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Iodine-Promoted N−H/α,β-C(sp^3)-Trifunctionalization of L-Proline: Access to 3,4-Dihydrobenzo[*b*][1,7]naphthyridines via Consecutive Decarboxylation/Ring Opening/Dicyclization

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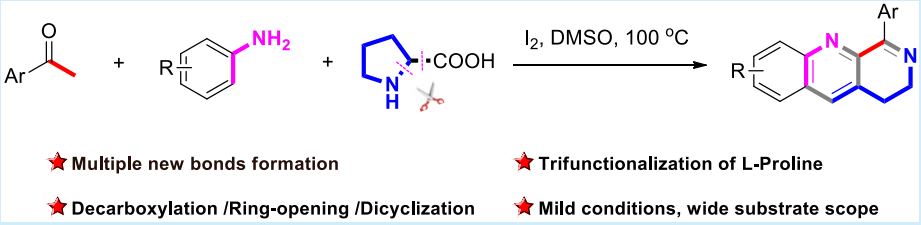
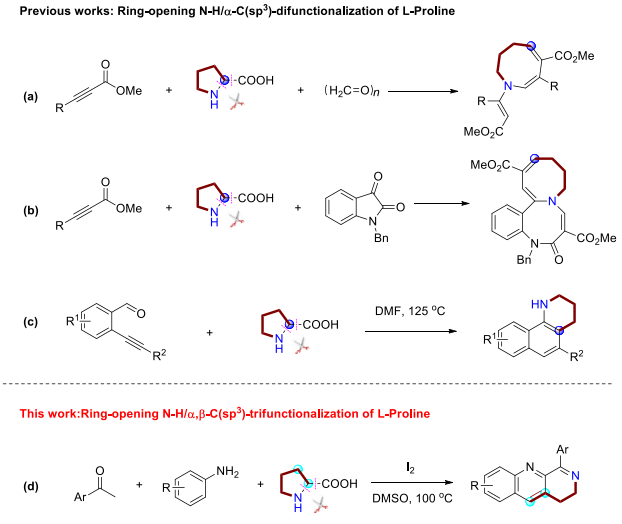
Supporting Information



ABSTRACT: A N−H/α,β-C(sp^3)-trifunctionalization of L-proline, proceeding through an iodine-promoted consecutive decarboxylation/ring-opening/dicyclization process, is achieved. This strategy affords structurally diverse fused *N*-heterocycles in good yields with a wide substrate scope. Preliminary mechanistic studies indicate that catabolism of L-proline might be involved in this cascade reaction and the *in situ* generated intermediate 4-aminobutanal was identified as the key intermediate. Notably, this domino strategy enriches the reactivity of versatile L-proline in the synthesis of fused heterocycles.

L-Proline and its derivatives are abundant biologically active natural products[1] and have been recognized as a versatile catalyst[2] as well as important synthons[3−6] in organic synthesis. Many organic chemists have reported the preparation of diverse pyrrolo-based compounds via decarboxylative annulations[3] or decarboxylation−coupling of L-proline.[4] More importantly, studies employing L-proline as a chain synthon via ring-opening reactions have been reported, but remain rare.[5,6] For example, Grigg and co-workers[5a] disclosed an interesting example of the N−H/α-C-difunctionalization of L-proline giving 1-azacyclooctadiene via a decarboxylative ring-opening reaction under mild conditions (Scheme 1a). Recently, the Yan group[5b] disclosed an appealing multicomponent reaction for the construction of unique eight polyheterocyclic compounds. Notably, L-proline and isatin rings were both opened in this reaction. Unfortunately, only five compounds have been reported (Scheme 1b). Furthermore, Kundu's group[6] disclosed a novel decarboxylative cyclization/ring expansion N−H/α-C-difunctionalization reaction for the construction of various fused-heterocycles from preprepared 2-alkynyl benzaldehydes and L-proline without using any additives (Scheme 1c). Although these studies provide straightforward and efficient processes for the construction of fused heterocyclic compounds, they have focused on the N−H/α-C-difunctionalization of L-proline via ring-opening processes. However, methods for the N−H/α,β-C(sp^3)-trifunctionalization of L-proline to construct fused heterocycles via a ring-opening process remain unexploited. Therefore, it is a challenging and meaningful goal in the area of organic synthesis.

