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Nucleophilic Addition of Enols and Enamines to α,β-Unsaturated Acyl Azoliums: Mechanistic Studies**

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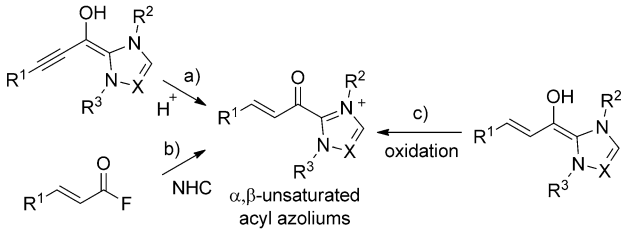
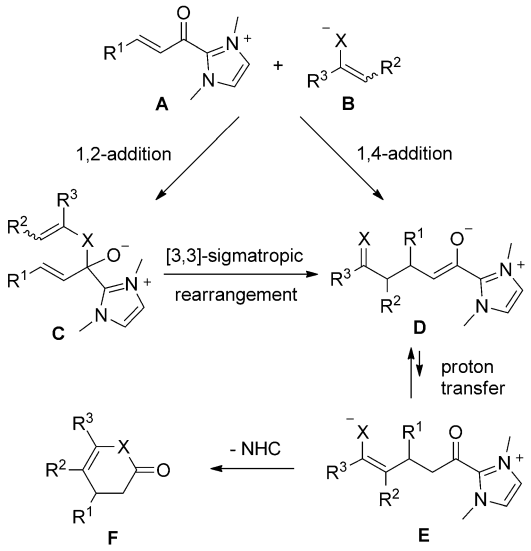
N-Heterocyclic carbenes (NHCs) have been successfully used as catalysts in various C–C bond-forming reactions.[1] Along this line, the chemistry of α,β-unsaturated acyl azolium ions has recently gained great attention. These reactive intermediates can be generated by three different routes: a) Protonation of the Breslow intermediate formed in the reaction of an ynal with an NHC;[2,3] b) reaction of an α,β-unsaturated acyl fluoride with an NHC;[4] and c) oxidation of the Breslow intermediate formed in the reaction of an enal with an NHC (Scheme 1).[5]



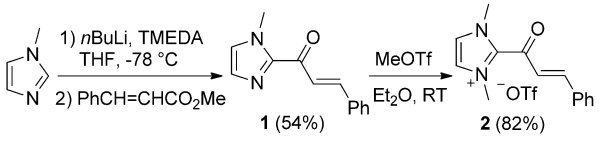
Scheme 1. Different routes for the generation of acyl azolium ions.

α,β-Unsaturated acyl azolium ions turned out to be reactive and synthetically highly useful electrophiles in intermolecular reactions with α-ketoenols,[6] β-diketones,[7] and enamines[8] for the preparation of dihydropyranones and dihydropyridinones. Two different mechanisms have been suggested for such transformations (Scheme 2). The deprotonated enol or enamine **B** can react with **A** by a Michael-type 1,4-addition to give enolate **D**.[7] Alternatively, the same intermediate **D** can be generated by 1,2-addition to generate **C**, which further reacts in a [3,3]-sigmatropic rearrangement to give **D**.[6,8] Proton transfer provides **E** and intramolecular acylation eventually leads to dihydropyranones or dihydropyridinones **F**. Herein we give experimental and theoretical support that an isolated acylazolium salt reacts with various nucleophiles by means of the 1,4-addition pathway. Moreover, we present the first X-ray structure of an α,β-unsaturated acyl azolium **A**.[9]



Scheme 2. Possible mechanisms for reaction of enols or enamines with acyl azolium ions **A** (NHC=*N*,*N*′-dimethylimidazoline, X = O, NH).

To properly investigate the reactivity of acyl azolium ions, we decided to prepare and fully characterize such an intermediate **A** and to study its reactivity towards different nucleophiles. The synthesis of **A** (R^1 = Ph) turned out to be surprisingly straightforward. *N*-Methylimidazole was deprotonated with *n*BuLi in THF at −78 °C in the presence of TMEDA. Subsequent addition of methyl cinnamate at that temperature afforded ketone **1** in 54% yield (Scheme 3).[10] Reaction of **1** with MeOTf in Et_2O at room temperature and



Scheme 3. Synthesis of acyl azolium **2**. TMEDA = tetramethylethylenediamine.

