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Formation of Non-Natural α,α -Disubstituted Amino Esters via Catalytic Michael Addition

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Abstract

The enolate monoanion of amino esters is explored, and the first catalytic Michael addition of α -amino esters is demonstrated. These studies indicate that the acidity of the α C–H is the primary factor determining reactivity. Thus, polyfluorophenylglycine amino esters yield novel α -amino esters in the presence of a catalytic amount of a guanidine derived base and Michael acceptors. Reactivity requires an acidic N–H, which is accomplished using common protecting groups such as N-Bz, N-Boc, and N-Cbz. Calculations and labeling experiments provide insight into the governing principles, in which a key C-to-N proton transfer occurs, resulting in an expansion of the scope to include a number of natural amino esters. The study culminates with a late-stage functionalization of peptidic γ -secretase inhibitor, DAPT.

Graphical Abstract

Amino acids and their derivatives are penultimate building blocks for many scientific areas.^{1,2} Not surprisingly, methodology aimed at derivatizing α -amino acids has received much attention.^{1,3–6} To perform selective carbon framework modifications of amino acids, one must contend with the presence of N–H units, which are more acidic than the dormant C–H. The use of a Schiff base is one strategy to alkylate an amino ester (Scheme 1A)⁷; which removes the acidic N–H proton and acidifies the C–H, facilitating formation of the requisite enolate.^{8–14} Nature accesses the requisite enolate via the cyclized/dehydrated aromatic

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Supporting Information

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oxazolone, using it to epimerize α -stereocenters.¹⁵ Indeed, the oxazolone enolate will react with a number of electrophiles, including Michael acceptors^{16–22} and is a common strategy for amino acid derivatization (Scheme 1B).²³ We became curious if a more direct route might be possible, specifically, one in which whether the enolate could be directly utilized without the need for an enolate surrogate (Scheme 1C–E).

While Michael addition to an amino ester enolate has not been explored (Scheme 1E), the *C*-alkylation with alkyl halides (Scheme 1C–D) has been extensively utilized.^{24–28} However, despite its use in the literature, key mechanistic questions remain unanswered — especially concerning the degree of deprotonation of the requisite enolate involved in the alkylation.^{24–26,29–31}

In 1976, Krapcho proposed that under basic conditions *N*-acyl or carbamate protected amino esters must react through a dianion intermediate³² (Scheme 1C). This logically stems from the fact that alkylation occurs at the less acidic α -carbon rather than at the more acidic N–H, and therefore must take place through the dianion in which the less stable carbanion reacts first. In 1985, Hoyer³³ proposed an alternative mechanism in which the substrate first undergoes a kinetic deprotonation of the N–H with stoichiometric base, followed by a proton transfer from the C–H to generate the reactive monoanionic enolate (Scheme 1D). We reasoned that if Hoyer's hypothesis were true, then addition of an amino ester to a Michael acceptor could regenerate the base, making the reaction catalytic (Scheme 1E).

We initiated our investigation using the conveniently synthesized *N*-benzoyl perfluoropyridinyl glycine (**A**, Table 1).³⁴ We anticipated that the perfluoroaryl unit would acidify the α C–H and tilt the equilibrium toward the enolate. To **A**, we added Hünigs base (DIPEA, 3 equiv) and methyl vinyl ketone (MVK, 3 equiv) in acetonitrile (0.5 M) (entry 1). Within 36 h we observed complete conversion of the starting material to a product alkylated at the carbon rather than at the nitrogen, and were able to isolate it in near quantitative yield.

While full conversion was achieved, the rate was rather modest. Switching to a stronger base such as tetramethylguanidine (TMG) (TMG-H⁺, pK_a in MeCN = 23.3 vs. ~18.8 for diisopropylethyl amine DIPEA-H⁺)³⁵ or NaOH, substantially increased the rates, and the reaction completed within 1 h (Table 1, entries 2–4). Despite its enhanced basicity, DBU (pK_a in MeCN = 24.3)³⁶ failed to give comparable rates and over time led to unidentified by-products in ¹⁹F NMR spectra. Using TMG, we next attempted to lower the base loading and run the reaction catalytically. We observed complete conversion using catalyst loadings of both 10 and 1 mol% (entries 6 and 7). However, upon dropping the loading to 0.1 mol% TMG, no product was observed (entry 8). This lack of reactivity could potentially be due to trace acidic impurities in the reaction mixture. However, we have previously observed TMG undergoing *N*-substitution of aromatic fluorides when subjected to highly electrophilic perfluoroaryl derivatives, and this could also explain the observation.^{37,38} Upon switching to the bulky bicyclic superbases, MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, pK_a 25.4 in MeCN),³⁹ the catalytic activity was completely restored using just 0.1 mol% both at room temperature and –20 °C (entries 9–10).

