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Synthesis of benzo[*c*][2,7]naphthyridine-6-ones *via* cascade aromatization/C(sp^2)–H amidation of 1,4-dihydropyridines

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ABSTRACT

A $K_2S_2O_8$-mediated cascade dehydrogenative aromatization/intramolecular C(sp^2)–H amidation of 1,4-dihydropyridines is described. This method provides an efficient access to multisubstituted benzo[*c*][2,7]naphthyridine-6-ones in 38–74% yields.

Introduction

Phenanthridinone and its aza-analogues are important tricyclic scaffolds in many natural alkaloids and synthetic products (Fig. 1).[1–3] Among them, benzo[*c*][2,7]naphthyridine-6-one exhibit potent inhibitory activities against ROCK, AAK1, and ALK kinases.[2] Besides, they are key synthetic blocks for amphimedine alkaloid and some anti-malarial agents.[3] Several synthetic methods towards benzo[*c*][2,7] naphthyridine-6-ones have been developed over the past decades. For instance, they were usually constructed through intramolecular nucleophilic substitution of 4-phenyl pyridine derivatives in step-wise or one-pot procedures (Scheme 1a).[2–4] They were also achieved *via* palladium-catalyzed arylation or AIBN/Bu_3SnH-mediated radical cyclization of nicotinamide derivatives (Scheme 1b),[5] Pictet-Spengler cyclization of 2-quinolinones with aromatic aldehydes (Scheme 1c),[6] and CpRuCl-catalyzed cycloaddition of α,ω-diyne with ethyl cyanoformate (Scheme 1d).[7]

Radical C—H functionalization has been broadly employed as a powerful tool in heterocycle synthesis.[8–11] For example, 3,4-benzocoumarins and phenanthridones were efficiently prepared from 2-arylbenzoic acids[9] and amides[10] through intramolecular radical cyclization. And recently, we developed a practical synthesis of 2-quinolinone *via* $K_2S_2O_8$-mediated C(sp^2)–H amidation of Knoevenagel products.[11] On the other hand, oxidative aromatization provides an efficient method for the preparation of arenes and heterocycles.[12–14] In particular, the aromatization of Hantzsch 1,4-dihydropyridines to pyridines were extensively studied.[13,14] Inspired by these reports, and in continuation of our interest in the synthesis of fused pyridine derivatives,[11,15] herein we described an efficient cascade aromatization/C(sp^2)–H amidation of 1,4-dihydropyridines to construct benzo[*c*][2,7]naphthyridine-6-ones (Scheme 1e).

Results and discussion

Initially, 1,4-dihydropyridine **1a** was used as the model substrate to explore and optimize the reaction conditions. When **1a** was treated with 3 equiv of $K_2S_2O_8$ in CH_3CN/H_2O (1:1, v/v) under reflux (80 °C, oil bath temperature) for 2 h, the desired product **2a** was isolated in 57% yield (Table 1, entry 1). Comparable yields were obtained when $Na_2S_2O_8$ or $(NH_4)_2S_2O_8$ was used (Table 1, entries 2 and 3). However, replacing $K_2S_2O_8$ with other oxidants including $CuCl_2$, Ag_2O, ceric ammonium nitrate (CAN), *tert*-butyl hydroperoxide (TBHP), and H_2O_2, failed to give the desired product (Table 1, entries 4–8). Persulfate was a strong oxidant with a high redox potential of 2.01 V,[14f] which might make it an effective oxidant for this cascade reaction. Then, several solvents were screened. The CH_3CN/H_2O mixture was found to be superior to other solvent systems, such as acetone/H_2O, THF/H_2O, and

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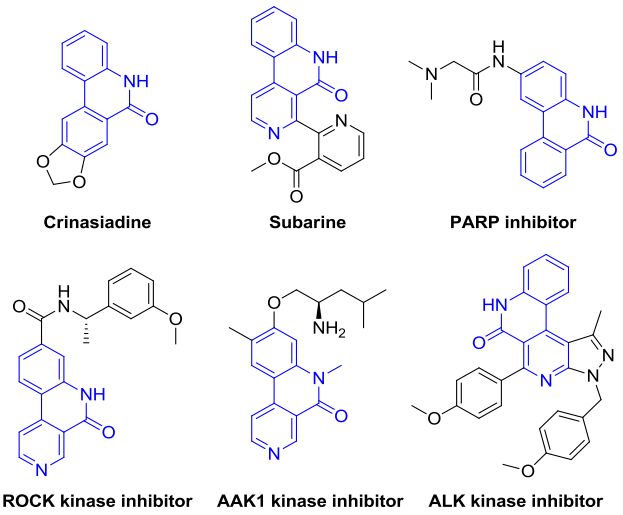
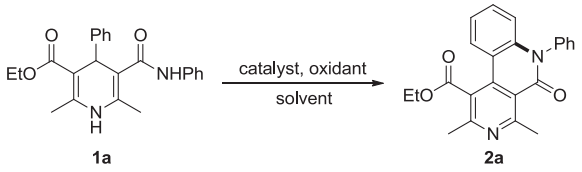