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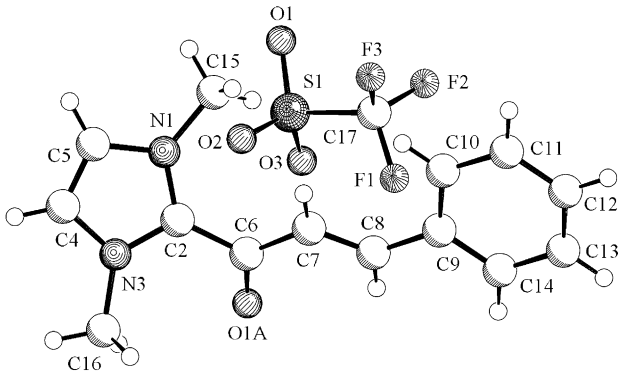
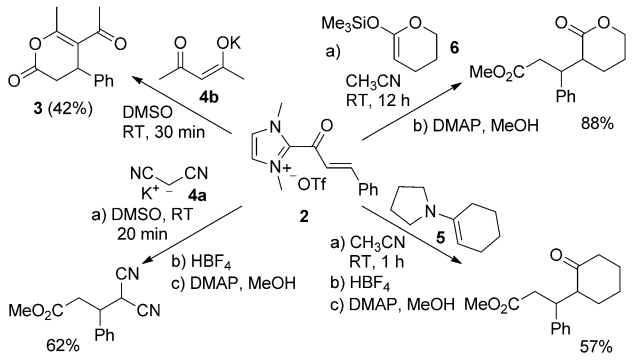


Figure 1. Molecular structure of **2** representing an example of a compound of type **A**.

purification by recrystallization provided acyl azolium salt **2** in 82% yield.

X-ray structure analysis (Figure 1)[11] showed that the C(7)=C(8) bond and the carbonyl group are nearly perfectly coplanar (torsion angle = 6.2(9)°). In this conformation, the carbonyl moiety ideally activates the olefin for a 1,4-addition reaction. The plane of the five-membered ring is twisted with respect to the carbonyl group (torsion angle 35.5°).

We first studied the reaction of the acyl azolium salt **2** with various nucleophiles in CH_3CN or DMSO at room temperature (RT). β-Diketones and β-ketoesters are well known to react with acceptors **A** to afford compounds of type **F**. Indeed, reaction of **2** with deprotonated acetylacetone delivered **3** (Scheme 4). In the reactions with deprotonated malonodinitrile **4a**, enamine **5**, and ketene acetal **6** the corresponding

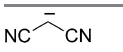
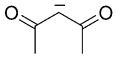
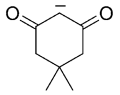
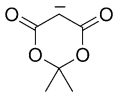
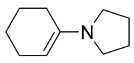
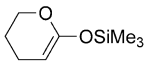


Scheme 4. Reactions of **2** with various nucleophiles. DMSO = dimethyl sulfoxide, 4-DMAP = dimethylaminopyridine.

product acyl azolium salts were difficult to isolate. The intermediate azolium salts obtained after nucleophilic addition were therefore first treated with 1 equiv HBF_4 (for **4a** and **5** for enolate protonation) followed by MeOH and *N*,*N*-dimethylaminopyridine (DMAP, 2 equiv) to provide the corresponding methyl esters in moderate to good yields (57–88%).

The kinetics of the addition reaction of **4**–**6** to **2** were followed by photometric monitoring of the decay of the absorbance of **2** at 20°C in anhydrous DMSO or CH_3CN at $\lambda_{max} = 333$ nm (in DMSO) or at $\lambda_{max} = 326$ nm (in CH_3CN) using the previously described equipment.[12] All kinetic experiments were performed under pseudo-first-order conditions using an excess of nucleophiles. From the exponential decay of the UV/Vis absorbance of **2**, the pseudo-first-order rate constants k_{obs} (s^{-1}) were obtained. Plots of k_{obs} versus the concentrations of the nucleophiles were linear with negligible intercepts (Tables S1–S6 in the Supporting Information). The slopes of these linear plots gave the second-order rate constants k ($M^{-1}s^{-1}$), which are listed in Table 1. We found

Table 1: Second-order rate constants for the reactions of **2** with the nucleophiles **4**, **5**, and **6** at 20°C.

