Azomethine Ylides

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Metal-Free Decarboxylative Cyclization/Ring Expansion: Construction of Five-, Six-, and Seven-Membered Heterocycles from 2-Alkynyl Benzaldehydes and Cyclic Amino Acids**

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Abstract: *A one pot synthesis of 1H-benzo[g]indoles, tetrahydrobenzo[h]quinolines, and naphtho[1,2-b]azepines from 2-alkynyl benzaldehydes and cyclic amino acids is reported. The salient feature of the strategy involves formation of three new bonds (one C–N and two C–C bonds) by a metal-free decarboxylation/cyclization/one-carbon ring expansion sequence in one pot.*

In recent years, decarboxylative cyclization has emerged as a powerful tool for the synthesis of annulated poly-heterocyles.[1] Among a variety of carboxylic acid substrates employed for this purpose, the cyclic amino acid (*S*)-proline has been applied for the synthesis of structurally diverse pyrrolo-based polycyclic ring systems (Figure 1) by an azomethine ylide pathway.[2] Seidel et al. reported the synthesis of polycyclic ring systems by treating (*S*)-proline with an aldehyde, linked to the indole, by the 1,6-annulation of an azomethine ylide.[3] Cohen et al. developed a methodology for the synthesis of pyrrolo benzoxazines by using a metal-free decarboxylative cyclization strategy.[4] Recently, Yang et al. reported the construction of pyrano[2,3-*b*]pyrrole and pyrrolizinone by treating (*S*)-proline with aldehyde and a diketone.[5] Interestingly, in all the above strategies, the (*S*)-proline, after decarboxylation, was an integral part of the poly-heterocycle to furnish the annulated pyrrolo-based compounds. In contrast, Grigg et al. reported an unusual decarboxylative three-carbon ring expansion during the condensation of (*S*)-proline with formalin and activated internal alkynes by 1,3-dipolar cycloaddition reaction with an azomethine ylide, thus furnishing 1-azacyclooctadiene.[6]

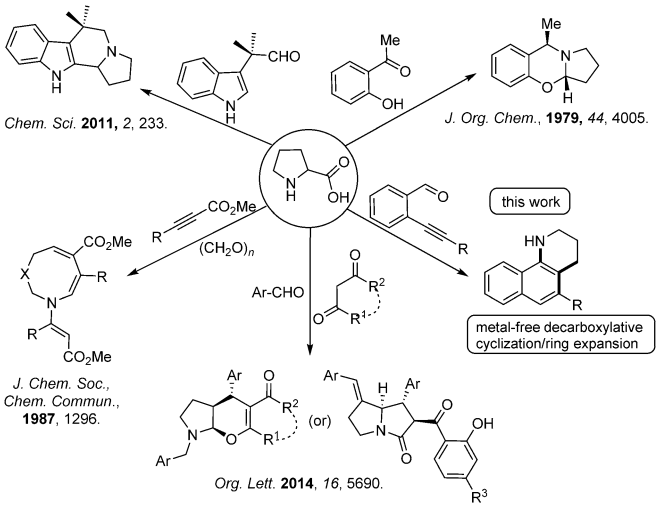

Figure 1. Literature reports and our proposed methodology involving (*S*)-proline as a substrate for the synthesis of annulated poly-heterocycles by an azomethine ylide pathway.

However, this strategy had limitations in terms of substrate scope and afforded products in poor yields. Herein we report the one-pot decarboxylative cyclization/one-carbon ring expansion reaction under metal-free conditions from readily available cyclic amino acids and 2-alkynyl benzaldehydes. The studies are a continuation of our ongoing interest in one-pot syntheses of annulated poly-heterocycles from alkynes.[7]

Our studies commenced with the condensation of 2-phenyl ethynyl benzaldehyde (**1a**) with (*S*)-proline (**2a**) in DMF at 100 °C for 8 hours under metal-free conditions to yield a new product (**3a**) in 56 % yield upon isolation (Table 1, entry 1). The structure of **3a** is characterized as 5-pheyl-1,2,3,4-tetrahydrobenzo[h]quinoline and is based on NMR and mass spectral studies.[8] In an attempt to improve the yield of **3a**, several solvents were screened and the reaction was carried out at variable temperatures. The employment of solvents like DMSO and toluene had no significant effect on the yield of **3a** when compared to those for DMF (entries 2 and 3), whereas condensation in xylene and DCE afforded **3a** in reduced yields (entries 4 and 5). Next, we carried out the reaction in DMF at different temperatures (entries 6–8) and pleasingly, heating the reaction mixture at 125 °C for 4 hours furnished **3a** in 70 % yield upon isolation.

