Acyl Donor Intermediates in N-Heterocyclic Carbene Catalysis: Acyl Azolium or Azolium Enolate?

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Dedicated to Professor Siegfried Hünig on the occasion of his 100th birthday

Abstract: Azolium enolates and acyl azolium cations have been proposed as intermediates in numerous N-heterocyclic carbene (NHC) catalyzed transformations. Acetyl azolium enolates were generated from the reaction of 2-propenyl acetate with both saturated (SIPr) and aromatic (IPr) NHCs, isolated, and characterized (NMR, XRD). Protonation with triflic acid gave the corresponding acetyl azolium triflates which were isolated and characterized (NMR, XRD). Acyl azolium cations have been proposed as immediate precursors of the ester product, for example, in the redox esterification of α,β-enals. Studies with d1-acetyl azolium triflate suggest that ester formation originates instead from an azolium enolate intermediate. Furthermore, the acetyl azolium enolate selectively reacted with alcohol nucleophiles in the presence of amines. While the acetyl azolium cation did not react with alcohols, an ester-selective reaction was induced by addition of base, by intermediate formation of the acyl azolium enolate.

In recent years, the synthetic application of N-heterocyclic carbenes (NHCs) has been extended beyond classical α-δ-umpolung of simple aldehydes. As shown in Scheme 1a, α-δ-umpolung of α,β-unsaturated aldehydes with NHCs opens a pathway to homoenolate chemistry, through the formation of the diamino dienol I. Additionally, an OH-Cγ proton shift in the diamino dienol I leads to the azolium enolate II. The latter behaves as an enolate equivalent and serves as the source of yet another broad spectrum of products.

Besides applications in umpolung strategies, NHCs have also served as nucleophilic catalysts, for example, in the transesterification of activated esters. As shown in Scheme 1b, the acyl azolium cation III is believed to result from the interaction of the NHC catalyst with an activated carboxylic acid derivative. Note that a crossover exists between the two types of NHC-catalysis shown in Scheme 1a and b. γ-Protonation/tautomeration may equilibrate the diamino dienol I with the acyl azolium cation III. Another “cross-over point” is the azolium enolate II which is accessible from both the diamino dienol I and the acyl azolium cation III by β-deprotonation. Finally, the acyl azolium cation III can also be accessed by oxidative NHC catalysis, that is, from aldehydes in the presence of a suitable oxidant [Scheme 1, pathway (c)].

In 2005, Scheidt et al. and Bode et al. reported the NHC-catalyzed redox esterification of enals, leading from α,β-unsaturated aldehydes to saturated esters (Scheme 2). The mechanism proposed by Scheidt and Bode for this transformation is shown in Scheme 2, pathway A: As a key step, γ-protonation of the initially formed diamino dienol I affords the azolium enol IV. Tautomeration of the latter gives the acyl azolium cation III. Ester formation is completed by attack of the alcohol nucleophile on the latter. Note, however, that the occurrence of acyl azolium cations III in redox esterification has not been substantiated by isolation, or spectroscopically. We wondered whether ester formation...
may instead proceed through the azolium enolate stage (II, Scheme 2, pathway B). From II, a single-step reaction with the alcohol component to the product ester can be formulated, with regeneration of the NHC catalyst. In 2012, Chi et al. exploited a reverse crossover and reported that NHC catalysis can be used for the generation of azolium enolates II from activated esters. After reaction with the NHC catalyst, β-deprotonation of the initially formed acyl azolium cation III affords an azolium enolate II (Scheme 1b). The latter can be reacted with various electrophiles, affording for example, γ,δ-unsaturated δ-lactams with N-tosyl imines, again, none of the intermediates postulated for such reverse crossover reactions had been characterized.

To probe the acyl transfer chemistry discussed above, we envisaged the acetate-based azolium enolates 1–3ae (Scheme 3) and the acyl azolium cations 1,2aa (Scheme 4) as model systems. This choice was based on the simplicity of the acyl residue, and on our earlier experience that the use of SIPr, IPr as the carbene component provides sufficient stability for the characterization and even isolation of intermediates postulated for NHC catalysis. This approach had enabled us earlier to generate and probe Breslow intermediates involved in the NHC-catalyzed umpolung of simple aldehydes, related intermediates of α,β-enal umpolung, and even later stages of azolium enolate chemistry. In an elegant study by Maji and Mayr, azolium enolates have been prepared earlier by the reaction of NHCs with ketenes, and analyzed thoroughly with regard to their structure and reactivity towards benzhydrylum ions.