Nucleophile		N/s_N[a]	$k/M^{-1}s^{-1}$
	**4a**	19.36/0.67	2.29×10^{5}[b]
	**4b**	17.64/0.73	5.84×10^{4}[b]
	**4c**	16.27/0.77	9.03×10^{3}[b]
	**4d**	13.91/0.86	2.75×10^{2}[b]
	**5**	16.42/0.70	4.96×10^{2}[c]
	**6**	10.52/0.78	6.19×10^{-2}[c]

[a] Nucleophile-specific parameters N and s_N from Ref. [13]. [b] Solvent DMSO. [c] Solvent CH_3CN.

that switching the counteranion in **2** from OTf^- to I^- did not greatly affect the k value of the addition reaction with $acac^-$. Addition of $acac^-$ to the iodide salt at 20°C in DMSO occurred with a rate constant of $6.14\times10^{4}\,M^{-1}s^{-1}$ (Table S7 in the Supporting Information) which compares well with the value measured for triflate **2** ($5.84\times10^{4}\,M^{-1}s^{-1}$).

Figure 2 shows that $(\lg k)/s_N$ correlates linearly with N as required by Equation (1),[12] which calculates second-order

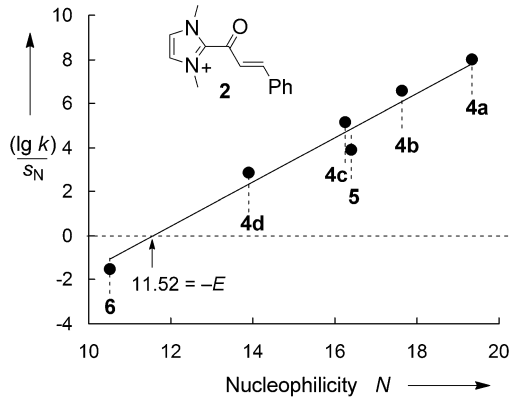


Figure 2. Plot of $(\lg k)/s_N$ versus N for the reactions of **2** with the nucleophiles **4**, **5**, and **6** (solvents are specified in Table 1). Slope of the correlation line is fixed to 1.0 as required by Equation (1).

rate constants from the electrophile-specific parameter E and two solvent-dependent nucleophile-specific parameters N and s_N. One can therefore conclude that the rate-determining step of the reactions of **2** with **4–6** is mechanistically analogous to the reactions of **4–6** with benzhydrylium ions which react by C–C bond formation (see reactions on p. S43 in the Supporting Information). These adduct formations have previously been used to derive the N and s_N parameters listed in Table 1.[12]

$$\lg\, k_{20\,^\circ C} = s_N(E+N) \qquad (1)$$

The kinetic experiments do not exclude attack of these nucleophiles at the carbonyl group of **2** in a rapid preequilibrium step, which is kinetically irrelevant. Since initial carbonyl attack followed by [3,3]-sigmatropic rearrangement cannot be formulated for all the nucleophiles listed in Table 1, however, one would have to postulate that this stepwise process can only lead to the observed products if it proceeds with the same rate as the direct attack of these nucleophiles at the conjugate position of **2**, a rather unlikely construction.

According to Equation (1), the negative intercept on the abscissa of Figure 2 yields $E = -11.52$ for **2** (by minimization of $\Delta^2 = \Sigma[\lg k - s_N(N+E)]^2$), which is compared with other electrophiles in Figure 3. This plot shows that owing to the

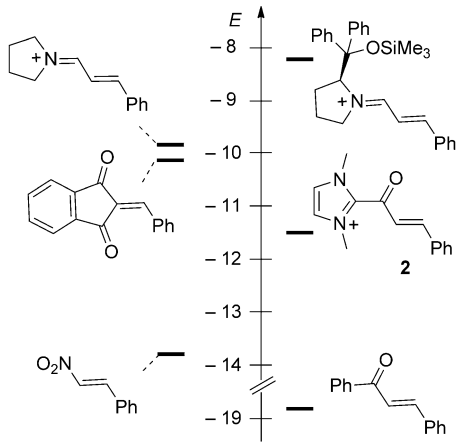


Figure 3. Comparison of electrophilicity parameter E of **2** and other electrophiles. E parameters from Ref. [13]:

strong electron-withdrawing nature of the imidazolium ring, **2** is seven orders of magnitude more electrophilic than a structurally analogous chalcone, comparable to highly electron-deficient neutral Michael acceptors such as benzylidene malononitriles and 2-benzylidene indan-1,3-diones.[13] However, its electrophilicity is 1000 times lower than that of the structurally related iminium ion derived from Hayashi–Jorgensen pyrrolidine and 10^4 to 10^6 lower than those derived from MacMillan's imidazolidinones.[13]

