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Benzoic Acid Catalyzed Annulations of α-Amino Acids and Aromatic Aldehydes Containing an *ortho*-Michael Acceptor: Access to 2,5-Dihydro-1*H*-benzo[*c*]azepines and 10,11-Dihydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepines

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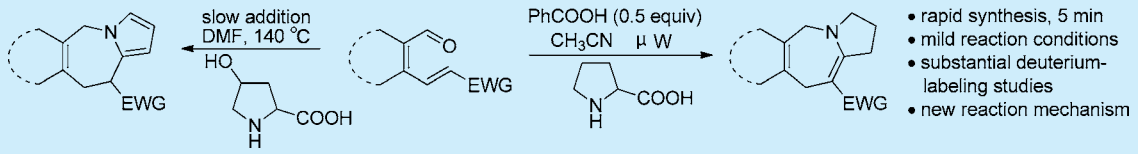
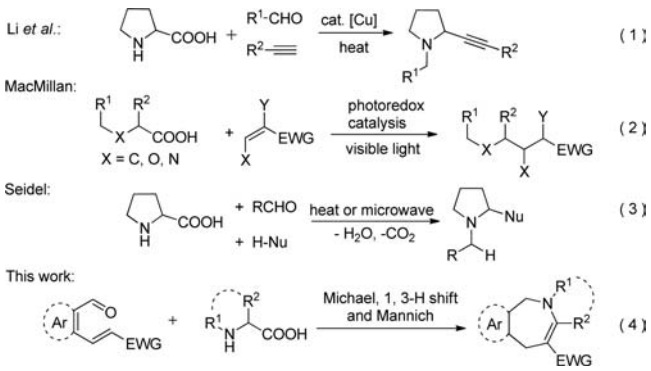
Supporting Information



ABSTRACT: A novel one-pot efficient synthesis of 2,5-dihydro-1*H*-benzo[*c*]azepines and 10,11-dihydro-5*H*-benzo[*e*]pyrrolo-[1,2-*a*]azepines from α-amino acids and aromatic aldehydes containing an *ortho*-Michael acceptor is reported via decarboxylative annulations without metal catalysts in yields of 52−91%. Under microwave irradiation, this protocol provides rapid access to polycyclic ring systems (only 5 min in most cases).

Benzazepines are important structural skeletons in a wide range of medicinal agents and biologically active compounds.[1] Therefore, the development of an efficient and convenient synthetic access to such a polycyclic framework is of considerable interest. Azeomethine ylides are versatile intermediates and have been employed in the construction of medium-sized nitrogen-containing heterocycles via 1,3-dipolar cycloadditions,[2] 1,5- and 1,7-electrocyclizations,[3] or other forms of cycloadditions.[4] To the best of our knowledge, the feasibility of azomethine ylides as a Michael donor has not been exemplified. Herein, we report the use of azomethine ylides, generated in situ from decarboxylation of amino acids with an ortho- Michael acceptor aromatic aldehyde, in a decarboxylative Michael−1,3-hydrogen shift−Mannich and retro-Michael ring opening cascade reaction to prepare the alternatively difficult-to-access 2,5-dihydro-1*H*-benzo[*c*]azepines and 10,11-dihydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepine derivatives. In general these processes take only 5 min.

Decarboxylative couplings are a powerful and facile reaction for the efficient construction of a carbon−carbon or carbon−heteroatom bond.[5] Over the past several years, metal-catalyzed decarboxylative cross-couplings have received significant attention due to their high efficiency, selectivity, and convenience.[6] For example, Myers described a palladium-catalyzed decarboxylative coupling reaction of arene carboxylates with olefinic substrates.[7] And in 2006, Gooßen presented a safe and convenient cross-coupling strategy for the large-scale synthesis of biaryls via copper-catalyzed decarboxylation of easily accessible arylcarboxylic acid salts.[8] Recently, Li developed a novel CuBr-catalyzed decarboxylative coupling reaction of α-amino acids (eq 1).[9] Moreover, MacMillan demonstrated decarboxylative sp^3−sp^2 cross-coupling of amino