Fig. 1. Representative examples of phenanthridinones and benzo[*c*][2,7]naphthyridine-6-ones.

DMSO/H_2O (Table 1, entries 9–11). Furthermore, the ratio of CH_3CN to H_2O was examined (Table 1, 12–15), and the results indicated that CH_3CN/H_2O (2:1, v/v) was the best choice (65% yield, Table 1, entry 13). When the reaction temperature was decreased to 50 °C, no desired product was observed (Table 1, entry 16). Besides, the use of $AgNO_3$ or CuCl as a catalyst did not improve the yield (Table 1, entries 17 and 18).

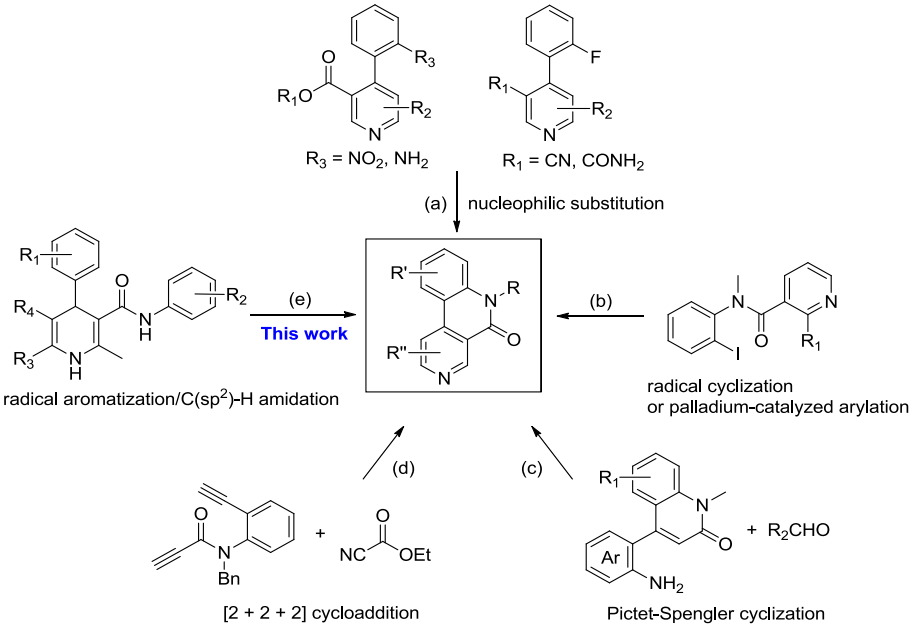
With the optimized conditions in hand (Table 1, entry 13), the scope of the reaction was investigated, and the results were shown in Table 2. First, dihydropyridines **1b**–**k** with a substituted phenyl group at the C-4 position were examined. Substituents at the *para*-position (Me, OMe, F, Cl, Br, CF_3) and *meta*-position (Me, OMe, Cl) of the phenyl ring were tolerated, delivering products **2b**–**k** in 38–74% yields. Among them, a *p*-Me substituent (**1b**) was beneficial to the reaction, while a strong electron-donating (*p*-OMe) or electron-withdrawing (*p*-CF_3) group led to a much lower yield. The C—H amidation exhibited high regioselectivity for substrates **1h**–**k**, which occurred at the less hindered site. Probably due to the steric hindrance effect, substrates with an *ortho*-substituent of the phenyl ring failed to yield the desired products (not shown). Then, dihydropyridines **1l**–**r** bearing a substituted aniline moiety were employed. Substrates with a Me (**1l**, **1o**) or Cl (**1m**, **1q**) group

Table 1
Optimization of reaction conditions.[a]