Based on literature reports, a plausible mechanism for the synthesis of 5-phenyl-1,2,3,4-tetrahydrobenzo[h]quinoline (**3a**) is depicted in Figure 2. The initial condensation of 2-alkynyl benzaldehyde and (*S*)-proline produces the imine

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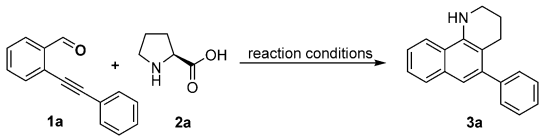
Table 1: Optimization for the synthesis of the 5-aryl-1,2,3,4-tetrahydrobenzo[h]quinoline **3a**.[a]



Entry	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	DMF	100	8	56
2	DMSO	125	8	58
3	toluene	110	6	61
4	xylene	100	6	51
5	DCE	90	8	42
6	DME	85	8	40[c]
7	DMF	110	6	60
8	DMF	125	4	70

[a] All reactions were performed with 1 equivalent of **1a** and 1.1 equivalents of **2a**. [b] Yield of isolated product. [c] Reaction mixture contains unidentified polar impurities. DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

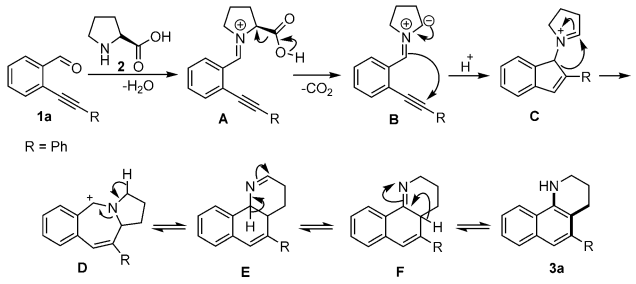
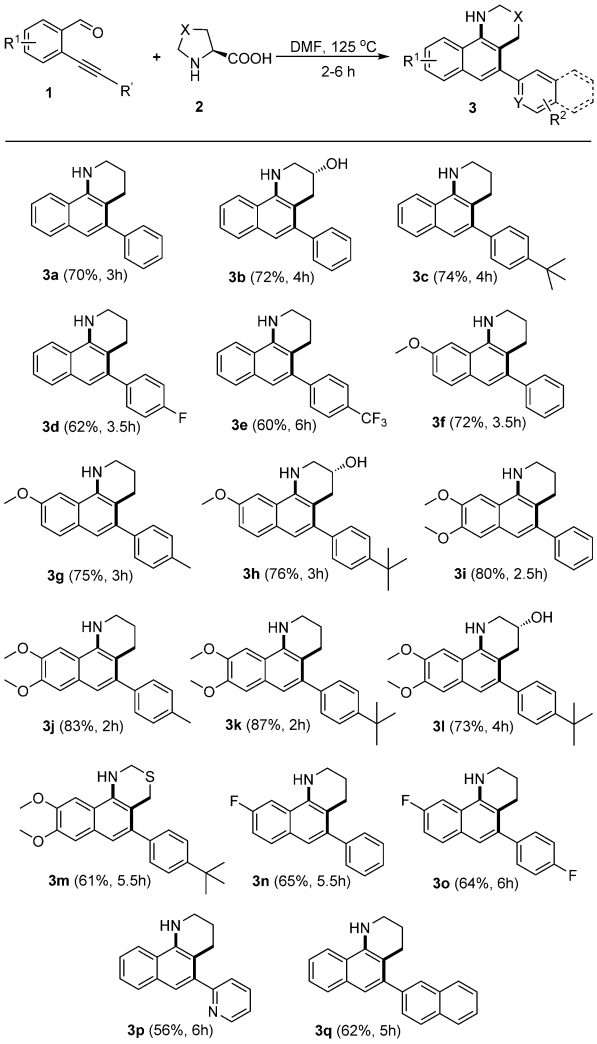


Figure 2. Plausible mechanism for the synthesis of 5-phenyl-1,2,3,4-tetrahydrobenzo[h]quinoline (**3a**).