acids via merging photoredox with nickel catalysis in 2014 (eq 2).[10] In contrast to these metal-catalyzed decarboxylative coupling reactions, the metal-free decarboxylative cross-coupling reaction of amino acids could also be a viable addition. More recently, Seidel et al. have described a series of elegant metal-free decarboxylative α-functionalizations of amino acids based on a kind of iminium ion pair generated from protonation of dipole by pronucleophile H-Nu (eq 3).[11] And Pan described the use of 2-carboxyindoline in the formation of *N*-alkylindoles by decarboxylative redox amination.[12] In addition to these representative cycloadditions and protonation/nucleophilic additions, Yang et al. also reported a new mode of reactivity for azomethine ylides to achieve difunctionlization of secondary α-amino acids via pseudo-four-component reactions.[13]

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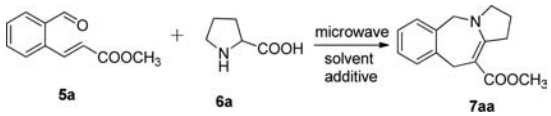
In continuation of our research on the redox amination−aromatization cascade reactions of 4-hydroxyproline with aromatic aldehyde,[14] here, we report an unprecedented decarboxylative C−C bond coupling reaction of amino acids via a novel process that azomethine ylides serve as a nucleophilic donor instead of a site to accept the attack of nucleophiles. To the best of our knowledge, this work represents the first synthesis of 2,5-dihydro-1*H*-benzo[*c*]-azepines involving a 1,3-hydrogen shift in azomethine ylides chemistry; there is no report regarding the synthesis of 10,11-dihydro-5*H*-benzo[*e*]pyrrolo[1,2-*a*]azepines from α-amino acids and aromatic aldehydes.

We embarked on our studies with the reaction of (*E*)-methyl 3-(2-formylphenyl)acrylate **5a** and L-proline **6a**. The desired annulation product **7aa** was obtained in 32% yield in toluene (Table 1, entry 1). To promote the reaction efficiency, we

Table 1. Optimization of Reaction Conditions[a]



5a 6a 7aa

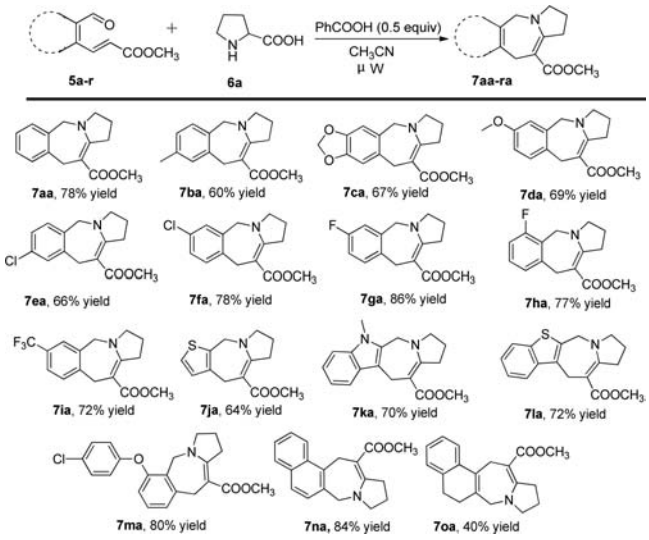
entry	solvent	additive[b]	temp (°C) (power)[c]	time (h)	yield (%)[d]
1[e]	toluene	none	140	12	32
2[e]	CH_3CN	PhCOOH	100	12	54
3[e]	CH_3CN	PivOH	100	12	57
4	CH_3CN	PivOH	120 (70 W)	0.3	62
5	CH_3CN	PhCOOH	120 (70 W)	0.3	67
6	CH_3CN	PhCOOH	120	0.1	78
7[f]	CH_3CN	PhCOOH	120	0.1	53
8[g]	CH_3CN	PhCOOH Na_2SO_4	120	0.1	23
9[g]	CH_3CN	PhCOOH 4 Å MS	120	0.1	45
10	CH_3CN	none	120	0.1	23