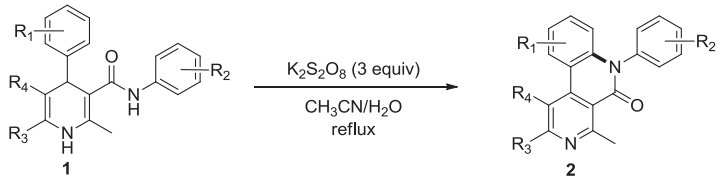
Entry	Oxidant	Solvent	Time (h)	Yield[b] (%)
1	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	2	57
2	$Na_2S_2O_8$	CH_3CN/H_2O (1:1)	2	56
3	$(NH_4)_2S_2O_8$	CH_3CN/H_2O (1:1)	2	53
4	$CuCl_2$	CH_3CN/H_2O (1:1)	2	0
5	Ag_2O	CH_3CN/H_2O (1:1)	2	0
6	CAN	CH_3CN/H_2O (1:1)	2	0
7	TBHP	CH_3CN/H_2O (1:1)	2	0
8	H_2O_2	CH_3CN/H_2O (1:1)	2	0
9	$K_2S_2O_8$	Acetone/H_2O (1:1)	2	23
10	$K_2S_2O_8$	THF/H_2O (1:1)	2	0
11	$K_2S_2O_8$	DMSO/H_2O (1:1)	2	49
12	$K_2S_2O_8$	CH_3CN/H_2O (1:2)	2	52
13	$K_2S_2O_8$	CH_3CN/H_2O (2:1)	1.5	65
14	$K_2S_2O_8$	CH_3CN/H_2O (4:1)	1.5	63
15	$K_2S_2O_8$	CH_3CN/H_2O (8:1)	4	24
16[c]	$K_2S_2O_8$	CH_3CN/H_2O (2:1)	4	0
17[d]	$K_2S_2O_8$	CH_3CN/H_2O (2:1)	1.5	62
18[e]	$K_2S_2O_8$	CH_3CN/H_2O (2:1)	1.5	55

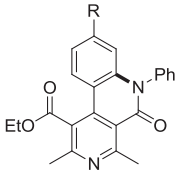
[a] Reaction conditions: **1a** (1 mmol), oxidant (3 mmol), solvent (30 mL), 80 °C (oil bath).
[b] Isolated yields.
[c] Reaction occurred at 50 °C (oil bath).
[d] CuCl (10% mol) was added.
[e] $AgNO_3$ (10% mol) was added.



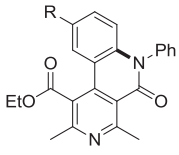
Scheme 1. Synthetic approaches towards benzo[*c*][2,7]naphthyridine-6-ones.

Table 2
Synthesis of benzo[*c*][2,7]naphthyridine-6-ones 2 from 1,4-dihydropyridines **1**.[a,b]

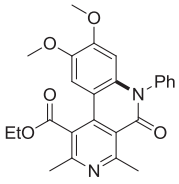




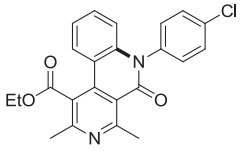
2a, R = H, 65%, 1.5 h
2b, R = Me, 74%, 1 h
2c, R = OMe, 38%, 2 h
2d, R = F, 60%, 1.5 h
2e, R = Cl, 53%, 2 h
2f, R = Br, 51%, 2 h
2g, R = CF_3, 42%, 3 h



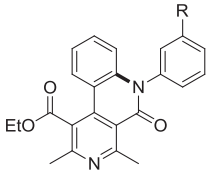
2h, R = Me, 63%, 2 h
2i, R = OMe, 54%, 2 h
2j, R = Cl, 58%, 2 h



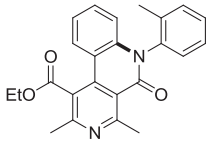
2k, 49%, 2 h



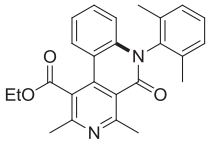
2l, 67%, 1.5 h



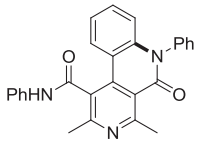
2m, R = Me, 71%, 1 h
2n, R = OMe, 55%, 2 h
2o, R = Cl, 73%, 1 h
2p, R = NO_2, 47%, 2 h