Satisfied, we next investigated the substrate scope of the Michael acceptor (Scheme 2A). The reaction is quite general and, in addition to MVK (**2a**), will abide many commercially available mono-substituted Michael acceptors. Both ethyl and *t*-butyl acrylates (**2b** and **2c**) gave excellent yields, though a subtle difference was observed, potentially due to the greater steric demand of the *t*-butyl acrylate. Acrylonitrile gave nearly quantitative yield (**2d**), as did unsaturated sulfones (**2e** and **2f**). Diactivated fumaronitrile also underwent addition, giving a diastereomeric ratio of 1.5/1 (**2g**). Resubjecting the product to the catalyst and solvent resulted in the erosion of the dr to 1.2/1, suggesting that selectivity may be challenging to maintain. Additionally, *N*-phenylmaleimide (**2h**) worked under these conditions, albeit at a noticeably diminished rate compared to the mono-substituted alkenes, but nonetheless resulted in high yield of a mixture of diastereomers, which could be partially resolved upon isolation. It is worth noting that reaction with nitroalkenes failed to give the product and instead appeared to react with the base. Additionally, many β -substituted alkenes failed to react appreciably with **1a**.

Next, we explored the scope of the aryl side chain (Scheme 2B). More acidic substrates (**3a** and **3b**) underwent smooth addition. It is noteworthy that Touzin⁷ observed that *N,N*-dimethyl- α -amino ester enolates readily undergo 1,2-addition to ketones, whereas we exclusively observed 1,4-addition to α,β -unsaturated ketones (**2a**, and **3a-3h**). In fact, not even in the case of activated perfluoroaryl ketones (**3c**), did we observe 1,2-addition. Perfluoroarylesters (**3d**) and less stabilized enolates such as perfluorobiphenyl, perfluoronaphthalene amino esters (**3e** and **3f**), and even trifluorophenyl glycine (**3g**), 4-Cl-phenyl glycine (**3h**), and phenylglycine (**3i**) worked well and gave excellent yields. However, attempts to use benzoyl protected glycine (**3j**) failed to convert to produce any product, even with elevated temperatures and higher catalyst loading.

Next, to make the reaction more broadly useful, we investigated the nitrogen protecting groups standard to peptide coupling for the phenyl glycine methyl ester (Scheme 2C). We found that both *N*-Boc (**4a**) and *N*-Cbz (**4b**) protecting groups facilitated smooth addition, giving similar yields to the *N*-benzoyl group. Not surprisingly, when we attempted to use the base-labile *N*-Fmoc protected phenyl glycine, the substrate underwent decomposition (**4c**).

Next, we turned our attention to the reaction mechanism. While Hoye's mono-anion/proton shift mechanism seemed consistent (Scheme 1D), with certain substrates we qualitatively observed a rate dependence on the loading of the electrophile which appeared to be greater than first order. We wondered if the first step of the reaction might be an aza-Michael addition which effectively removes the more acidic N-H, allowing the base to deprotonate the α C-H. This would generate the requisite enolate, which would then undergo Michael addition, revealing the product via a retro-aza-Michael reaction

In order to probe the idea of temporarily masking the acidic proton, we minimized the geometries and calculated energies using DFT (B3LYP/6-311+G(2d,p)). The *N*-alkylated species (**comp-B**, Figure 1) was endothermic by 1.7 kcal/mol when compared to the starting materials, but +9.5 kcal/mol when compared to the *C*-alkylated final product (**comp-C**). The endothermic nature of the *N*-alkylation is reasonable, considering that there are no examples in the literature of the product of an aza-Michael addition to an α -amino acid derivative,⁴⁰

perhaps due to the loss of a stabilizing H-bond in the product. Thus, our calculations explained why the *N*-alkylated product was never observed, but suggested that **comp-A** and **comp-B** were energetically close enough to allow for transient *N*-alkylation. To probe this scenario, we subjected unreactive *N*-Bz glycine methyl ester (Scheme 2B, **3j**) to modified conditions, allowing us to study the proposed first step, reversible *N*-alkylation (eq 1).

Upon exposure of the protected glycine (Scheme 3, **A**) to MTBD and CD₃OD, rapid deuterium incorporation was observed at *N* (**int-1**). Then, protio-MVK was added to the reaction mixture. As expected, no *N*- (**int-2**) or *C*-alkylation (**3j**) was observed. Decisively, we did not observe deuterium exchanging into the MVK (D-MVK), which would support transient and reversible *N*-alkylation. Thus, we concluded that Hoyer's mechanism was likely operative in our system.

The implication was that substrates that underwent C–C bond formation were doing so because the lowered pK_a of the αC–H allowed sufficient quantities of the reactive enolate to form. However, substrates devoid of acidifying functional groups, such as simple glycine and other α-alkyl amino esters were not sufficiently acidic to form the requisite enolate. To test this, we examined commercially available Boc-protected trifluoroalanine methyl ester, which indeed gave **4d** (eqn 2) in 83% isolated yield.

