Heterocycle Synthesis

A Mild Synthesis of Bicyclic Alkoxyoxazolium Salts from Proline and Pipecolic Acid Derivatives

Eleonora Spinozzi, Adriano Bauer, and Nuno Maulide

Abstract: A regio- and chemoselective preparation of bicyclic alkoxyoxazolium salts from amide derivatives of proline and pipecolic acid by electrophilic amide activation is reported. Mechanistic NMR experiments suggest an unusual role for the base and highlight the effect of substitution pattern of the substrates.

Introduction

The high abundance of carboxamides in combination with their distinct, mild nucleophilic properties makes them an interesting target for the investigation of organic reactions. Already in the 19th century it was observed that primary amides react readily with dehydrating agents such as PCl₅ or concentrated sulfuric acid to give nitriles. This resulted in an early recognition that the poor electrophilicity of the carbonyl-carbon of carboxamides can be readily enhanced by electrophilic activation. Robinson and Gabriel discovered independently that acylated α-amino ketones form oxazoles upon treatment with similar dehydrating agents (Scheme 1a). The resulting oxazole products can be alkylated, although this requires highly reactive alkylating agents (Scheme 1b). Recently, the electrophilic activation of tertiary amides has been used for the synthesis of certain N-aryloxazolium salts (Scheme 1c). However, that report restricted itself to the formation of oxazolium salts derived from aromatic amides.

Herein we would like to report the synthesis of bicyclic oxazolium salts based on proline- and pipecolic acid-derived amides (Scheme 1d). The products display interesting reactivity and can be converted to complex structures by formal cycloaddition.

Results and Discussion

As part of our interest in electrophilic amide activation, we recently investigated the suitability of proline as a chiral auxiliary for certain α-functionalization reactions. However, when 1a (Scheme 2) was subjected to electrophilic activation using tri-...
fluoromethanesulfonic anhydride (triflic anhydride) and 2-iodopyridine, quantitative and fast formation of the oxazolium salt 2a was observed.\[11\] Surprisingly, slight modification of the aliphatic backbone of the amide lead to a dramatic change in reactivity: when the linear propionamide 1b (Scheme 2) was employed instead of 2-methylpropionamide 1a, mostly recovered starting material was observed. Conversion of 1b did not improve with other bases or with elevated temperature.

It is noteworthy that not only do the reaction mixtures of 1a and 1b differ considerably in appearance,\[12\] but in situ \(^1\)H-NMR spectra of those two mixtures in deuterated DCM are also strikingly different (Figure 1). As shown, while the reaction mixture of 1a shows almost exclusively the product and the base after 5 minutes of reaction time, the spectrum of 1b under the same reaction conditions is much more complicated.

The successful reaction of 1a most likely proceeds via interception of the activated amide 3a (Figure 1) by the pendant ester moiety, with a subsequent (formal) elimination of trifluoromethanesulfonic acid (triflic acid).

In the case of 1b, although trace amounts of the product can be detected, other species dominate the spectrum. The species characterized by a signal at ca. 5.0 ppm, labelled as 4b (Figure 1), appears to be the main compound. The structure of 4b has been assigned as a 2-iodopyridine adduct by 2D-NMR analysis (see Supporting Information for details) and is a common intermediate in the electrophilic amide activation regime.\[10d\]

Interestingly, not even traces of an analogous species derived from 1a can be detected by \(^1\)H NMR under the same reaction conditions. These findings suggest that, in the case of 1a, limited accessibility of the \(\alpha\)-proton (by virtue of the \(\alpha\)-substituent) slows deprotonation and formation of enaminate-type adducts; this in turn is likely to greatly favor oxazolium formation in these systems.

These observations would suggest that omitting the base might allow oxazolium formation even in “unbranched” substrates such as 1b. In the event, such a simple modification (Scheme 3) indeed led to the expected oxazolium 2b in 82 % yield.\[13\] The \(^1\)H NMR spectrum of 1b in d\(_2\)-DCM after 5 minutes reaction time (Figure 2) now shows clean product formation, with a species assigned as intermediate 3b as the major compound in the mixture. The conspicuous absence of vinylic C-H resonances, indicative of a slower deprotonation, should be noted.

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Several other bicyclic, alkoxoxazolium salts could be synthesized through this procedure in good to excellent yields (Scheme 3). Halogens such as chloride (2d) or bromide (2i) were
Figure 2. Upper NMR trace: reaction of 1b with Tf₂O (1.1 eq.) in d₂-DCM after 5 minutes reaction time. The multiplet at 4.8 ppm is assigned to the cation 3b (the only other species present in considerable amounts is the desired oxazolium product). Lower NMR trace: reaction of 1a with Tf₂O (1.1 eq.) in d₂-DCM after 5 minutes reaction time.

tolerated. Pleasingly, an additional ester on the aliphatic chain does not interfere in the process. It is also noteworthy that a phenyl ring in proximity to the activated amide (2c) does not trigger Friedel-Crafts reactivity. The reaction was also found to be amenable to pipecolic acid derivatives (2f–2j).

We noted that the products structurally resemble münchnones to some extent. The latter are well-known for their ready participation in interesting (3+2) cycloadditions. In the event, we achieved a reductive formal [2+2]-cycloaddition of oxazolium salt 2b with dimethyl acetylenedicarboxylate (DMDA) leading to product 6b in good yield and as a single diastereoisomer (Scheme 4).

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Keywords: Amide activation · Oxazolium · Chemoselectivity · Cycloaddition · Synthesis design

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Conclusion
Herein we reported that bicyclic, alkoxyoxazolium salts can be readily prepared from simple proline- and pipecolic acid derivatives. Mechanistic experiments highlighted a deleterious role for the base. The products lend themselves to synthetic elaboration by cycloaddition reactions.
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[12] The reaction mixture of 1b is a deep red clear solution, while the reaction mixture of 1a is slightly yellowish.

[13] The formal elimination of triflic acid was accomplished by quenching the reaction with water saturated-DCM. Similar results were achieved when the base was added after stirring the mixture of substrate and triflic anhydride for 14 h.

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