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Tandem Oxidative Ring-Opening/Cyclization Reaction in Seconds in Open Atmosphere for the Synthesis of 1-Tetralones in Water−Acetonitrile

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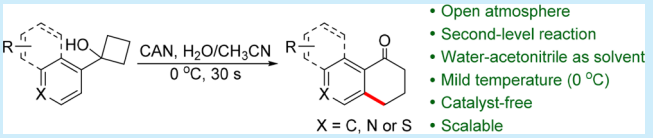
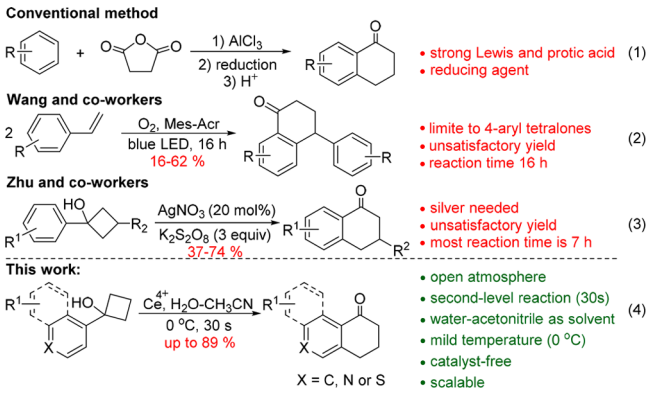
Supporting Information

ABSTRACT: A mild and practical tandem oxidative ring-opening/cyclization reaction mediated by Ce^{4+} for the synthesis of 1-tetralones is presented. This rapid transformation was completed within 30 s and conducted in an open reactor at 0 °C in a water−acetonitrile mixture. Various cyclobutanol derivatives are transformed into desired products in good to high yields, and this reaction can be easily scaled up to the gram scale.



The tetralone structural motif exists widely in natural products and other bioactive molecules.[1] Tetralone is also commonly used as an organic building block in the synthesis of complex compounds.[2] However, the development of synthetic strategies to achieve 1-tetralones is still in an early stage.[3] The most conventional method for synthesizing 1-tetralones is the Haworth reaction.[4] This approach is a multistep process containing Friedel−Crafts acylation and reduction, followed by Friedel−Crafts acylation (Scheme 1, eq 1). Usually, a large amount of strong Lewis acid, protic acid, and reducing agent are required in these transformations. In addition, the application scope of the procedure is limited mainly by the poor compatibility with the sensitive functional groups in the harsh reaction conditions. Recently, Wang and co-workers have reported a photocatalytic strategy for obtaining 4-aryl tetralones (Scheme 1, eq 2).[5] This method is limited to obtain 4-aryl tetralones and results in a poor yield in most cases. A long reaction time was required to complete the transformations. A silver-catalyzed ring-opening reaction for achieving 1-tetralones was developed by Zhu and co-workers (Scheme 1, eq 3).[6a] However, the yield of 1-tetralones is still unsatisfactory with only up to 40−60%. The reaction time is also greater than or equal to 7 h in most cases. Similarly, palladium- or copper-catalyzed oxidative ring-opening/cyclization reactions of cyclobutanol derivatives were reported.[6b,c] The use of a noble metal catalyst[6b] or expensive oxidant[6c] increased the synthesis cost. All the above-mentioned methods exhibit a common limitation that an electron-withdrawing group substituted substrate could not be applied in the transformations or only a poor yield can be obtained (Scheme 1, eqs 1−3). Therefore, a general strategy for achieving 1-tetralones with extensive functionality tolerance is desired. Herein, we described a Ce(IV)-mediated oxidative ring-opening reaction of cyclobutanol for achieving 1-tetralones (Scheme 1, eq 4). This transformation is very quick and can finish within 30 s. Additionally, the operation is rather simple because the reaction is conducted in an open atmosphere at 0 °C.

Scheme 1. Strategies for the Synthesis of 1-Tetralones



Our investigation commenced with the ring-opening reaction of 1-(naphthalen-1-yl)cyclobutan-1-ol (**1a**) using $Ce(NH_4)_2(NO_3)_6$(2.5 equiv) (CAN) as an initiator and water/acetonitrile (1:1) as solvent at 0 °C in an open tube for 30 s (Table 1). The desired cyclization product 2,3-dihydrophenanthren-4(1*H*)-one (**2a**) was delightedly achieved at 68% yield (entry 1). Encouraged by this result, the reaction temperature and solvents were checked (entries 1−11). The lower reaction temperature at 0 °C is found to be the most suitable (entry 1). Furthermore, the reaction provides the best result in the water/acetonitrile = 1:1 (v/v) solvent mixture. We reduced the amount of mixture solvents slightly to 1 mL to

