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A novel acetyl chloride-mediated cascade transformation involving three components (benzyl carbamate, ethyl glyoxylate and arene nucleophiles) is reported. Aryl orthogonally protected α-amino acids are obtained in a one-pot cascade, using a mild AcOH/ACl system, via a critical autocatalytic dehydration-activation step ensuring an original and efficient Friedel–Crafts orchestration.

Facile and scalable synthesis of α-amino acids has attracted significant attention in the past decades. Several synthetic methods of functionalizing α-iminoglycinates 6 to access α-amino acids or esters have been reported (Strecker,† Mannich or Friedel–Crafts reactions). While these methods have proven to be applicable for the enantioselective synthesis of α-amino esters, both access to the starting α-iminoglycinates 6 (1 to 3 steps) and late stage protecting group manipulations required several synthetic steps to produce marketable α-amino acids or esters, leading to a lengthy overall sequence.1,3 On the other hand, α-hydroxy 3,4 α-alkoxy;6 α-acetoxy;6 and α-halogeno 5 glycinate esters which are valuable in situ precursors of α-iminoglycinates 6, have been less studied for functionalizing the glycine α-stereocenter. Thus, only sparse examples of cascade reactivity (so called multicomponent reactions) to synthesize α-amino esters in a single step have been reported.8

We decided to develop a suitable procedure for a novel and versatile one-pot synthesis of α-amino esters bearing marketable carbamate protecting groups.9 In this communication, a reliable synthesis of racemic α-amino ester derivatives 8 is described taking advantages of an unprecedented autocatalytic process and the high reactivity of chloroaminal intermediate 5 to initiate the desired Friedel–Crafts arylation (Scheme 1). To this end, a single pot transformation of primary carbamate 1 with ethyl glyoxylate 2 and arene nucleophiles 7 was envisioned. If the reaction would advance in an orderly fashion, the desired α-amino esters 8 could arise through a pathway involving three main steps: 1) condensation, 2) activation and 3) arylation. To be successful, these three steps would need to be perfectly orchestrated to direct the desired arylation of advanced intermediates 5 or 6 with arene 7 and circumvent the direct condensation with ethyl glyoxylate 2. Supporting this idea, the work from Fessner established a rare example of one pot multicomponent Friedel–Crafts using acetic acid and excess of hydrochloric acid gas to form racemic α-arylated amino acids.8

Inspired by this appreciable precedent, we envisioned that the highly regioselective Friedel–Crafts reaction could be redesigned to become more effective and suitable for asymmetric catalysis applications.

A proposed concept, rationalizing a possible orchestration between three components 1, 2 and 7 is outlined in Scheme 1. Catalytic amount of acid would facilitate the condensation between benzyl carbamate 1 and ethyl glyoxylate 2 to form hemiaminal 3. Next, acetyl chloride would simultaneously activate hemiaminal 3 to deliver chloroaminal 5 while trapping water thereof generating acetic acid and rending the process autocatalytic in acid.

**Scheme 1.** Concept of autocatalysis in AcOH promoting simultaneously both condensation and activation steps (steps 1/2) to chloroaminal 5

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c000000x
During the chlorination step, a putativeonium 4 would be formed which will likely undergo nucleophilic displacement to in situ deliver the activated chloroaminal 5. Finally, the arylation will likely proceed via an S$_\text{N}$1 mechanism through iminium 6 to ultimately provide the desired α-amino ester 8.

In our initial studies for the synthesis of activated aminals (such as chloro, bromo, or acetoxy from hemiaminal 3) (step 2), acetyl chloride was found the most efficient and milder reagent in the prospect of a tandem process. Our first attempts at a one pot reaction between benzyl carbamate 1, ethyl glyoxylate 2 and 1,3 dimethoxybenzene 7a, with catalytic amounts of acetic acid and excess of acetyl chloride confirmed the anticipated nucleophilic chemoselectivity issues leading to multiple uncontrolled arylation (Table 1). In chloroform and ethyl acetate (entries 1 & 2), reaction profiles differ but both by-products 9 or 10 from direct glyoxylate 2 arylations were isolated. To our delight, the reaction in ethyl acetate yielded the desired α-amino ester 8a in 28% in the first attempt.

To gain more insight into the proposed concept of autocatalysis and the reaction mechanism, control experiments starting from hemiaminal 3 and other plausible reaction intermediates acetoxy- and chloroaminal 5 were investigated. Interestingly, addition of aren 7a to hemiaminal 3 (or acetoxy-derivative) afforded the bis- arylated product 10 along with the desired α-amino ester 8a in 35% and 16% yield respectively. This result supports that hemiaminal 3 has a high tendency to fragment (retro-condensation) before undergoing successive arylation leading to 10.$^{11}$

Table 1. Attempts of a one pot synthesis of α-amino esters 8a

<table>
<thead>
<tr>
<th>entry</th>
<th>Solvent, Temperature</th>
<th>time (h)</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl$_3$, RT</td>
<td>18</td>
<td>9 (57%) 10 (22%)</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl acetate, RT</td>
<td>18</td>
<td>8a (28%) 10 (17%)</td>
</tr>
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</table>

$^a$Hemiaminal 3 was isolated in 13% yield.