NMR monitoring revealed that the addition of 2-propenyl acetate to a solution of the saturated imidazolidin-2-ylidene SIPr in [D₈]THF at room temperature resulted in the smooth formation of the azolium enolate 1ae, together with the acetone adduct of SIPr, 4 as a 1:1 mixture [Scheme 3, (i)]. In [D₈]THF, the azolium enolate 1ae displayed two characteristic singlets in its 1H NMR at δ = 3.03 (s, 1H, H6) and 2.65 (s, 1H, H7), and 13C NMR resonances at δ = 76.5 (C10) and 153.2 (C9) ppm. The azolium enolate 1ae crystallized from the reaction mixture, and single crystals suitable for X-ray crystallography could be obtained (Scheme 3, bottom left).

As a typical azolium enolate feature, the planar enolate moiety and the imidazolinium ring are tilted relative to one another, by ca. 47°. The C=C distance of the enolate moiety nicely reflects its double-bond character [1.356(2) Å]. The SIPr-acetone adduct 4 was clearly identified by NMR (see the Supporting Information). A control experiment revealed that the strongly basic NHC SIPr reacts smoothly with acetone in [D₈]THF at RT, yielding exclusively the1:1 adduct 4.

When the unsaturated imidazolin-2-ylidene IPr was reacted with 2-propenyl acetate [Scheme 3, (ii)] in [D₈]THF at room temperature, acetone was liberated which, however, did not react further with IPr. Again, the azolium enolate 2ae crystallized from the reaction mixture. X-ray diffraction (Scheme 3, bottom right) confirmed the constitution of the azolium enolate. The planar enolate moiety and the (planar) imidazolinium ring are strongly tilted relative to one another, by ca. 53°, and the C=C distance [1.345(3) Å] within the enolate moiety proves its double bond character. The solubility of 2ae in [D₈]THF turned out to be so low that the crystalline material had to be redissolved in [D₈]MeCN for NMR characterization. In the latter solvent, 2ae displayed characteristic singlets in its 1H NMR at δ = 3.09 ppm (s, 1H, H6) and 2.75 ppm (s, 1H, H7) and 13C NMR resonances at δ = 77.7 (C10) and 132.7 (C9) ppm. When IMes was used as the

Scheme 3. Preparation and X-ray crystal structures of the azolium enolates 1–3ae. [96]

Scheme 4. Preparation and X-ray crystal structures of the acyl azolium triflates 1aa-OTf and 2aa-OTf. [98]
NHC component, NMR analogously indicated the formation of the azolium enolate 3ae (see the Supporting Information). Unfortunately, no crystals of 3ae suitable for XRD could be obtained.

As summarized in Scheme 4, the acetyl azolium cations 1aa and 2aa were prepared, as triflates, from the azolium enolates 1ae and 2ae by protonation with trifluoromethane-sulfonic acid (TfOH). In [D2]DCM, the instantaneous disappearance of the enolate proton resonances and appearance of a new singlet at $\delta = 1.95$ ppm (3H, H10) in the $^1$H NMR, and of new $^{13}$C resonances at 28.1 (C9) and 29.3 (C10) ppm in the $^{13}$C NMR indicated the formation of the acetyl azolium salt 1aa-OTf. Its unsaturated counterpart 2aa-OTf shows almost identical new resonances. We succeeded in crystallizing both acetyl azolium triflates 1aa-OTf and 2aa-OTf, and their X-ray crystal structures are shown in Scheme 4. In both cases, the acetyl moiety is again significantly tilted relative to the heterocyclic ring. In the case of the saturated acetyl azolium salt 1aa-OTf, the dihedral angle O1-C9-C8-N1 amounts to ca. $-57.4^\circ$, and somewhat smaller, yet significant, in the case of the aromatic azolium salt 2aa-OTf [O1-C9-C8-N2 ca. $31.4^\circ$].

When exposed to benzyl alcohol (1 equiv) in [D8]THF ($^1$H NMR observation) at RT, the azolium enolate 1ae was instantaneously converted to benzyl acetate (Scheme 5). The adduct of benzyl alcohol with SIPr (5) was formed as by-product. The analogous reaction of 2ae with benzyl alcohol was studied in [D2]DCM, for solubility reasons. Again, ester formation was instantaneous, with IPr (as its DCl salt) being formed as by-product.

