Azomethine Ylides

Deutsche Ausgabe: DOI: 10.1002/ange.201504429
Internationale Ausgabe: DOI: 10.1002/anie.201504429

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]

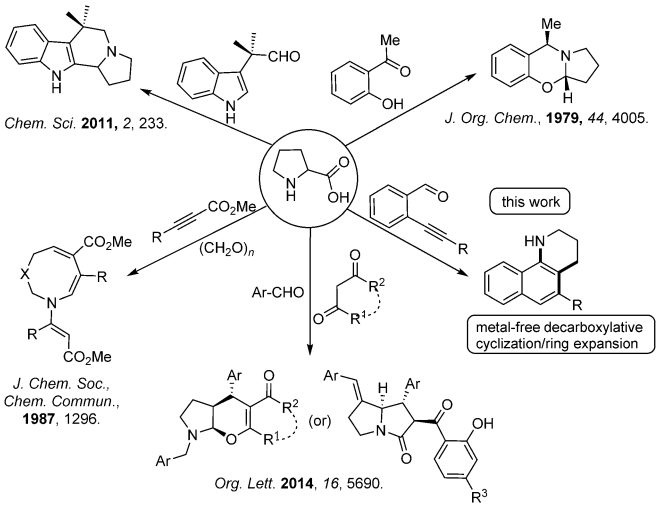

Figure 1. Literature reports and our proposed methodology involving (*S*)-proline as a substrate for the synthesis of annulated poly-heterocycles by an azomethine ylide pathway.

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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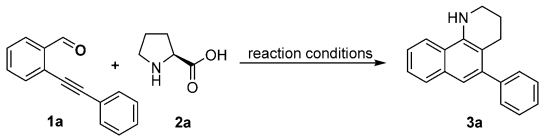
[**] S.S. and G.S. thank CSIR, and R.K. thanks UGC New Delhi for the fellowships. We also acknowledge CDRI-SAIF facilities for obtaining analytical data, and are grateful to the reviewers for suggestions pertaining to the mechanism. CDRI communication No. 9006.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504429.

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.

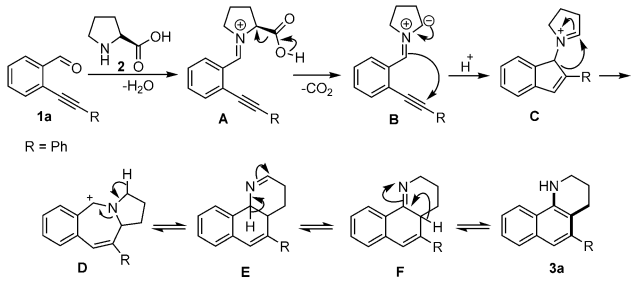
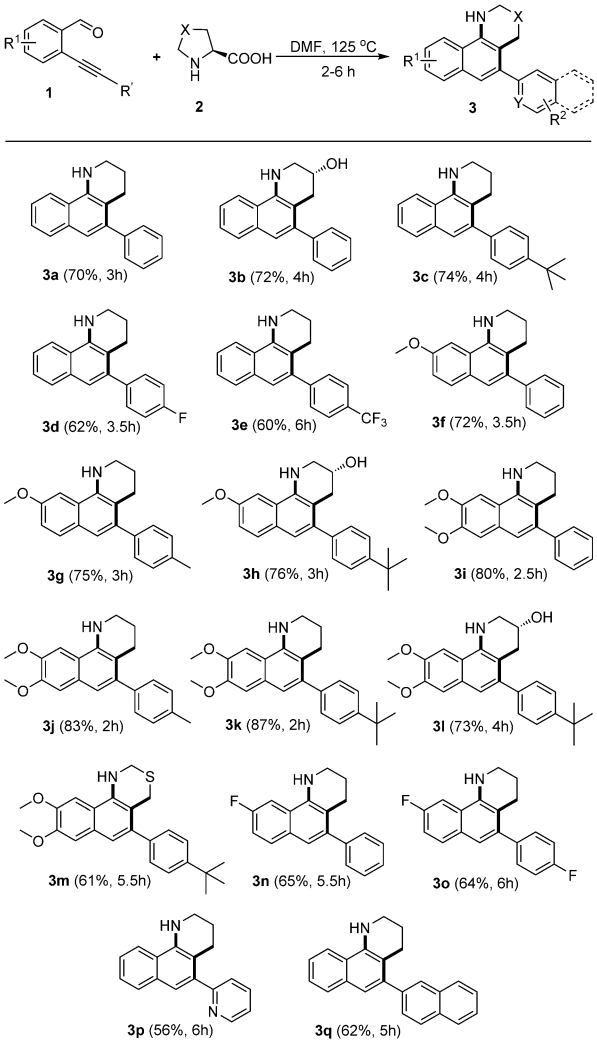


Figure 2. Plausible mechanism for the synthesis of 5-phenyl-1,2,3,4-tetrahydrobenzo[h]quinoline (**3a**).