[a]Reaction conditions: aldehyde **5a** (0.2 mmol, 1.0 equiv), proline **6a** (0.4 mmol, 2.0 equiv), and solvent (2.0 mL). [b]Unless otherwise noted, 0.5 equiv of additive was used. [c]Unless otherwise noted, 100 W microwave irradiation was performed. [d]Determined by analysis of crude mixture by ^1H NMR with dibromomethane as internal standard. [e]Reactions were performed under conventional thermal conditions, oil temperature. [f]0.2 equiv of additive was used. [g]1.0 equiv of anhydrous sodium sulfate and 18 mg of 4 Å molecular sieve were used, respectively.

studied the impact of solvent, additives, and other reaction parameters (Table 1). Initially, under conventional thermal reaction conditions including slow addition of aromatic aldehyde, the highest yield was 57% (entries 1−3) in Table 1 (see Supporting Information (SI)). Gratifyingly, the efficiency of the reaction vastly increased when the reaction was performed under microwave irradiation in acetonitrile (62%, entry 4). When benzoic acid was used as an additive, the reaction yield was further improved to 67% (entry 5). It was found that the power of irradiation, reaction time, temperature, and additives (entries 7−10) were critical for the addition annulation process (more details were provided in the SI). Under microwave irradiation (100 W, 120 °C, 5 min), the model reaction catalyzed by 0.5 equiv benzoic acid gave **7aa** in the highest yield in acetonitrile (entry 6).

With the optimal conditions in hand, we then examined the scope of aromatic aldehydes (Scheme 1). These efficient

Scheme 1. Scope of Aromatic Aldehydes[a]



[a]Reactions were carried out using aromatic aldehyde (0.5 mmol, 1.0 equiv), L-proline (2.0 equiv), and benzoic acid (0.5 equiv) in acetonitrile (3.0 mL) under μW irradiation at 120 °C for 5 min. Isolated yields. μW = microwave.

decarboxylative C−C bond coupling reactions proved to be viable with a broad range of aromatic aldehydes, affording the structurally diverse 2,5-dihydro-1*H*-benzo[*c*]azepine products (**7**). As illustrated in Scheme 1, a broad spectrum of substituents of aromatic aldehydes were compatible in excellent yields with electron-donating (products **7ba**−**da**), -neutral (product **7aa**, **7na**), and -withdrawing (products **7ea**−**ia**) substituents, respectively. Moreover, heterocycle (**7ja**) and benzo-fused heterocycles containing nitrogen (**7ka**) and sulfur (**7la**) reacted with L-proline in moderate yields. Furthermore, an aromatic aldehyde with steric hindrance was also compatible in the decarboxylative Michael addition annulation reaction, delivering **7ma** in 80% yield. Notably, this additive annulation protocol is also amenable to the use of a nonaromatic unsaturated conjugate aldehyde, albeit with a low yield (**7oa**, 40% yield). Interestingly, when a nonaromatic aldehyde (**5o**) was oxidized to an aromatic aldehyde (**5n**), the reaction became much more efficient under the optimal reaction conditions with good yield (**7na**).

We next investigated the scope of the electron-withdrawing group under the optimized reaction conditions (Scheme 2). Different electron-withdrawing groups, such as ethyl acrylate, butyl acrylate, *tert*-butyl acrylate, and acrylonitrile substituents, were compatible and afforded the corresponding benzazepines (**7pa**−**7sa**) with good yields. Moreover, in order to further expand the scope of this methodology, we then turned our attention to the reaction of different amino acids with aromatic aldehydes. To our delight, for catenarian amino acids, such as sarcosin, the reaction effectively engaged in the process with good results (**7ab**, **7db**). *N*-Benzylglycine (**6c**), L-thioproline (**6d**), and *trans*-4-hydroxyproline showed good yields in the formation of **7ac**−**7ae** too. It was noted that reactions of substrates bearing a *para*-cyanophenyl-substituted alkene or *para*-ester group with *trans*-4-hydroxyproline (**6e**) afforded aromatization products (**7te**−**7ye**) in moderate yields. Slow addition and high boiling point polar solvent which could raise the reaction temperature were likely able to allow tuning of inherent unfavorable kinetic and thermodynamic parameters to