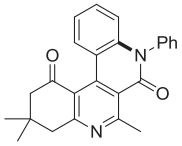
2q, 68%, 1 h



2r, 65%, 1 h



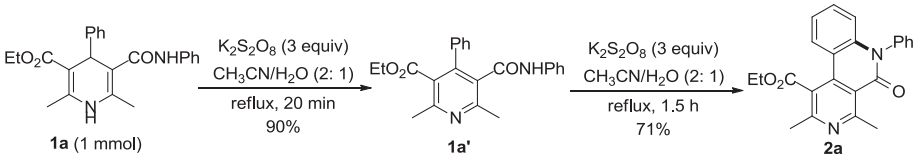
2s, 53%, 1.5 h



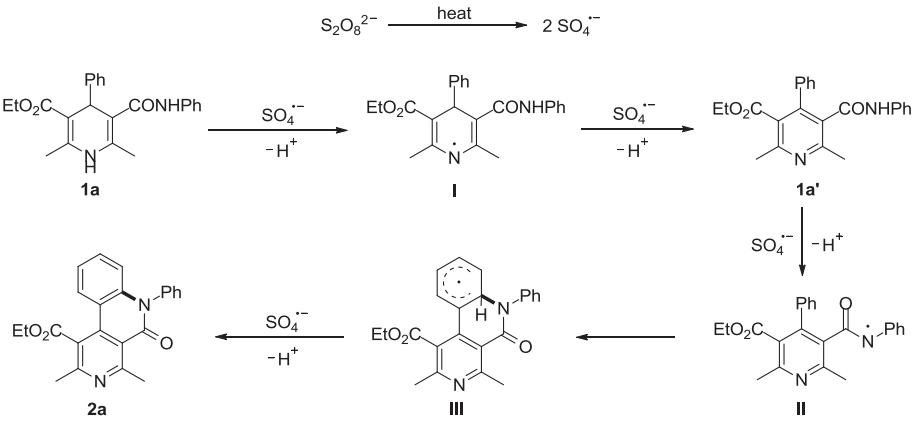
2t, 46%, 1.5 h

[a] Reaction conditions: **1** (1 mmol), $K_2S_2O_8$ (3 mmol), CH_3CN/H_2O (2:1, 30 mL), reflux (80 °C, oil bath).
[b] Isolated yields.

underwent the reaction smoothly, affording corresponding products in 67–73% yields. In contrast, the presence of an *m*-OCH_3 (**1n**) or *m*-NO_2 (**1p**) group reduced the reactivity, which resulted in a longer reaction time and lower yield. Notably, the reaction of *ortho*-dimethyl substituted substrate **1r** proceeded well to give product **2r** in 65% yield. Moreover, symmetric substrate **1s** containing two amide groups was also amenable to this protocol, affording **2s** as the main product. When polyhydroquinoline **1t** was used as a substrate, tetracyclic product **2t** was obtained in 46% yield.



Scheme 2. Preparation of **2a** in a two-step manner.



Scheme 3. Plausible reaction mechanism.

In order to investigate the mechanism of this reaction, 2 equiv of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the reaction of **1a** under standard reaction conditions. The desired product **2a** was not observed, indicating that the reaction might involve a radical mechanism. In addition, **2a** was prepared in a two-step manner (Scheme 2). Under standard reaction conditions, **1a** was rapidly converted into pyridine intermediate **1a′** in 90% yield. And the cyclization of **1a′** proceeded smoothly under the same conditions to afford **2a** in 71% yield.

On the basis of the experimental results and previous reports, a possible mechanism for this transformation is proposed in Scheme 3. Initially, sulfate radical anion is generated by thermal decomposition of $K_2S_2O_8$.[9–11] Dihydropyridine **1a** reacts with sulfate radical anion to give radical intermediate **I** *via* single electron transfer/deprotonation or hydrogen-atom abstraction mechanism. Further oxidation of radical **I** forms the aromatized intermediate **1a′**.[14b,d] Then, intermediate **1a'** is converted into amidyl radical **II** in the presence of sulfate radical anion, which undergoes intramolecular cyclization to give aryl radical **III**.[9–11] Finally, product **2a** is obtained by oxidation of intermediate **III**.

In summary, we have developed an efficient approach to benzo[*c*][2,7]naphthyridine-6-ones from 1,4-dihydropyridines using $K_2S_2O_8$ as the oxidant under catalyst-free conditions. The transformation involves a cascade aromatization/C(sp^2)–H amidation process. The advantages of the present protocol include readily accessible starting materials, broad substrate scope, short reaction time, and easy operation.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.06.009.

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