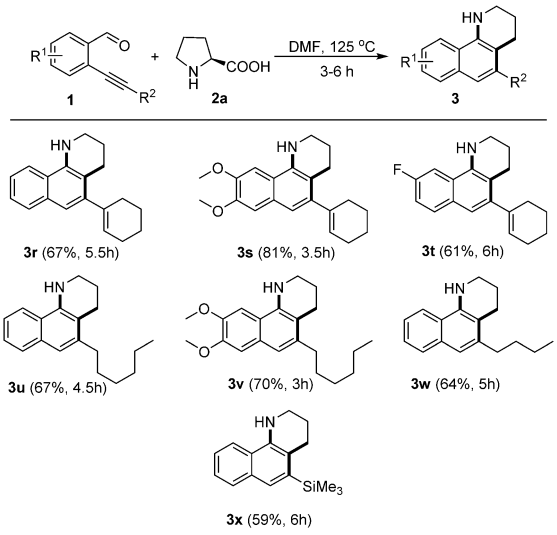
Scheme 1. Substrate scope for the synthesis of 5-aryl-1,2,3,4-tetrahydrobenzo[h]quinolines (**3**).

intermediate **A**, which then undergoes decarboxylation to produce the azomethine ylide intermediate **B**.[9] Then **B**, as per Baldwin's rule,[10] undergoes a highly favored 5-*endo dig* cyclization after the abstraction of a proton to produce the intermediate **C** which may then undergoes a one-carbon ring expansion to yield a stable benzyl cation[11] (**D**). Alternately, **B** could also undergo a [3+2] cycloaddition. However, this would result in a highly constrained four-membered ring adjacent to the aromatic group, and seems unlikely to occur. In the next step **D** undergoes further modification to yield the intermediate **E** which eventually rearranges to give the final product **3a.**

Next, we studied the scope and limitations of the strategy by introducing diversity into both the reactants **1** and **2**. For this we introduced variety of substituents, such as electron-withdrawing and electron-donating groups (R^1), on the phenyl ring of **1** (Scheme 1). Similarly, substitution (R′) was also introduced to **1** on the alkyne portion, that is, with substituted aromatic and naphthyl rings. Accordingly, seventeen compounds (**3**) were synthesized and the results are summarized in Scheme 1. As is evident, the yield of **3** increased in the presence of electron-donating groups (R^1), such as dimethoxy (**3i–k**), whereas in the presence of an electron-withdrawing group (F), the yield was found to be marginally reduced (**3n** and **3o**). Similarly when R′ is an aryl ring bearing electron-donating groups, such as methyl or *tert*-butyl, the corresponding **3** was furnished in more than 74% yield. In the presence of F or CF_3 groups the corresponding **3d** and **3e** were obtained in about 60% yield upon isolation. Employment of a naphthyl ring (R′) furnished **3q** in 62% yield upon isolation.

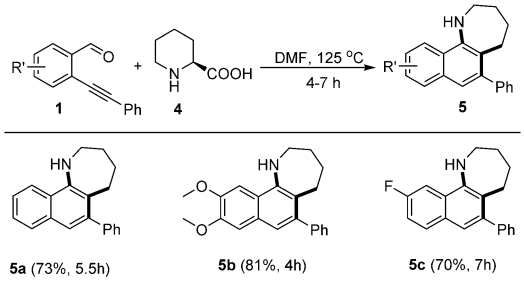
Diversity in the reactant **2** was introduced by replacing the cyclic amino acid (*S*)-proline with the analogous acids (2*S*,4*R*)-4-hydroxyproline (**2b**) and (*R*)-4-thioproline (**2c**). Accordingly, condensation of **1a**, **1e**, and **1h** with **2b** furnished the corresponding **3b, 3h**, and **3l** in 72–76% yields (Scheme 1). Similarly, condensation of **2c** with **1h** afforded **3m** in 61% yields.

In an attempt to further study the versatility of our strategy, the alkynes **1** were substituted (R^2) with an aliphatic moiety such as hexyl, octyl, cyclohexenyl, and trimethylsilyl groups (Scheme 2). Pleasingly, the aliphatic substitutions were well tolerated and produced the corresponding **3** in 59–81% yields.



Scheme 2. Substrate scope for the synthesis of 5-alkyl-1,2,3,4-tetrahydrobenzo[h]quinolines (**3**).