Scheme 1. Ring-Opening of L-Proline



Multicomponent bicyclization reactions (MBRs), representing an unmatched opportunity to expand the structural diversity and molecular complexity of desired products, are regarded to be among the most powerful and reliable tools for the synthesis of fused heterocyclic scaffolds.[7] Although, several excellent MBR studies have been reported,[8] the development

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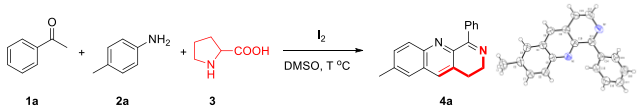
of a new convenient and environmentally friendly MBR from commercially available and simple substrates is urgent and significant in organic synthesis. As part of our continuing research interest in the preparation of diverse heterocycles,[9] we now report iodine-promoted MBRs for the preparation of 3,4-dihydrobenzo[*b*][1,7]naphthyridines from commercially available aryl methyl ketones, arylamines, and L-proline via a decarboxylation/ring-opening/dicyclization process under mild conditions (Scheme 1d).

Initially, acetophenone (**1a**), *p*-toluidine (**2a**), and L-proline (**3**) were reacted in the presence of I_2 in DMSO at 90 °C. As our first attempt, we were happy to notice that product **4a** was obtained in 72% yield (Table 1, entry 1), with the structure of

Table 1. Representative Optimization of the Dicyclization Reaction[a]



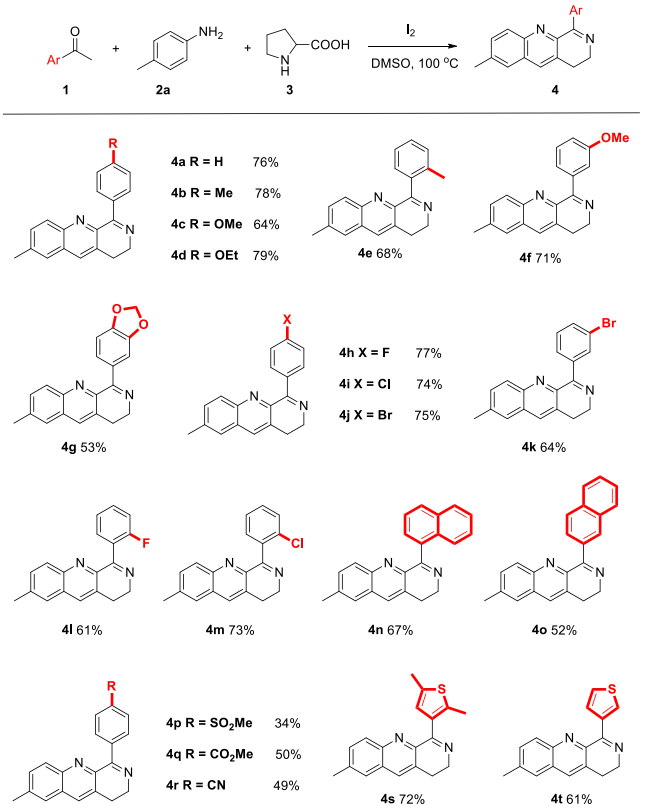
entry	I_2 (equiv)	**3** (equiv)	temp (°C)	additive	yield (%)[a]
1	1.6	1.0	90		72
2	1.6	1.0	100		76
3	1.6	1.0	110		74
4	1.6	1.0	120		69
5	1.6	1.5	100		71
6	1.6	2.0	100		68
7	0.1	1.0	100		trace
8	0.5	1.0	100		27
9	1.0	1.0	100		65
10	2.0	1.0	100		72
11	1.6	1.0	100	oxone	77
12	1.6	1.0	100	TBHP	75
13	1.6	1.0	100	TFA	72
14	1.6	1.0	100	HI	75
15	1.6	1.0	100	HAc	71

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3** (*x* mmol), I_2 (*x* mmol), additive (1.0 equiv), indicated temperature, DMSO 2 mL, 2 h, unless otherwise noted. [b]Isolated yields.