To get further information on the reaction, we followed the transformation of **2** with acetylacetone in the presence of base by low-temperature ^{1}H NMR spectroscopy. We found that acetylacetone did not react with **2** at room temperature in [D_8]THF in the absence of base. The NMR sample was then cooled to −78 °C and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 1.5 equiv) was added. The NMR tube was quickly transferred into the NMR probe, which was precooled to −40 °C. The resonances of the acyl azolium **2** fully disappeared and new broad signals belonging to an intermediate of type **D** appeared (see Figure S1 in the Supporting Information). In agreement with the kinetic experiment using **4b**, this NMR study revealed that the reaction of **2** with deprotonated acetylacetone is very fast at low temperatures (< 30 s, time necessary for mixing and transfer to the NMR probe). An intermediate of type **C** resulting from 1,2-addition was not detectable, either because it was not formed or because the sigmatropic rearrangement was very fast. We noted that when the probe was warmed to −20 °C the NMR signals remained unchanged. However, further warming to room temperature led to formation of **3** (see Scheme 4) which represents a compound of the general structure **F**. Hence, this NMR experiment showed that intramolecular acylation from **E** to **F** under liberation of the carbene requires temperatures above −20 °C. We performed additional NMR experiments with deprotonated malonodinitrile and 3-aminocrotononitrile as nucleophiles and unambiguously identified the corresponding 1,4-addition products (see the Supporting Information). No indication for the formation of an intermediate derived from a 1,2-addition reaction was obtained (3-aminocrotononitrile could react in a 1,2-addition by C–N bond formation). In all NMR experiments we could identify intermediates of type **D** (for acac$^-$ after O-silylation) but not the corresponding proton-transfer intermediates of type **E** (see the Supporting Information). Apparently the proton transfer from **D** to **E** is reversible with **D** dominating in the equilibrium.

Since neither the kinetic nor NMR experiments allowed us to exclude a rapid preequilibrium step in the reaction of **2** with deprotonated acetylacetone, we finally decided to study this particular transformation using high-level DFT calculations. We investigated the addition of deprotonated acetylacetone to **2** with a meta GGA functional (TPSS) including a correction for dispersion interactions using a triple zeta quality basis set (TPSS-D3(BJ)/def2-TZVP).[14] Furthermore, a continuum solvation model (COSMO)[15] was used in all calculations, simulating the solvent properties of THF ($\varepsilon = 7.58$) (for details see the Supporting Information).

The formation of a close ion pair (**2**/acac$^-$) in THF was found to be exothermic by −23.5 kcal mol^{-1} (Scheme 2, R^1 = Ph, $R^2 = COCH_3$, $R^3 = CH_3$, X = O). Attempts to calculate the energy of the corresponding intermediate **C** were unsuccessful, because it was not a local minimum in the solvent, but relaxed to the ion pair **2**/acac$^-$ showing that **C** cannot be an intermediate. On the other hand, 1,4-addition leads to an intermediate of type **D**, which has a relative energy of −25.8 kcal mol^{-1} with respect to the isolated reactants. We have located a transition-state structure for the C–C bond formation in the addition step (Figure 4). This structure also reveals that the 1,4-addition leads to the *cis* enolate, in agreement with the NMR studies (see the Supporting Information). The relative energy of this structure is −17.9 kcal mol^{-1}. The very low barrier ($\Delta E^{\neq} = 5.6$ kcal mol^{-1} with respect to **2**/acac$^-$, without ZPE correction) allows a facile and fast 1,4-addition even at low temperatures, as observed in the NMR experiment.

