridine to acryloyl chloride followed by a Michael addition of the nucleophilic α -carbon or by an alkylation of the activated carboxyl group. The proposed reaction mechanism is supported by a detailed structural analysis of intermediates and products.

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Sometimes, common reactions yield unexpected results, but the underlying mechanisms are often not investigated in detail. It is well-known that pyridine forms highly reactive *N*-acylpyridinium adducts with acid chlorides.¹ In the Einhorn variant of the Schotten–Baumann reaction,² esters and amides are efficiently synthesized by a nucleophilic attack of alcohols or amines on such *N*-acylpyridinium intermediates. However, in a corresponding reaction with acryloyl chloride we did not observe products of a simple alcohol acylation. Quite unexpectedly, we obtained a mixture of organic salts with the behavior of ionic liquids as the major products of the reaction. This was a rather remarkable result, taking into account an earlier report claiming successful acylation reactions with acryloyl chlorides and pyridine as a base.³ Still, the described effect has been briefly mentioned before: a mixture of different polar organic compounds of ionic nature was obtained when pyridine was added as a base in acylation reactions with acryloyl chloride.⁴ The first examination of the formed ionic products was performed by Hickmott in 1964,⁵ who assumed the formation of a derivative with the pyridinium group attached to the β -position of the ester. However, no spectroscopic and mechanistic characterizations were provided to support this conclusion. A similar reaction was also described in an earlier patent,⁶ although

no attempts to characterize its products have been taken. Since then, no additional reports about the formation of the postulated pyridinium ions using alkylation with acryloyl chloride have been published.

Quaternary ammonium compounds, including pyridinium derivatives, are widely used, for example, as surfactants, phase transfer catalysts, and disinfectants. Because of their accumulation in seas and lakes,⁷ replacement of ordinary alkyl chains in quaternary ammonium ions is desired. Quaternary ammonium compounds containing chains with the ester groups (so called 'esterquats') represent a good alternative to improve the biodegradation of such surfactants.^{8–10} Furthermore, compounds with pyridinium groups have an important role in the broad variety of applications as ionic liquids.^{11–13}

We propose that such alkylated pyridinium compounds can be efficiently prepared by using the overlooked β -addition of pyridine to acryloyl chloride. Following our work on the formation and reactivity of methacryloyl chloride dimers¹⁴ we decided to investigate this reaction using modern analytical methods. An insight into the structures of the ionic compounds and reaction intermediates formed upon mixing pyridine, acryloyl chloride, and water/alcohol was obtained by 1D- and 2D-NMR spectroscopy and mass spectrometry. These data gave evidence for the formation of several previously not described pyridinium ions and allowed us to propose the mechanisms of their formation.

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When we slowly added 1.1–1.5 equiv of pyridine to a solution of acryloyl chloride and an excess of alcohol or water in acetonitrile, the corresponding ester of carboxylic acid with pyridine attached to the β -position (**P1**, Fig. 1) was obtained. The former assumption concerning the formation of this β -addition product⁵ was then undoubtedly confirmed by spectroscopic data. According to recent literature reports, pyridinium derivatives of this type are commonly prepared using other methods: Michael addition to acrylic acid or its esters,¹⁵ nucleophilic substitution of halocarbons (pyridine + ClCH₂CHR'COOR'')¹⁶ or of β -propiolactone.¹⁷ However, the reaction times are usually rather long (several hours) and heating of the reaction mixtures is necessary, or, in the reaction with β -propiolactone, only the synthesis of the carboxylic acid (R = H for **P1**) is possible in a one step reaction.

In contrast, β -addition of pyridine to acryloyl chloride occurs instantaneously at room temperature and is highly exothermic. Protonated pyridine (C₅H₅NH⁺) was found as the only byproduct. If, however, pyridine was added to a solution of acryloyl chloride in acetonitrile (in the same stoichiometric ratio as before), a precipitate was obtained. Subsequent addition of an alcohol or water resulted in a mixture of protonated pyridine, **P1** and a previously undescribed type of pyridinium ion **P2**. **P2** with R = H was isolated and characterized. The product ratio strongly depends on the reaction conditions: elevated temperature increased the yield of **P2** (see Supplementary data, Section S2b). If four equivalents of pyridine were used, no decrease of the relative **P2**/**P1** ratio was observed. Additionally, the third type of pyridinium derivative with the bicyclic structure **P3** was formed in minor amounts. The structure of **P3** could be unambiguously identified within the mixture of alkylated pyridinium ions by detailed analysis of COSY, HSQC, and HMBC NMR spectra (see Supplementary data, Section S4i). While **P3** is stable in solution for a short period of time, unfortunately, all attempts failed to isolate **P3** in pure form. Chromatographic methods were developed to separate **P3** (with R = H) from the other pyridinium ions, still, it was not possible to characterize **P3** in pure form because of its degradation into a mixture of unidentifiable products (for details, see Supplementary data, Section S5). Dearomatization of one pyridine moiety may serve as an explanation for the instability of **P3**.