4a confirmed by X-ray crystallographic analysis (see Supporting Information). Even though the initial yield was acceptable, we aimed for further improvements. First, various temperatures were screened for this consecutive decarboxylation/ring-opening/dicyclization process, with 100 °C affording the best yield (Table 1, entries 1−4). Increasing the amount of L-proline led to a decreased yield of **4a** (Table 1, entries 5 and 6). Next, the effect of the iodine amount was investigated, with 1.6 equiv of iodine giving the best yield (Table 1, entries 7−10). Finally, diverse additives were tested, but no significant improvements were obtained (Table 1, entries 11−15).

With the optimized conditions in hand, we sought to investigate different substituents on the benzene ring of aryl methyl ketone. As shown in Scheme 2, substrates containing electron-rich substituents on the aromatic ring were smoothly executed giving the dicyclization products in satisfactory yields (53−79%, **4a**−**4g**). Halogen functional groups F, Cl, Br, also yielded the desired compounds in satisfied yields (61−77%, **4h**−**4m**). Notably, 1-naphthyl or 2-naphthyl methyl ketones could react in this reaction, affording products (**4n**, **4o**) in 67% and 52% yield, respectively. Moreover, electron-deficient

Scheme 2. Scope of Aryl Methyl Ketones[a,b]



[a]1.0 mmol scale. [b]Isolated yield of products **4**.

subatrates were also reactive and provided fused heterocycle products in moderate yields (34−50%, **4p**−**4r**). Gratifyingly, heteroaryl ketones were tolerated under the optimal conditions, leading to the fused heterocycles products (72% and 61%, **4s** and **4t**).

To further examine the generality of this domino process, various arylamines were employed in this iodine-promoted dicyclization reaction, with the results shown in Scheme 3. Arylamines with electron-rich (−OMe, −OEt, $-C(CH_3)_3$, $-CH(CH_3)_2$), halogen (F, Cl, Br, I), or electron-deficient ($-CO_2Et$) substituents at the *para*-position exhibited moderate to good reactivity under the optimized conditions (57−79%, **5a**−**5i**). Furthermore, a range of polysubstituted arylamines (3,5-dimethyl, 2,3-dimethyl, 3,4,5-trimethoxyl) successfully underwent the dicyclization process to deliver the desired products (55−67%, **5j**−**5l**). Unfortunately, other *α*-amino acids were not compatible with this trifunctionalization process. We assume that the desired products are unstable or the in situ generated intermediates of thiazolidine-4-carboxylic acid and 4-hydroxypyrrolidine-2-carboxylic acid might not be compatible in the first cyclization reaction. As for piperidine-2-carboxylic acid, the desired product can be detected by GC-MS in a trace amount.

Further demonstrating the synthetic practicality of this dicyclization process, a 10 mmol scale synthesis of 7-methyl-1-phenyl-3,4-dihydrobenzo[*b*][1,7]naphthyridine (**4a**) was carried out, giving **4a** in 54% yield (Scheme 4a). Next, late oxidative aromatization was conducted on **4a** to obtain a 7-methyl-1-phenylbenzo[*b*][1,7]naphthyridine compound (**7a**) in 87% yield (Scheme 4b).

