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N-Heterocyclic Carbene-Catalyzed Generation of α,β-Unsaturated Acyl Imidazoliums: Synthesis of Dihydropyranones by their Reaction with Enolates

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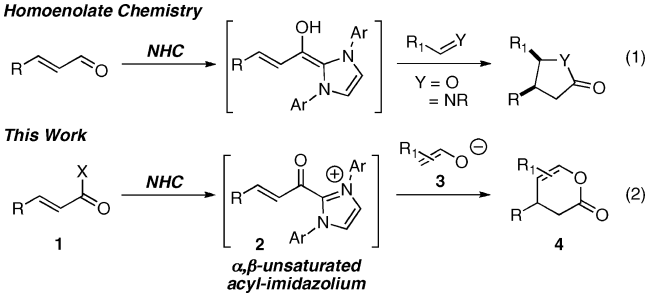
N-Heterocyclic carbene (NHC) catalyzed polarity reversal of the carbonyl group is central to a number of organic transformations, most notably the benzoin and Stetter reactions.[1a,c] More recently conjugated or redox active substrates have allowed access to reactive intermediates useful in reaction discovery.[1b,d] We have undertaken studies aimed at extending this family to include α,β-unsaturated acyl azoliums (i.e., **2**). While these intermediates were reported by Scheidt in his MnO_2 based oxidative esterification,[2a] their reactivity at the β-position is yet to be investigated. In comparison to homoenolates, which react as donors at the β-position (eq 1),[1d,3] the cationic nature of the acyl azolium, in combination with steric shielding, should generate an intermediate ideally suited to act as a conjugate acceptor. In this communication, we report the first conjugate addition reactions involving α,β-unsaturated acyl azoliums (eq 2).



To investigate the reactivity of α,β-unsaturated acyl azoliums, a method for their generation in the presence of an appropriate nucleophile was required. While a number of approaches could be envisaged, we chose to investigate the use of α,β-unsaturated enol esters (i.e., **5**).[4] When such substrates are exposed to Lewis basic catalysts,[5] fragmentation should liberate enolate **3** and the required α,β-unsaturated carboxylate **2**.[6,7] Conjugate addition into the acyl azolium, providing enolate **6**,[8] followed by proton transfer and acylation, should then afford pyranone **4**[9,10] and regenerate the catalyst (Scheme 1).

Investigations began with the reaction of thiamine (**A**) and enol ester **5a** in refluxing toluene (Table 1, entry 1). This readily available NHC fragmented enol ester **5a**, however, rather than affording **4a** *C*-acylation provided 1,3-diketone **7**.[11] When 100 mol % of the more nucleophilic tetramethyl carbene **B1** was reacted with enol ester **5a**, pyranone **4a** was obtained in 41% yield, accompanied by 22% of diketone **7** (Table 1, entry 2). Unfortunately, when carbene **B1** was used substoichiometrically no more than a trace of dihydropyranone **4a** was observed (Table 1, entry 3). To our delight, when catalysts derived from IMes·HCl **C1** and IDip·HCl **C2**, recognized in both homoenolate and transesterification catalysis,[3,6] were used, pyranone **4a** formed in high yield with good catalytic loading (Table 1, entries 4 and 5).

Finally the suitability of imidazolium derived catalyst **B2** and triazolium precatalyst **D** was investigated. Unfortunately neither proved suitable for this reaction (Table 1, entries 6 and 7).[12]

Scheme 1. Proposed Catalytic Pathway for the Formation of **4**

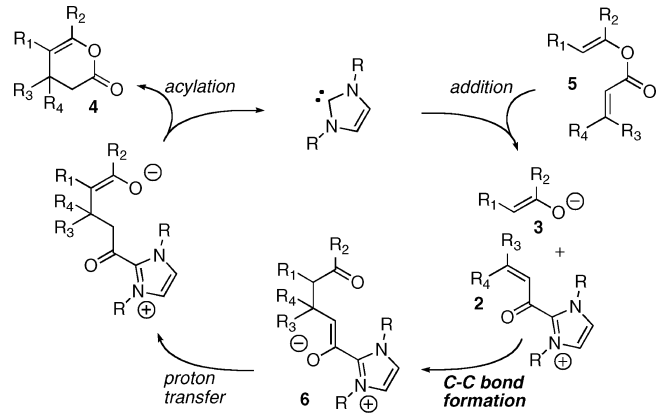
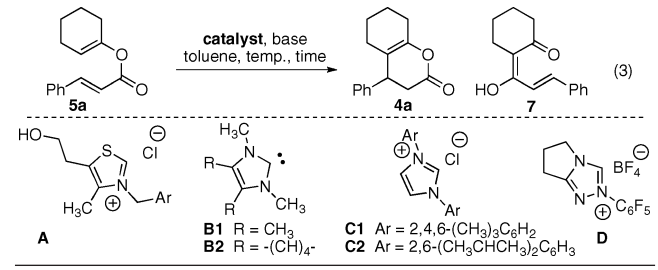


Table 1. Selected Optimization Studies



entry	catalyst (mol %)	temp/ time	base	yield[a]
1	**A** (100 mol %)	reflux/16 h	KHMDS	19 (**7**)
2	**B1** (100 mol %)	−78 °C/1 h	−	41
3	**B1** (10 mol %)	−78 °C/1 h	−	*trace*
4	**C1 (10 mol %)**	**reflux/16 h**	**KO^{t}Bu**	**86**
5	**C2 (10 mol %)**	**reflux/16 h**	**KO^{t}Bu**	**79**
6	**B2** (100 mol %)[b]	reflux/16 h	KO^{t}Bu	*NR*
7	**D** (100 mol %)	reflux/16 h	KO^{t}Bu	*NR*

[a] Isolated yield following flash column chromatography. [b] Catalyst **B2** generated by deprotonation of the corresponding imidazolium chloride.