Reactions were performed with: catalysis A: 1 (1.0 mmol), 2 (1.3 mmol), acetic acid (10 mol%) at RT, in chloroform; autocatalysis B: similar reaction condition to A with acetyl chloride (2.5 mmol); Conversions are reported using a quantitative $^1$H NMR technique [ref 13] with mesitylene as internal standard.

Also, treatment of chloroaminal 5 with D$_2$O regenerates the deuterated-hemiaminal 3 demonstrating that water should be entirely excluded from the reaction media to achieve full conversion to the α-chloroglycinate 5 and enable the cascade reaction.

Due to the lack of controlled reactivity in one pot (Table 1), we then examined the condensation and activation steps in more details (Fig. 2, steps 1/2). Xu$^{10}$ and others$^{12}$ demonstrated that both acidity and amount of Brønsted acid used to catalyze the condensation between carboxamides and alkyl glyoxylates are important to efficiently produce hemiaminals. As shown by the slow rate of the acid catalysis (10 mol%) (Fig. 1; catalysis A), the modest conversion to hemiaminal 3 may likely result from the reversibility of the condensation.$^{10,11}$ Upon addition of acetyl chloride, the reaction proceeded more quickly to full conversion in 3 and further afforded the desired chloroaminal 5 in good yield (Fig. 1; autocatalysis B). These kinetic experiments support that acetyl chloride displaces the reaction equilibrium towards hemiaminal 3 and chloroaminal 5.$^5$ Thus, acetyl chloride was found to not only activate hemiaminal 3, but also trap the water formed during the reaction, producing acetic acid which autocatalyzes and accelerates the first step of the cascade (Scheme 1).$^{14}$ It is important to notice that acetic and hydrochloric acid are the main reaction by-products and that the reaction was not compatible with the use of molecular sieves.$^{15}$ Several solvents were also tested in the reaction (toluene, THF, ethyl acetate, chloroform and acetonitrile), and full conversion in chloroaminal 5 was established either in acetonitrile or chloroform at 60°C.$^{10}$

We then examined the tandem cascade reaction in the preselected solvents (Table 2). Experiments were conducted with reduced amount of ethyl glyoxylate (1.05 equiv.) to avoid any formation of arylation by-products 9-10. In ethyl acetate, the cascade reaction was messy (Table 2, entry 1) leading to a difficult isolation of the desired product 8a in a modest 9% yield. After optimization, both reactions in CHCl$_3$ and CH$_3$CN effectively delivered the α-amino ester 8a at variable temperature (Table 2, entries 2-4). The best result was obtained in chloroform at 60 °C leading to the isolation of α-amino ester 8a in 82% yield (Table 2, entry 3).

Having established two sets of conditions in CHCl$_3$ and CH$_3$CN for Friedel–Crafts reaction, we turned our attention to the scope of the cascade reaction with a series of challenging arene nucleophiles (Table 3). According to the empirical nucleophilicity scale from Mayr,$^{15}$ we discovered that the most reactive arenes (N factor$>3.0$) reacted regioselectively in CHCl$_3$ at low temperatures (Method A) while less reactive arenes (N factor$<1.5$) reacted more cleanly in
CH$_2$CN and at higher temperatures (Method B). Several phenolic and aniline derivatives 8a-e were selected to compare their innate reactivity (electronic and steric factors) while heteroaromatic substrates also showed a broad scope of reactivity as demonstrated by the range of temperature utilized for the synthesis of 8f-j. Pyrrolyl 8fg, furanyl 8h and indolyl 8i-j aminooxime derivatives were prepared in high yields as single regioisomers. Finally, anthracenyl product 8k was obtained easily in 82% yield, while the more unusual and complex chalcone α-amino ester derivative 8l was isolated in a reasonable 39% yield.

In summary, we reported a one pot synthesis of aryl α-amino acid bearing orthogonal protecting groups via Friedel–Crafts reaction employing activated iminiums generated from inexpensive, commercially available starting materials. Our results show this cascade to be autocatalytic in acetic acid and mediated by acetyl chloride to shuttle water out of the system. This novel one pot synthesis is efficient and versatile as highlighted by the synthetic scope of aryolated α-amino esters 8a-I prepared. Ongoing studies are aimed at developing an asymmetric variant of this transformation and expanding the scope to additional classes of nucleophiles.

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Table 3. Scope for the synthesis of racemic α-amino esters 8b-I

<table>
<thead>
<tr>
<th>Method A/B</th>
<th>Reaction Conditions</th>
<th>Isolated Yield (%)</th>
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</thead>
<tbody>
<tr>
<td>Method A</td>
<td>AcOH (15 mol%) 60°C</td>
<td>8b (48%) 8c (72%) 8d (71%)</td>
</tr>
<tr>
<td>Method B</td>
<td>AcCl (2.5 equiv) 60°C</td>
<td>8e</td>
</tr>
</tbody>
</table>


Notes and references