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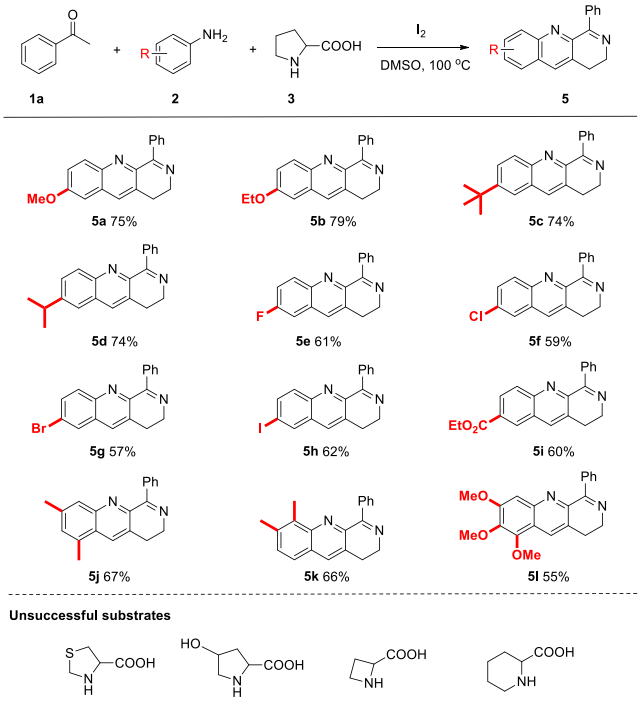
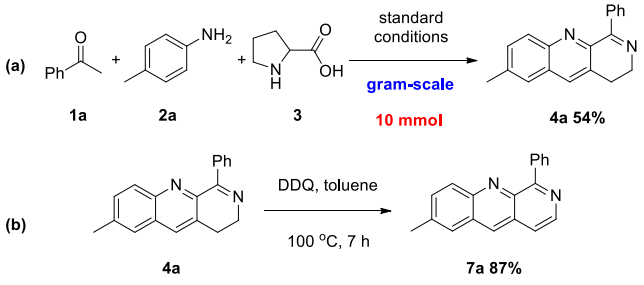
Scheme 3. Scope of Anilines[a,b]



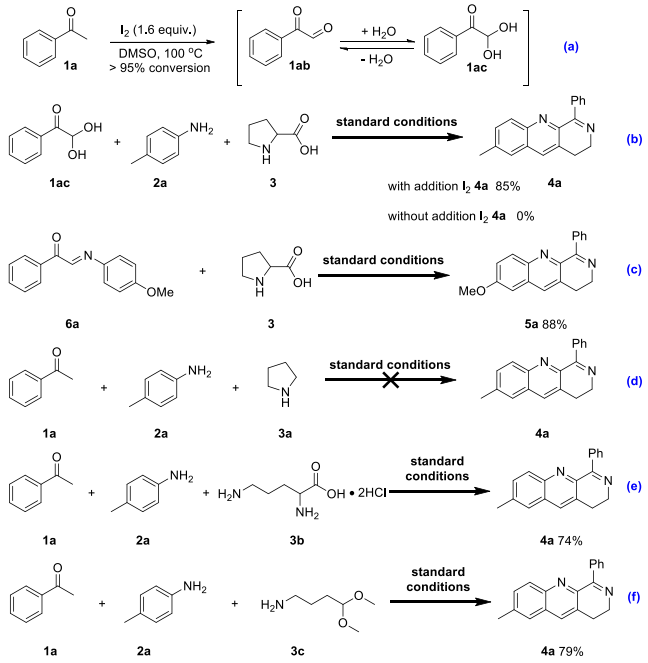
[a]1.0 mmol scale. [b]Isolated yield of products **5**.

Scheme 4. Gram-Scale Experiments and Late Oxidation Aromatization



To gain some insight into the plausible mechanism for this novel consecutive decarboxylation/ring-opening/dicyclization process, a set of control experiments were conducted. Initially, phenylglyoxal **1ab** and hydrated species **1ac** were obtained in quantitative yield when acetophenone (**1a**, 1.0 mmol) was heated with I_2 (1.6 mmol) in DMSO at 100 °C (Scheme 5a). Next, when acetophenone **1a** was replaced with hydrated species **1ac** for the reaction with **2a** and **3** under the optimized conditions, this reaction proceeded smoothly, but without any dicyclization products **4a** obtained in the absence of I_2 (Scheme 5b). As expected, desired product **5a** was obtained in 88% yield when *C*-acylimine **6a** and **3** were mixed under standard conditions (Scheme 5c). These results confirmed that hydrated species **1ac** and *C*-acylimine **6a** were intermediates in this domino reaction and highlighted the vital role of iodine in this multicomponent cascade reaction. However, **3a** did not react smoothly with substrates **1a** and **2a** to afford product **4a** (Scheme 5d). This result implied that **3a** might not be an intermediate in this cascade dicyclization reaction. Inspired by our previous work,[10] we speculated that L-proline might initially undergo catabolism to generate chain intermediate 4-aminobutanal, which would then participate in the cascade