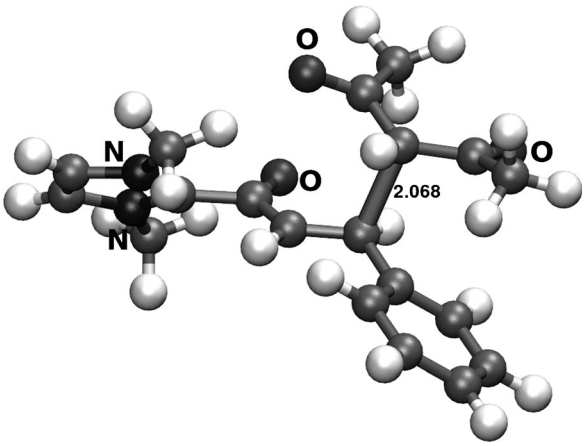


Figure 4. DFT-D3(BJ) + COSMO-optimized transition-state structure for the 1,4-addition of deprotonated acac to acyl azolium **2**. The C–C distance is given in Å.

In order to address solvent effects we also calculated the energy difference ΔE between the ion pair (**2**/acac$^-$) and the 1,4-adduct, and the 1,4-addition barrier $\Delta E^{\neq}$ in DMSO ($\varepsilon = 46.7$) and CH_3CN ($\varepsilon = 37.5$). We obtained very similar values indicating that solvent effects are weak for this reaction (DMSO: $\Delta E^{\neq} = 6.3$ kcal mol^{-1}, $\Delta E = -1.4$ kcal mol^{-1}; CH_3CN: $\Delta E^{\neq} = 6.2$ kcal mol^{-1}, $\Delta E = -1.5$ kcal mol^{-1}). The calculated barrier fits very well with the activation enthalpy $\Delta H^{\neq} = 4.9$ kcal mol^{-1} calculated from $\Delta G^{\neq} = 10.7$ kcal mol^{-1} derived from the kinetic experiment (see Table 1) assuming $\Delta S^{\neq} = -20$ e.u.

Since many NHC-catalyzed reactions have been conducted with triazole-derived carbenes, we conducted additional calculations for the reaction of acac$^-$ with the triazole congener of **2** (see Scheme 1, $R^1 = Ph$, $R^2 = R^3 = Me$, $X = N$) and found the addition reaction starting with the ion pair to be slightly more exothermic (THF: $\Delta E = -4.7$ kcal mol^{-1}, $\Delta E^{\neq} = 4.0$ kcal mol^{-1}; CH_3CN: $\Delta E = -4.2$ kcal mol^{-1}, $\Delta E^{\neq} = 4.4$ kcal mol^{-1}). Consequently, reaction barrier was even lower. Interestingly, for the triazole system we found an intermediate of type **C** for the 1,2-addition pathway. However, the energy difference with respect to the ion pair was + 13.3 kcal mol^{-1} (THF) and therefore the 1,2-addition pathway at least with deprotonated acetylacetone can also be excluded for the triazole derivative.

In conclusion, we have reported the synthesis and full characterization of the acyl azolium ion **2**. High level DFT-calculations and kinetic experiments clearly showed that acetylacetone, malonodinitrile, enamine **5**, and silylenol ether **6** react with the α,β-unsaturated acyl azolium **2** by means of a 1,4-Michael-type addition reaction. Based on the kinetic experiments and on the calculations the two-step mechanism by 1,2-addition followed by [3,3]-sigmatropic rearrangement for the key C–C-bond formation can be excluded.

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Communications

Organocatalysis

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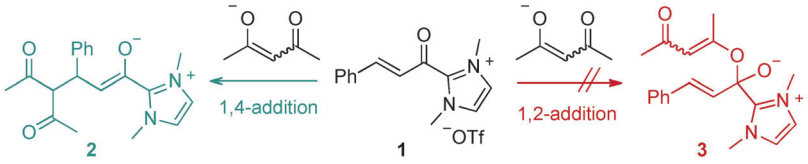
Nucleophilic Addition of Enols and Enamines to α,β-Unsaturated Acyl Azoliums: Mechanistic Studies



1,4 but not 1,2! The reactivity of **1** towards different nucleophiles (deprotonated β-diketones, enamines, and malonodinitrile) was investigated by NMR and kinetic experiments. These investigations proved that C–C bond formation occurs by a Michael-type 1,4-addition and not by a 1,2-addition and subsequent [3,3]-sigmatropic rearrangement. The first X-ray structure of an α,β-unsaturated acyl azolium salt (**1**) is also presented.