Mechanistically, the ester formation may proceed either by a discrete proton transfer from the alcohol to 1,2ae, affording the acyl azolium cation 1,2aa as intermediate (Scheme 5, pathway A). Our NMR monitoring did not indicate accumulation of any intermediate which, however, does not exclude this possibility, as the formation of 1,2aa may be rate-limiting. Alternatively, a concerted proton/acyl-transfer may be envisaged (Scheme 5, pathway B). When 1ae was exposed to BnOD instead of BnOH, a moderate kinetic isotope effect of ca. 1.4 was observed (see Tables S1 and S2 in the Supporting Information for $k_D/k_H$ data).

While neither one of the two results above allows a clear distinction, the following set of experiment advocates for the azolium enolate as the immediate ester precursor: We first established that in the absence of base, the acetyl azolium salt 1aa-OTf does not react with benzyl alcohol (or other alcohols). Stoichiometric addition of DBU, however, results in instantaneous ester formation. Again, it may be argued whether the base deprotonates the alcohol, or converts the acetyl azolium salt 1aa-OTf into the azolium enolate 1ae (as in Scheme 5). We addressed the latter question by using the trideuterated acetyl azolium triflate 1aa-d3-OTf (Scheme 6). $^1$H NMR monitoring of this transformation clearly showed that in the resulting benzyl acetate, exactly one of the three acetyl deuterons had been exchanged for a proton (see the Supporting Information for $^1$H NMR spectral data). As depicted in Scheme 6, this formation of benzyl acetate-d3 is compatible only with deprotonation of the acetyl azolium cation (to the azolium enolate 1ae-d3, pathway A), and not with alcohol deprotonation (pathway B). In the latter case, full D-retention, that is, formation of benzyl acetate-d3 should have been expected. NMR monitoring showed that no concomitant H/D-exchange occurs at the acetyl group’s $\alpha$-position in the course of the ester formation. Another control experiment, in the absence of benzyl alcohol, confirmed that treatment with DBU cleanly and instantaneously converts the acetyl azolium triflate 1aa-d3-OTf to the azolium enolate 1ae-d3.

We conclude from the above studies that for the acetyl system 1,2aa-OTf/1,2ae—and analogously for other acyl azolium ions carrying at least one $\alpha$-proton—ester formation most likely proceeds via the azolium enolate state. For the redox esterification of $\alpha$,$\beta$-enals, a modified, and in fact simplified mechanistic picture results (Scheme 7): In the first step, the diamino dienol is generated from the substrate enal and the NHC catalyst. Tautomerization of the latter by OH-$\alpha$-shift gives the azolium enolate II which can react directly with the alcohol component to the saturated ester product, with regeneration of the catalyst. We are well aware that this simple scheme does not explain the often complex influence
of the nature and amount of base used for transforming azolium precatalysts to their active form. It is clear, however, that the equilibria NHC/NHC-H⁺ and I/II alone bear sufficient potential for pronounced influence by acids and bases.

In 2010, Studer et al. reported their intriguing observation that alcohols can selectively be cinnamoylated, in the presence of amines, under conditions of oxidative NHC-catalysis.[10,18,19] With this in mind, we decided to evaluate the ester/amide selectivity of our azolium enolate/acyl azolium pair 1ae/1aa-OTf. We studied their reactivity towards benzyl alcohol (BnOH) and benzyl amine (BnNH₂) by 'H NMR in [D₂]DCM, the results are summarized in Table 1. Exposure of the azolium enolate 1ae to BnOH (entry 1) and BnNH₂ (entry 2) resulted in smooth and quick ester formation, and sluggish amide formation, respectively. When 1ae was exposed to an equimolar mixture of BnOH and BnNH₂, formation of benzyl acetate was favored by a factor of 5.5 over amidation (entry 3). Control experiments established that there is no secondary ester-to-amide transformation (see the Supporting Information). Therefore, the ester-to-amide ratio reflects the kinetic preference for esterification. On the basis of the proposed single-step conversion of the azolium enolate (Scheme 5, pathway B), its preference for esterification can be explained by the higher acidity of RO–H versus RNH–H.