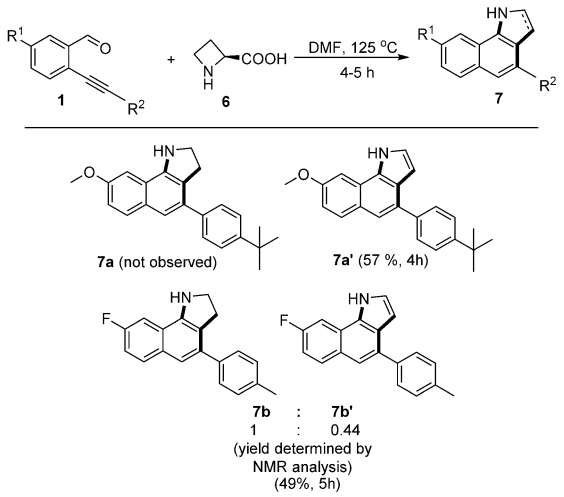
After successfully demonstrating the efficacy of the strategy with five-membered cyclic amino acids (**2**), we next replaced it with the six-membered amino acid **4** (pipecolic acid) with a goal of obtaining azepine-based products by a one-carbon ring expansion. Accordingly, **1** was treated with **4** under the optimized reaction conditions to give naphtho-[1,2-b]azepines (**5**; Scheme 3). As shown, the substituted 2-alkynyl benzaldehydes **1a**, **1h**, and **1k** underwent smooth conversion to yield the corresponding products **5** in good yields.



Scheme 3. Synthesis of naphtho[1,2-b]azepines (**5**) by a decarboxylative cyclization/one-carbon ring expansion reaction.

The generality of the present methodology was further demonstrated by employing the four-membered cyclic amino acid azetidine 2-carboxylic acid (**6**; Scheme 4). We envisaged that under these reaction conditions, a decarboxylative cyclization/ring expansion may furnish indole-based products. Accordingly, condensation of **1g** and **1v** with **6** afforded the corresponding benzo[g]indoles **7** in 49 to 57% yields. There is no literature precedence dealing with the synthesis of these benzo[g]indoles by a decarboxylative cyclization/one-carbon expansion strategy.[12]

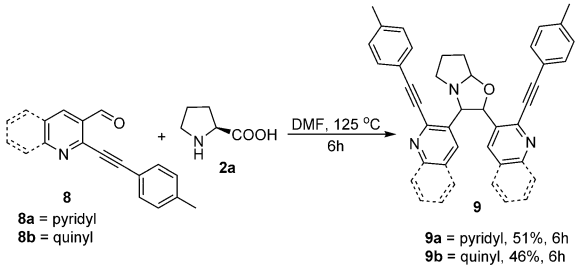
After successfully incorporating a variety of cyclic amino acids, attempts were made to replace **1** with 2-alkynyl heteroaryl aldehydes to examine their ability to undergo



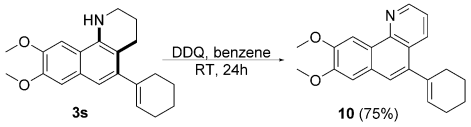
Scheme 4. Synthesis of 1*H*-benzo[g]indoles (**7**).

condensation by a decarboxylative cyclization/one-carbon expansion sequence. In our preliminary studies, condensation of 2-alkynyl pyridine/quinoline aldehydes (**8a** and **8b**) with **2a** furnished the hexahydropyrrolo[2,1-b]oxazoles[13] **9** as the only products without undergoing the one-carbon ring expansion (Scheme 5). The reaction mechanism may involve azomethine ylide formation and subsequent cycloaddition of a yet another molecule of the 2-alkynyl heteroaryl aldehyde to afford **9**. This reactivity may be attributed to the poor electron density at the carbonyl carbon atom of the 2-alkynyl heteroaryl aldehyde compared to that of the 2-alkynyl benzaldehyde, thus preventing intramolecular cyclization.

Finally, utility of the products **3** was demonstrated by treating **3s** with DDQ in benzene at room temperature for 24 hours, thereby furnishing the fully aromatized compound benzo[h]quinoline **10**, which belongs to a class of azaarenes reported in the literature to have diverse pharmacological properties[14] (Scheme 6).



Scheme 5. Synthesis of hexahydropyrrolo[2,1-b]oxazoles (**9**).



Scheme 6. Transformation of **3s** into the benzo[h]quinoline **10**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In conclusion we have developed a metal-free decarboxylative cyclization/ring expansion reaction in one pot by treating cyclic (four-, five-, or six-membered) amino acids with 2-alkynyl benzaldehydes. This novel methodology offers three new bond formations (one C–N, two C–C bonds) with the generation of five-, six-, or seven-membered heterocycles by an azomethine ylide/one-carbon ring expansion sequence.

Keywords: amino acids · azomethine ylides · heterocycles · ring expansion · synthetic methods

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