We postulated that we could selectively acidify the αC–H over the N–H by making the ester component more electron withdrawing. The *N*-Bz trifluoroethyl esters of several natural amino acids which were otherwise unreactive (Scheme 4) provided the necessary acidification of the C–H to turn on reactivity. Admittedly, the reactions are more sluggish than previous substrates, and required both higher catalyst loadings and higher temperatures, but nonetheless reached full conversion at room temperature. Attempted reaction of the methyl ester indicated the essential nature of the trifluoroethyl ester component (**5a** vs **5b**). The trifluoroethyl esters facilitated both the desired reaction, but were also found to be prone to hydrolysis (from adventitious H₂O). We found that switching the solvent from MeCN to DCM was essential to prevent hydrolysis.

Having established the importance of the α-substituent in facilitating the reaction, we speculated we could use the difference in reactivity between α-aryl and α-alkyl amino acids to perform selective modification of peptides possessing such units. We synthesized dipeptide Boc-Ala-Phg-OMe to test our hypothesis and after subjecting the dipeptide to our reaction conditions (Scheme 5, eqn 3), we were pleased to observe a single regioisomer in which *C*-alkylation occurred exclusively at the phenyl glycine subunit in good yield (**6a**, 73% yield, 92% BRSM). The reaction took place with little stereoinduction (dr 1.2/1), leaving open the possibility of external control. To assess the reactivity as a function of the sequence, we next inverted the order of the dipeptide (Scheme 5, eq 4), such that the reactive Phe unit was an amide rather than an ester. While the rate was noticeably diminished, we

were pleased to observe the desired product in which C-alkylation occurred exclusively at the phenyl glycine subunit (**6b**, 38% yield, dr 1.6/1, 69% BRSM). With more development, this reactivity could potentially be extended to acidic units not at the C-terminus of peptides. Importantly, previous efforts to selectively alkylate peptides through multianion approaches were often fraught with solubility issues when dealing with polythiated peptides at low temperatures.^[18] The monoanion approach circumvents this issue altogether.^[18a, 19] Finally, we examined the dipeptide DAPT which is a γ -secretase inhibitor^[20] and has been shown *in vivo* to selectively inhibit the formation α -amyloid^[20] involved in Alzheimer's disease.^[20] More generally, it is thought to indirectly inhibit NOTCH, an important α -secretase substrate^[21] involved in autoimmune and proliferative diseases.^[21] Exposing DAPT to just 1.05 equiv of MVK and 50 mol% MTBD led to full conversion to give **6c** in 90% yield. Similarly, the reaction was sluggish compared to the simple phenylglycine derivative. One potential reason for this is the addition of H-bond donors, which could stabilize, and therefore, retard the attack of the requisite carbanion on the electrophile. Additionally, it is expected that there will be greater populations of unproductive aza-anions that must funnel to the reactive enolate. A deuterium labeling study (see Supporting Information) indicated that both N-Hs exchanged, as did the α C-H of the phenylglycine unit. No scrambling was observed at the corresponding alanine α C-H.

In conclusion, we have investigated the direct activation of useful amino acid derivatives. In contrast to current alkylation strategies, we have demonstrated the ability to access the enolate through a strategy that involves funneling of a monoanion to the reactive carbanion. The operational simplicity, high chemo-selectivity, and the fast rate of the reaction make it particularly attractive for further development. This reaction significantly expands access to non-natural amino acids derivatives, as we have demonstrated strategies to elaborate both natural, non-natural amino esters, and the ability to selectively functionalize the more acidic residues within small peptides.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. DFT calculations:
B3LYP/6-311+G(2d,p) optimized geometries for starting materials and products.

A. α,α -disubstituted amino acids from azomethine ylides **B. α,α -disubstituted amino acids from oxazolone enolate** **C. Krapcho 1976: Dianion mechanism** **D. Hoya 1985: Monoanion mechanism** **E. This work: α,α -disubstituted amino acids directly from enolate** **Scheme 1.**

The use of enolates and equivalents to access α,α -disubstituted amino acids

A. Michael Acceptors

B. Alpha substituent

C. Common protecting groups

Scheme 2.

Exploration of the Michael acceptor, α -substituent, and the amino protecting group.

Scheme 3.
(retro)aza-Michael reaction

Scheme 4.
Michael reaction of natural amino esters

Scheme 5.
Late-stage modification of peptides

Table 1.

Optimization of Reaction Conditions

entry	MVK(equiv)	base	mol %	<i>t</i> (°C)	time (h)	%conv ^a	%NMR yield ^b
1	3	DIPEA	300	22	36	100	>99
2	3	TMG	105	−20	1	100	>99
3	3	DBU	105	−20	1	71	64
4	3	NaOH	105	−20	1	100	92
5	1.05	TMG	105	−20	1	100	>99
6	1.05	TMG	10	−20	1	100	>99
7	1.05	TMG	0.1	−20	1	100	<3
8	1.05	TMG	0.1	45	48	<3	<3
9	1.05	MTBD	0.1	−20	1	100	>99
10	1.05	MIBD	0.1	22	1	100	>99

^aConversion determined by ¹⁹F NMR.^bYields determined by ¹⁹F NMR relative to trifluoroacetic acid as internal standard.