In contrast, the reactivity pattern of the acetyl azolium triflate 1aa-OTf is simply that of an activated carboxylic acid derivative. In line with earlier observations by Studer et al.[18] 1aa-OTf did not react with BnOH (Table 1, entry 4), while exposure of 1aa-OTf to BnNH₂ resulted in instantaneous formation of BnNHAc (entry 5). When the acetyl azolium salt 1aa-OTf was treated with benzyl alcohol in the presence of DBU (entry 6), rapid conversion to the ester occurred. When exposed to an equimolar mixture of BnOH and BnNH₂ in the presence of DBU (entry 7), exactly the same ester-to-amide ratio resulted as it was found before for the azolium enolate 1ae (entry 3). This result is in line with our earlier conclusion that in the presence of base, the acetyl azolium cation 1aa is first deprotonated to the azolium enolate 1ae, and that ester/amide formation proceed from the latter (Scheme 6). In the absence of DBU, an amide-to-ester ratio of 8:1 was observed (Table 1, entry 8). As no free SIPr results in the course of the amidation/esterification of 1ae (instead, the imidazolium triflate of SIPr), the ester formation may be promoted by H-bonding of the alcohol to the amine.[18,19] Studer et al. also reported that for ester-over-amide selective acetylation, 2-propenyl acetate can be used with IMes as catalyst, and the corresponding acetyl azolium cation was proposed as reactive intermediate.[18b] However, according to our results (Scheme 3), also the IMes-catalysis of ester formation from alcohols and 2-propenyl acetate should proceed via the azolium enolate 3ae.

In summary, several acetyl azolium enolates and azolium triflates have been prepared, characterized, and employed to probe the mechanism of ester formation in NHC catalyzed transformations. Our study shows that these azolium enolates react readily with alcohols and suggests that ester formation in fact proceeds via the azolium enolate stage. Furthermore, the azolium enolate studied showed pronounced ester-over-amide selectivity. The selectivity observed in NHC catalyzed acetylations with vinyl acetates thus corresponds to the selectivity of the primarily formed acetyl azolium enolate. We finally wish to reiterate that for stability reasons, our study was carried out with Dipp/Mes-substituted imidazole/imidazoline based azolium enolates and acyl azolium cations. NHC catalysts applied in practical synthesis are typically of different, for example, triazolium, types. It appears reasonable to assume that the conclusions drawn here do apply to the latter classes of NHC catalysts as well.Nevertheless, mechanistic analysis will ultimately be required in each individual case to scrutinize this assumption.

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**Conflict of interest**

The authors declare no conflict of interest.

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**Table 1:** Reactivity of the azolium enolate 1ae and of the acetyl azolium triflate 1aa-OTf towards BnOH and BnNH₂.

| Entry | Reagent | Nucleophile | Ester/ Amide |
|-------|---------|-------------|--------------|
| 1[a]  | 1ae     | BnOH (1.5 equiv) | 100:0 |
| 2[b]  | 1ae     | BnNH₂ (1.5 equiv) | 0:100 |
| 3[c]  | 1ae     | BnOH : BnNH₂ (1:1) | 5:5:1 |
| 4     | 1aa-OTf | BnOH (1.5 equiv) | No reaction |
| 5[d]  | 1aa-OTf | BnNH₂ (1.5 equiv) | 0:100 |
| 6[e]  | 1aa-OTf | BnOH (1.5 equiv) | 5:5:1 |
| 7     | 1aa-OTf | BnOH : BnNH₂ (1:1) | 5:5:1 |
| 8[f]  | 1aa-OTf | BnOH : BnNH₂ (1:1) | 1:8 |

Reaction conditions: 0.023 mmol of 1ae/1aa-OTf, 0.034 mmol of BnOH/ BnNH₂, 0.5 mL [D₂]DCM, 18 h at RT. [a] Full conversion was observed after 7 h. [b] 28% conversion was observed after 18 h. [c] 0.023 mmol of BnOH and BnNH₂ each. [d] 86% Conversion was observed after 18 h. [e] Full conversion was observed after 6 h. [f] 82% Conversion was observed after 18 h.

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[13] Under Studer’s conditions, a cinnamoyl azolium cation was proposed as the acylating agent—with no option to be deprotonated to an azolium enolate. The thorough mechanistic analysis of this synthetically highly interesting transformation led Studer et al. to the conclusion that the alcohol substrate is activated by a second NHC molecule, by H-bonding, such that its oxidation state is lowered to an azolium enolate. The thorough mechanistic analysis of this synthetically highly interesting transformation led Studer et al. to the conclusion that the alcohol substrate is activated by a second NHC molecule, by H-bonding, such that its reactivity outrun's that of the competing and intrinsically more nucleophilic amine (Ref. [18a,b]).