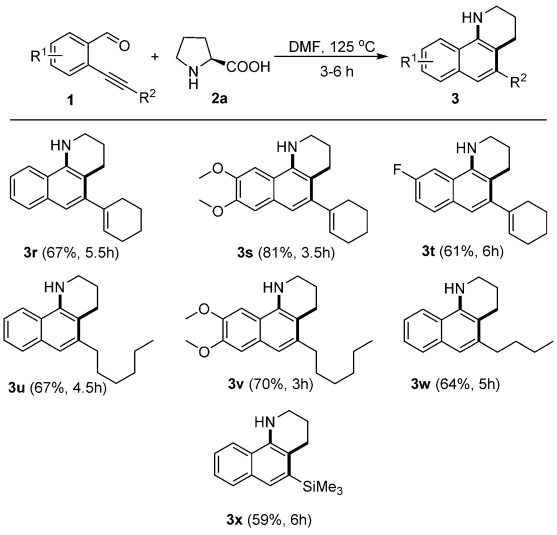
Scheme 1. Substrate scope for the synthesis of 5-aryl-1,2,3,4-tetrahydrobenzo[h]quinolines (**3**).

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.

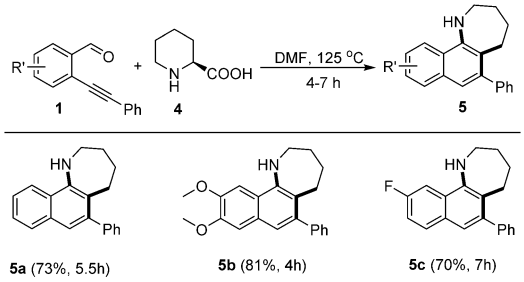
Diversity in the reactant **2** was introduced by replacing the cyclic amino acid (*S*)-proline with the analogous acids (2*S*,4*R*)-4-hydroxyproline (**2b**) and (*R*)-4-thioproline (**2c**). Accordingly, condensation of **1a**, **1e**, and **1h** with **2b** furnished the corresponding **3b, 3h**, 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**).

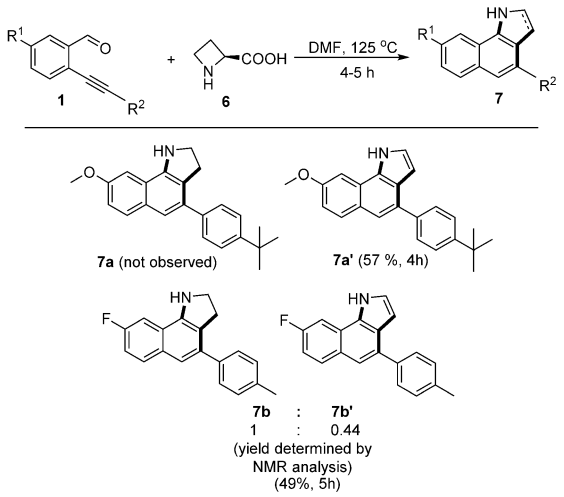
After successfully demonstrating the efficacy of the strategy with five-membered cyclic amino acids (**2**), we next replaced it with the six-membered amino acid **4** (pipecolic acid) with a goal of obtaining azepine-based products by a one-carbon ring expansion. Accordingly, **1** was treated with **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]

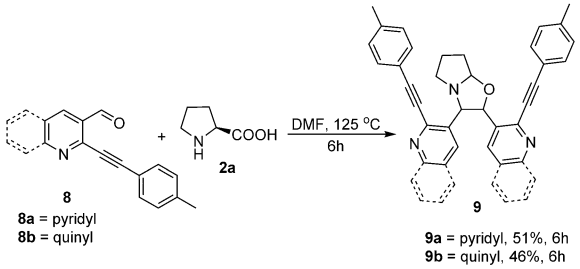
After successfully incorporating a variety of cyclic amino acids, attempts were made to replace **1** with 2-alkynyl heteroaryl aldehydes to examine their ability to undergo



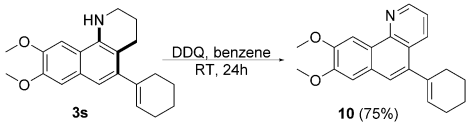
Scheme 4. Synthesis of 1*H*-benzo[g]indoles (**7**).

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

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 9564–9567
Angew. Chem. **2015**, *127*, 9700–9703

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Received: May 15, 2015
Published online: July 6, 2015