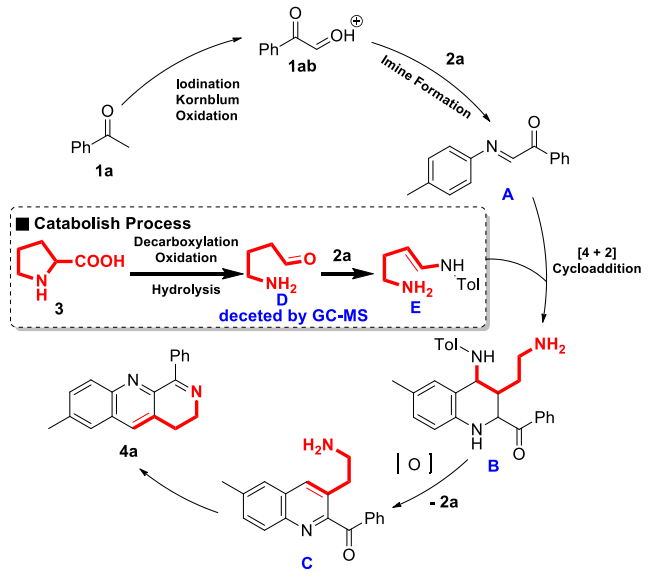
Scheme 5. Control Experiments



cyclization. Fortunately, when **3b** was used as a surrogate of 4-aminobutanal, the desired product was obtained in 74% yield (Scheme 5e). To further verify this hypothesis, desired product **4a** was formed with a yield of 79%, when **3c** was mixed with **1a** and **2a** under standard conditions (Scheme 5f).[11]

On the basis of the above experimental investigation and previous reports,[12] a plausible mechanism for the construction of 3,4-dihydrobenzo[*b*][1,7]naphthyridines was proposed, as shown in Scheme 6. The transformation begins with the formation of phenylglyoxal **1ab** via iodination and Kornblum oxidation. Intermediate **1ab** then undergoes a dehydration reaction with *p*-toluidine **2a** to produce imine intermediate **A**. Meanwhile, a cascade reaction (L-proline catabolism) proceeds through an I_2-triggered sequential decarboxylation, oxidation, and hydrolysis reaction to give ring-opening product **D**

Scheme 6. Proposed Mechanism



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(deceted by GC-MS; see the Supporting Information), which then reacts with **2a** to generate enamine intermediate **E** through dehydration and tautomerization processes. *In situ* generated intermediate **E** and **A** undergo a Povarov-type reaction to afford intermediate **B**, which then undergoes oxidative aromatization and deamination[12a,c] to form **C**. Finally, desired product **4a** is obtained through intramolecular dehydration condensation.

In summary, we have developed an iodine-promoted cascade strategy for the synthesis of 3,4-dihydrobenzo[*b*][1,7]-naphthyridines. This represents the first example of a N−H/α,β-C(sp^3)-trifunctionalization of L-proline via a consecutive decarboxylation/ring-opening/dicyclization process. Furthermore, this novel strategy enriches the reactivity of L-proline. Notably, this study reports an excellent multicomponent bicyclization reaction (MBR) under mild conditions using commercially available starting materials. Further studies toward applications of such N−H/α,β-C(sp^3)-trifunctionalization of L-proline are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01277.

Experimental procedures, product characterizations, crystallographic data for **4a**, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1901642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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