These simple synthetic procedures can be proposed for the synthesis of different **P1** and **P2** derivatives. As a representative example, we have purified and characterized a **P1**-type derivative including a thioester and a **P2**-type derivative including methacryloyl and butylamine as structural elements (Fig. 2). A variety of other combinations of starting materials for this three component reaction was screened using ESI-MS (see Supplementary data, Section S3).

The second important goal of this study was the elucidation of the reaction mechanism yielding the identified structures **P1**–**P3**. In the mechanism suggested by Hickmott,⁵ an acylium ion (Fig. 3) was proposed to be the key intermediate in the process of the formation of **P1** as well as of the traces of expected esterification

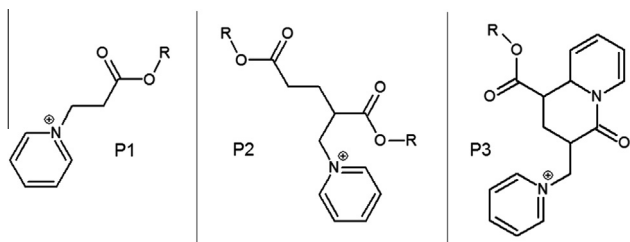


Figure 1. Identified structures of alkylated pyridinium ions formed by reactions between acryloyl chloride, pyridine, and ROH. For NMR and MS data, see Supplementary data, Section S4.

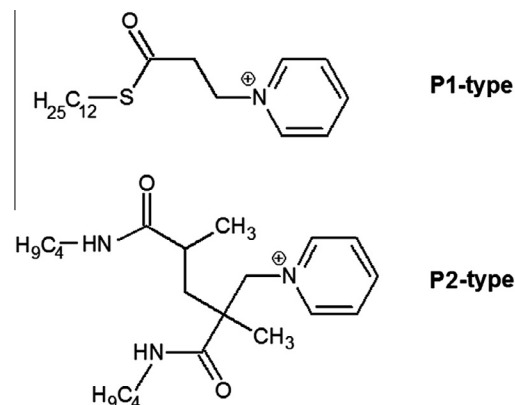


Figure 2. Molecular structures of **P1** and **P2** derivatives that have been synthesized and isolated. For synthesis, see Supplementary data, Section S2 and for spectroscopic characterization, Sections S4e and S4g.

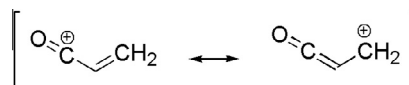


Figure 3. Mesomeric structure of the intermediate acylium ion proposed by Hickmott.⁵

products, which were not observed in our case. However, this mechanism cannot justify the formation of additional ionic products **P2** and **P3**. We propose that the formation of three different pyridinium derivatives can be explained by an attack of pyridine to the β -position of acryloyl chloride (Scheme 1). Although, to our knowledge, α,β -unsaturated acid chlorides have never been described as Michael acceptors, this fact can be explained by their high reactivity leading to a preferred nucleophilic substitution at the electrophilic carbonyl carbon. On the other hand, it has been shown before that Michael addition of pyridine to acrylic acid with the formation of pyridinium salts is possible,¹⁵ which serves as a confirmation of the possibility of the direct β -addition of pyridine. The reaction of pyridine with acrylic acid proceeds slowly at elevated temperatures. Presumably, pyridine attacks the acryloyl chloride or acrylic acid in a frontier orbital controlled reaction, and the considerably lower LUMO energy of acryloyl chloride compared to acrylic acid (see calculated data in S7) explains the higher reactivity of the former.

On the basis of the available experimental data we can propose the following reaction mechanism (Scheme 1). The bipolar intermediate **I** formed from pyridine and acryloyl chloride reacts with an alcohol or water leading to ionic compounds of type **P1**. Then, the α -carbon of the carbonyl group is protonated by the acidic alcohol hydrogen, which was confirmed by a reaction within methanol-*d*₄ (see S4d). If no alcohol or water is present in the reaction mixture, the nucleophilic α -carbon reacts with a second acryloyl chloride in a Michael addition, in which the bipolar intermediate **II** is formed.

This reaction sequence resembles a known side reaction of the Baylis–Hillman reaction.¹⁸ A broad variety of α,β -unsaturated carbonyl compounds have been listed as applicable substrates in the Baylis–Hillman reaction but, according to a recent review Letter,¹⁹ acid chlorides ‘could not find a proper place in the list of electrophiles’. Supplementary results from reactions performed with an excess of pyridine, which still afforded the formation of significant amounts of **P2** lead to the assumption that intermediate **I** is not stable at higher temperatures in contrast to **II** or that two molecules of intermediate **I** react by formation of **II** and pyridine. The second bipolar compound **II** either reacts with alcohol or water forming **P2** or reacts with pyridine. In this process, the pyridine

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