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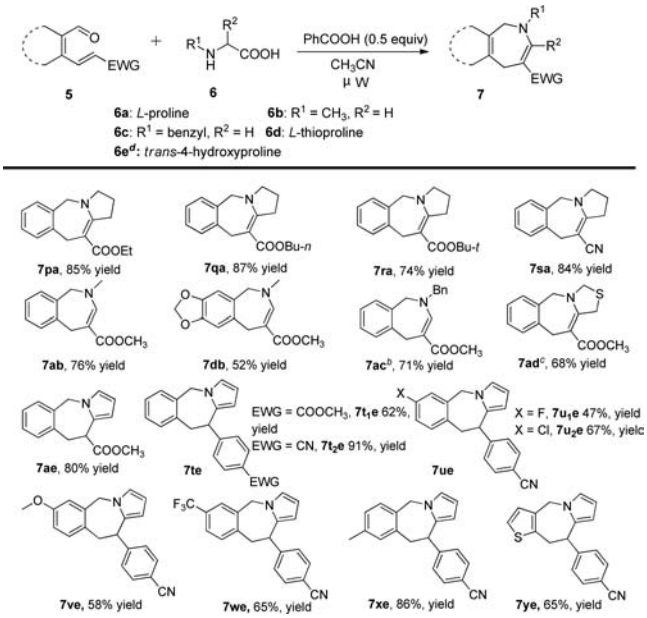
Scheme 2. Scope of Michael Acceptor and Amino Acids[a]

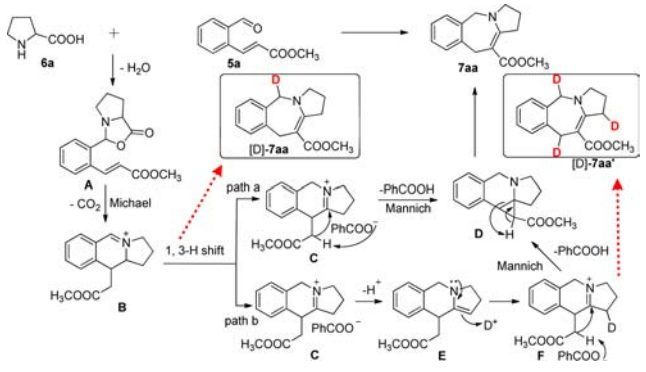


[a]Reactions were carried out using aromatic aldehyde (0.5 mmol, 1.0 equiv), amino acids (2.0 equiv), and benzoic acid (0.5 equiv) in acetonitrile (3.0 mL) under μW irradiation at 120 °C for 5 min. Isolated yields. [b]Slow addition of aromatic aldehyde **5a** to *N*-benzylglycine in DMF under Ar at 140 °C. [c]μW irradiation at 120 °C for 10 min. [d]Slow addition of aromatic aldehyde **5t**−**y** to L-hydroxyproline in DMF under Ar at 140 °C in 30 min without any additives.

form medium size rings.[15] And the structure of **7we** was confirmed by X-ray crystallography.

1,7-Electrocyclization with intramolecular 1,5-hydride transfer and then simple migration of a double bond normally accounted for this reaction.[16,3e] However, during deuterium-labeling studies, we found that this Brønsted acid catalyzed redox process was different. In the labeling studies (Scheme 4, eqs 5−8), we unexpectedly found that the reaction of the deuterated aromatic aldehyde [D]-**5p** and L-proline **6a** under the optimal conditions afforded the compound **7pa** without any deuterated substances (eq 5). That is, this process could not undergo 1, 5-hydride transfer. We speculated that intramolecular Michael addition and then the Mannich process might account for this reaction (Scheme 3). The condensation of **5a** with L-proline gives rise to the oxazolidinone[17] **A** which