The reactions' scope was investigated across a range of α,β-unsaturated acceptors and enolates (Chart 1). Aromatic, heteroaromatic, and aliphatic α,β-unsaturated esters all reacted readily to give the corresponding pyranones (**4a**−**d**). β-Disubstituted acyl azoliums were found to be good substrates, allowing efficient construction of quaternary carbon centers (**4d**, **4f**, **4m**). Ketone and aldehyde enolates derived from cyclic, acyclic, aromatic, and 1,3-diketones were investigated in the transformation providing good yields of the expected dihydropyranones. In the case of 1,3-diketones, the reaction preceded readily at 0 °C, even with a β-disubstituted acyl azolium intermediate (**4m**).

While the generation of acyl azoliums and enolates from enol esters proved useful, these should also be accessible from α,β-unsaturated acid fluorides **8** and TMS enol ethers **9** (eq 5). In this

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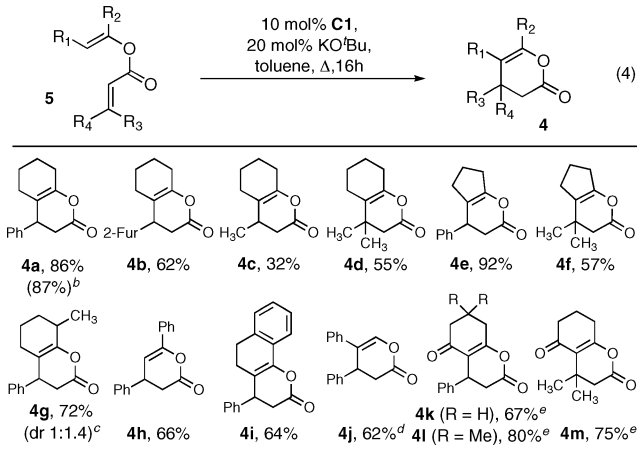
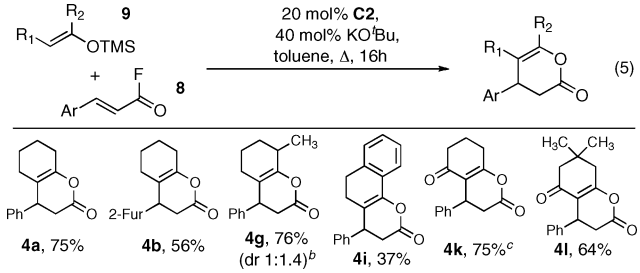
Chart 1. Scope of NHC Catalyzed Rearrangement[a]



[a] Isolated yield. [b] Performed on 5 mmol of **5a**. [c] Ratio determined by ^{1}H NMR spectroscopy. [d] 20 mol % **C2**, 40 mol % KO^{t}Bu at −78 °C then warmed to rt. [e] 20 mol % **C1**, 40 mol % KO^{t}Bu at 0 °C.

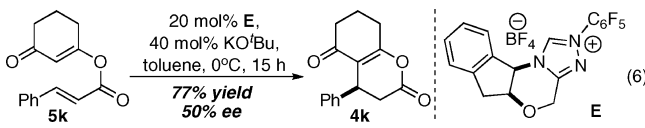
scenario addition of the NHC into the acid fluoride would instigate deprotection of the enol ether, unmasking the enolate.[13] When various α,β-unsaturated acid fluorides were reacted with TMS enol ethers in the presence of 20 mol % **C2** and 40 mol % KO^{t}Bu, the dihydropyranones formed in good yield (Chart 2).

Chart 2. Scope of Intermolecular NHC Catalyzed Reaction[a]



[a] Isolated yield. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] 10 mol % **C1**, 20 mol % KO^{t}Bu at 0 °C.

Recently, highly enantioselective Stetter and benzoin reactions have been achieved using chiral NHCs.[1a] When catalysts derived from either chiral triazolium[14] or imidazolium[15] salts were exposed to enol ester **5a**, pyranone **4a** failed to form. However, when the reaction was attempted with enol ester **5k** and the catalyst derived from triazolium **E**, pyranone **4k**[16] formed in good yield and 50% ee (eq 6). While this level of induction is modest, it is comparable to the state-of-the-art for reactions in which bond formation β to the carbonyl group occurs (eq 1).[2b,3a,12a]



In summary, we have achieved the first conjugate addition reactions into α,β-unsaturated acyl azoliums. A range of conjugate acceptors, included those containing β-disubstitution, reacted smoothly with a variety of enolates to afford the expected dihydropyranones in good yields. This transformation complements NHC-catalyzed homoenolate chemistry that involve β-donation (eq 1).[1d,3] An enantioselective variant of this reaction has been achieved with triazolium **E**. Exploration of the utility of this new type of azolium intermediate and the application of pyranones, known medicinal agents,[17] and useful building blocks in organic synthesis[10a,b] is ongoing.

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Supporting Information Available: Characterization data, NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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