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The imidazoles 1a–g add to the CC-double bond of the iminium ion 2 with rate constants as predicted by the equation log $k = s_N(N + E)$. Unfavourable proton shifts from the imidazolium unit to the enamine fragment in the adduct 3 account for the failure of imidazoles to take part in iminium-activated aza-Michael additions to enals.

Since MacMillan’s pioneering work in 2000,1 the so-called iminium activation has become one of the most attractive methods in asymmetric synthesis.2 In his seminal paper, MacMillan showed that $\alpha\beta$-unsaturated aldehydes can be activated by the addition of catalytic amounts of chiral secondary amines; the initially generated iminium ions undergo fast Diels–Alder reactions with dienes to give cycloadducts, which release the chiral catalyst upon hydrolysis.3 By using this strategy it has become possible to realise a large variety of enantioselective organic reactions.4

In 2007, Jørgensen et al.5 and Vicario et al.6 independently reported the first enantioselective aza-Michael additions of nitrogen heterocycles to aliphatic unsaturated aldehydes (Scheme 1), using diarylprolinol silyl ethers or imidazolidinones as catalysts.

While these reactions proceeded readily with tetrazoles and triazoles, they generally failed with imidazoles and benzimidazoles.

Only 4,5-dicyano-imidazole was found to react with moderate yield and low enantioselectivity with aliphatic enals utilizing MacMillan’s second generation imidazolidinone as a catalyst.5 Under the same conditions, the parent imidazole 1e gave only traces of the product.

We now report the kinetics and mechanism of the reactions of imidazoles with the iminium ion 2 and rationalise why imidazoles, in contrast to triazoles and tetrazoles, do not undergo organocatalytic aza-Michael additions.

In previous work we have shown that the rates of the reactions of carbocations and Michael acceptors with $\pi$- and $\sigma$-nucleophiles can be described by eqn (1),7 where $k_2$ is a second-order rate constant in M$^{-1}$ s$^{-1}$, $s_N$ is a nucleophile-specific sensitivity parameter, $N$ is a nucleophilicity parameter, and $E$ is an electrophilicity parameter.

$$\log k_2 (20 \degree C) = s_N(N + E) \tag{1}$$

Using the known reactivity parameters $N$ and $s_N$ of the imidazoles 1a–g (Table 1) and the electrophilicity parameter of the cinnamaldehyde-derived iminium ion 2 with $E = -7.37$, we had calculated second-order rate constants of 300–3000 M$^{-1}$ s$^{-1}$ by eqn (1) indicating that the reactions of 2 with 1a–g should proceed readily.

Accordingly, treatment of the iminium salt 2–PF$_6$ with 4 equivalents of imidazole 1e leads to the formation of the enamine 3e, which bears a protonated imidazole ring. Adduct 3e, which incorporates two stereocenters, was formed as a 1:1 mixture of two diastereoisomers, as revealed by $^1$H and $^{13}$C NMR spectroscopy.

<table>
<thead>
<tr>
<th>Azoles</th>
<th>$N$</th>
<th>$s_N$</th>
<th>Azoles</th>
<th>$N$</th>
<th>$s_N$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>10.50</td>
<td>0.79</td>
<td>1e</td>
<td>11.74</td>
<td>0.76</td>
</tr>
<tr>
<td>1b</td>
<td>11.43</td>
<td>0.79</td>
<td>1f</td>
<td>11.79</td>
<td>0.77</td>
</tr>
<tr>
<td>1c</td>
<td>11.47</td>
<td>0.79</td>
<td>1g</td>
<td>11.90</td>
<td>0.73</td>
</tr>
<tr>
<td>1d</td>
<td>11.51</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^\circ N$ and $s_N$ refer to DMSO, as 4-(dimethylamino)pyridine was reported to have identical reactivity parameters in DMSO and acetonitrile ($\Delta N = 0.15$)$^8$ the variation of solvent does not affect the analysis in Table 2.

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‡ Electronic supplementary information (ESI) available: Details of the kinetic experiments, synthetic procedures and product characterisation. See DOI: 10.1039/c2cc31224g

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COMMUNICATION

Kinetics and mechanism of organocatalytic aza-Michael additions: direct observation of enamine intermediates†‡

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NMR spectroscopy. NOE analysis showed the preference of the (S,E)-conformation of the C(sp²)-N bond in both diastereoisomers as depicted in Scheme 2. As kinetically controlled additions of nucleophiles to 2 often proceed with high diastereoselectivity, the formation of 3c as a 1:1 mixture of diastereomers may either be explained by a reversible reaction of the iminium ion 2 with the imidazole 1c or by deprotonation of the imidazolidinone moiety in the intermediate iminium ion in the azetidine moiety to the carbonyl group, as suggested by Seebach et al.11 The latter mechanism can be excluded under the conditions of this work because we have recovered the enantiopure imidazolidinone 5 after hydrolysis of 3c, confirming that the configuration of the asymmetric center of the imidazolidinone 5 has not been affected.

In acetonitrile solution, the enamine intermediates 3c (or 4c) in the presence of excess imidazole are stable for more than 8 hours but decompose during several days. Addition of water to the enamine 3e leads to the formation of cinnamaldehyde. However, stirring of a solution of 3c-PF₆ in CD₃CN with dry K₂CO₃ led to the formation of 4c, which was characterised by ¹H and ¹³C NMR spectroscopy (see ESI).12,13

Jørgensen’s DFT calculations on the organocatalytic conjugate addition of 1,2,4-triazole to γ,β-unsaturated aldehydes showed that the addition of the triazole to the iminium ion is followed by a water-assisted proton transfer from the triazolium ring to the enamine as depicted in Scheme 3.4 In the case of the reactions of the azoles 1 with the iminium ion 2, the enamines 3 or their conjugate bases 4 were observed by NMR spectroscopy, and we did not observe an analogous proton transfer which may be explained by the lower acidities of the imidazolium ions compared to triazolium ions.