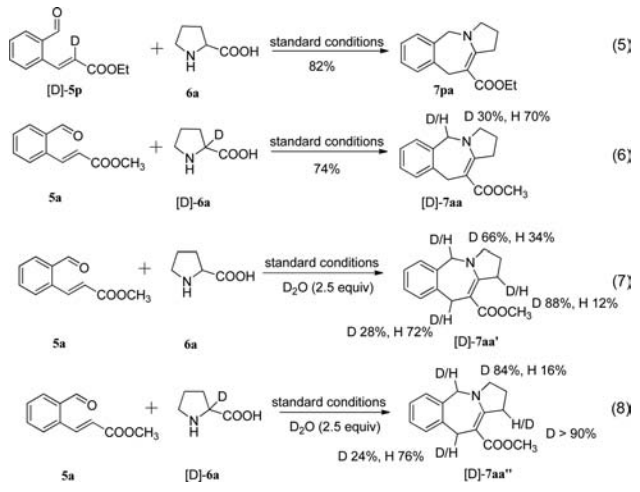
Scheme 3. Proposed Mechanism for Decarboxylative Michael Addition



undergoes decarboxylation to form the azomethine ylide. Subsequent intramolecular Michael addition of azomethine ylide results in the formation of iminium ion **B** which then undergoes a 1,3- hydrogen[18,16b] shift to give intermediate **C**. In the next step **C** undergoes a Mannich reaction and retro-Michael ring opening to afford the final product **7aa** (path a).

To understand the 1,3-hydride transfer process, we performed the reaction of DL-proline-2-d_1 [D]-**6a** with the substrate **5a** under the standard conditions. As expected, the corresponding deuterium product [D]-**7aa** was obtained successfully, although the deuterium content of the product was only about 30% probably due to a H/D exchange with water generating from a condensation reaction or the residual (Scheme 4, eq 6). To investigate whether water was directly

Scheme 4. Labeling Experiments



involved in the reaction, we added 2.5 equiv of D_2O into the mixture. It was found that the deuterium content of compound [D]-**7aa**′ (5-position) obviously increased (D 66%, eq 7); that is, water has participated in the 1,3-hydride transfer process. Furthermore, the deuterium content of the 5-position in compound [D]-**7aa**″ reached up to 84% when the reaction of aldehyde **5a** and DL-proline-2-d_1 [D]-**6a** with 2.5 equiv of D_2O was carried out under the standard conditions (eq 8). It just illustrates that the α-hydrogen of amino acids and water participate in the 1,3-hydride transfer process together. Interestingly, besides the 5-position deuterated compound [D]-**7pa**, **7aa**′, or **7aa**″ in the deuterium experiments, we also observered high deuterium content in the 1-position (eqs 7 and 8). We speculated that the active species **C**, formed from the 1,3-hydride shift, could undergo proton-mediated isomerization to afford the enamine **E**[13] and then deuteration of **E** produced the corresponding deuterium product **7aa**′ or **7aa**″ (path b). Lastly, no deuterium substance was obtained when **7aa** reacted with D_2O under the standard conditions.

In conclusion, we have developed a rapid synthesis of 2, 5-dihydro-1*H*-benzo[*c*]azepine derivatives from α-amino acids and aromatic aldehydes containing an *ortho*-Michael acceptor under relatively moderate conditions. In contrast to the widely outstanding study of 1,5-hydride shift and double bond migration processes, we have presented a new proposed mechanism; that is, an intramolecular Michael addition and a water-assisted 1,3-hydrogen shift with a Mannich reaction and retro-Michael ring opening process gave rise to final products. This strategy offers an opportunity for the rapid synthesis of

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useful molecular architectures. Further study of the reaction mechanism, new organic transformations, and the biological application of these compounds is underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02484.

Experimental procedures and spectral data for all new compounds (PDF)

Crystal data and structure for **7we** (ZIP)

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Notes

The authors declare no competing financial interest.

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