The different UV-absorbances of the iminium ions 2 and the adducts 3 allowed us to follow the kinetics of the reactions of 2 with the azoles 1a–g photometrically at the absorption maximum of the iminium ion 2 (370 nm). All kinetic experiments were performed under first-order conditions using a high excess of the nucleophiles 1a–g. From the exponential decays of the UV-absorbances of the electrophile 2, the first-order rate constants k₁obs were obtained.

Plots of k₁obs (s⁻¹) against the concentrations of the nucleophiles 1a–g were linear (Fig. 1) and their slopes gave the second-order rate constants k₂ values, which are summarised in Table 2.

The second-order rate constants thus obtained (Table 2) have been compared with those calculated by eqn (1) from the electrophilicity parameter E = -7.37 of the iminium ion 2⁹ and the N and σN parameters of the azoles.⁸ Table 2 shows that all calculated (kcalc) and experimental rate constants (k₁obs) match within a factor of two. This good agreement is impressive, as E(2) has been derived from reactions with C-nucleophiles and N and σN for the azoles 1a–g have been derived from their reactions with benzhydryl ions.⁷

Some of the reactions of the iminium ion 2 with imidazoles proceeded incompletely, and for the reactions with 1b and 1g the equilibrium constants K (Scheme 4) have been determined photometrically as described in the ESI.†

Table 2 Comparison of experimental (k₁obs) and calculated rate constants (kcalc) using eqn (1) for the reactions of the azoles 1a–g with the iminium ion 2 (E = -7.37) in CH₃CN at 20 °C

<table>
<thead>
<tr>
<th>Azoles</th>
<th>k₁obs/M⁻¹ s⁻¹</th>
<th>kcalc/M⁻¹ s⁻¹</th>
<th>k₁obs/kcalc</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2.75 x 1₀²</td>
<td>2.97 x 1₀²</td>
<td>0.93</td>
</tr>
<tr>
<td>1b</td>
<td>2.88 x 1₀³</td>
<td>1.61 x 1₀³</td>
<td>1.8</td>
</tr>
<tr>
<td>1c</td>
<td>3.01 x 1₀³</td>
<td>1.73 x 1₀³</td>
<td>1.7</td>
</tr>
<tr>
<td>1d</td>
<td>3.00 x 1₀³</td>
<td>3.00 x 1₀³</td>
<td>1.0</td>
</tr>
<tr>
<td>1e</td>
<td>2.84 x 1₀³</td>
<td>2.10 x 1₀³</td>
<td>1.4</td>
</tr>
<tr>
<td>1f</td>
<td>4.62 x 1₀³</td>
<td>2.53 x 1₀³</td>
<td>1.8</td>
</tr>
<tr>
<td>1g</td>
<td>4.15 x 1₀³</td>
<td>2.03 x 1₀³</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Scheme 4 Reversible additions of the imidazoles 1b and 1g to the iminium ion 2 in CH₃CN.
Determined for the reactions of the iminium ion which do not undergo proton shifts. The rate constants for generous support.

In conclusion, we have shown that the reactions of the azolium ion 1g with imidazoles proceed readily with formation of stable enamines which have been fully characterised by NMR spectroscopy. The failure of the azoles 1a–g to act as nucleophiles in iminium-activated processes is rationalised by the low acidities of the initially generated azolium species. This difference reflects that more reorganisation energy is needed than that for its reaction with diarylcarbenium ions. 8 This equilibrium constants (Table 3) shows that 1-(trimethylsilyl)-imidazole 1b is 1.84 times less nucleophilic than 1-methylimidazole 1g. Table 4 shows that diarylcarbenium ions add to imidazoles 1a–g with the iminium ion 1g with the iminium ion 1g.

Table 3 Equilibrium constants (K) for the reactions of azoles 1b and 1g with the iminium ion 2 (counterion PF6−) in CH3CN at 20 °C

<table>
<thead>
<tr>
<th>Azoles</th>
<th>K/M−1</th>
<th>ΔG°/kJ mol−1</th>
<th>ΔG°/kJ mol−1</th>
<th>ΔG°/kJ mol−1</th>
<th>kobs/s−1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>1.61 × 103</td>
<td>52.3</td>
<td>−18.0</td>
<td>61.0</td>
<td>1.79</td>
</tr>
<tr>
<td>1g</td>
<td>1.84 × 102</td>
<td>51.4</td>
<td>−12.7</td>
<td>57.6</td>
<td>22.6</td>
</tr>
</tbody>
</table>

Remarkably, the intrinsic barrier for the addition of the azole 1g to the iminium ion 2 is about 10 kJ mol−1 lower than that for its reaction with diarylcarbenium ions. 9 This difference reflects that more reorganisation energy is needed for the reactions of nucleophiles with diarylcarbenium ions than with unsaturated iminium ions due to the more extensive delocalization of the positive charge in diarylcarbenium ions.

In conclusion, we have shown that the reactions of the iminium ion 2 with 1,3-diazoles proceed readily with formation of stable enamines which have been fully characterised by NMR spectroscopy. The failure of the azoles 1a–g to act as nucleophiles in iminium-activated processes is rationalised by the low acidities of the initially generated azolium species which do not undergo proton shifts. The rate constants determined for the reactions of the iminium ion 2 with the azoles 1a–g are in good agreement with those calculated by eqn (1), showing the suitability of the benzhydrylium-based reactivity parameters N and sN for predicting reactivities toward iminium ions.

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Notes and references