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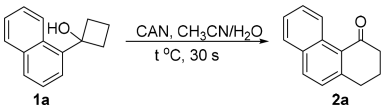
Table 1. Selected Optimization Results[a]



entry	t/°C	solvent/mL	CAN/equiv	yield/%
1	0	CH_3CN/H_2O = 0.8:0.8	2.5	68
2	9	CH_3CN/H_2O = 0.8:0.8	2.5	50
3	30	CH_3CN/H_2O = 0.8:0.8	2.5	30
4	0	H_2O = 1	2.5	35
5	0	CH_3CN = 1	2.5	28
6	0	DCM/H_2O = 0.5:0.5	2.5	0
7	0	THF/H_2O = 0.5:0.5	2.5	30
8	0	$Toluene/H_2O$ = 0.5:0.5	2.5	0
9	0	CH_3CN/H_2O = 0.5:0.5	2.5	70
10	0	CH_3CN/H_2O = 0.8:0.4	2.5	66
11	0	CH_3CN/H_2O = 0.4:0.8	2.5	25
12	0	CH_3CN/H_2O = 0.5:0.5	2	46
13	0	CH_3CN/H_2O = 0.5:0.5	3.0	44
14[b]	0	CH_3CN/H_2O = 0.5:0.5	2.5	69
15[c]	0	CH_3CN/H_2O = 0.5:0.5	2.5	56

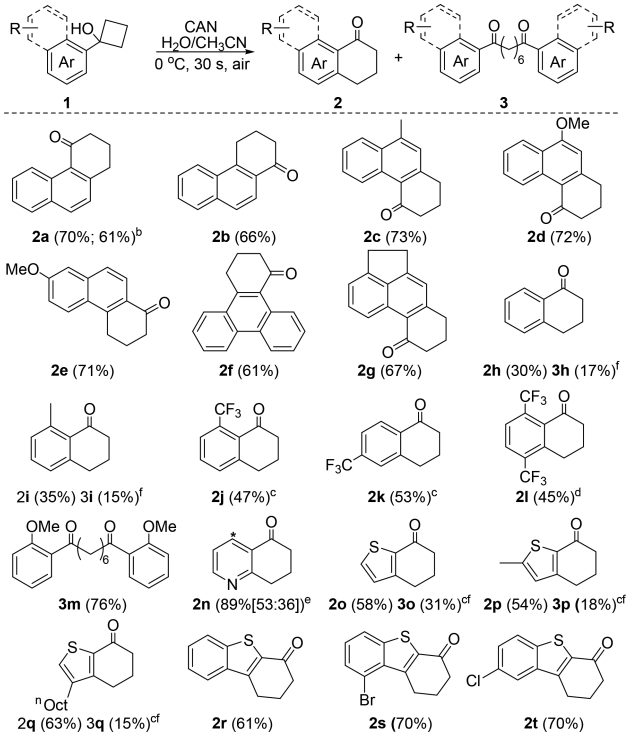
[a]Unless otherwise noted, all reactions were conducted at 0.1 mmol scale with CAN in an open tube for 30 s. Isolated yields were given. [b]Reaction time = 2 min. [c]Reaction time = 10 min.

achieve an improved yield of 70% (entry 9). The amount of CAN was then changed; notably, such change does not improve the transformation (entries 12−13). Finally, the reaction time was extended in minutes. The result appears not to be beneficial to the reaction (entries 14−15).

The scope of substrate was then examined using the reliable ring-opening reaction protocol (Scheme 2). Substrates based on naphthalene derivatives, including α- or β-naphthyl-substituted and phenanthryl substituted cyclobutanol **2a−g**, showed good yields. In particular, when **1b** and **1e** were used, the cyclization reaction would occur at the α-position. We speculated that the conjugated system of the polyclinic aromatic is beneficial to stabilize a free radical intermediate. However, in the case of using phenyl substituted substrates, only moderate yields are observed (**2h−l**). And when substrates that were unsubstituted or phenyl substituted with an electron-donating group were used, the cyclization products and homocoupling products were found together (**2h,i**). As a comparative example, 1-(2-methoxyphenyl)cyclobutan-1-ol (**1m**) was tested. Nearly no desired product is detected; however, a good yield of homocoupling product **3m** is formed.[7] Heteroaromatic substrates also could be converted to the desired product with good yields (**2n−t**). When pyridine-substituted substrate **1n** was used, the cyclization would occur at the ortho- and para- positions and yielded the desired product with 53% and 36% yields, respectively. It may be caused by the little difference of electron density with these two positions. When thiophene type substrates were used (**1o−q**), the homocoupling reaction also occurred as the side reaction. However, in the case of benzthiophene type substrates **1r−t**, the cyclization products would be found as the sole product. Significantly, the gram-scale reaction of **1a** was conducted under the unchanged reaction conditions and a comparable yield (61%) was achieved within 60 s.

From an ordinary perspective, this reaction is considered as a radical process. To verify this assumption, the control experiments of the tandem ring-opening/cyclization reaction

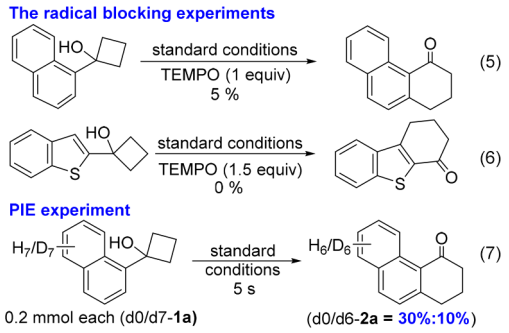
Scheme 2. Scope of Ring-Opening Reaction of Cyclobutanol Derivatives[a]



[a]Unless otherwise noted, all reactions were conducted at 0.2 mmol scale with 2.5 equiv of CAN in CH_3CN/H_2O = 1 mL/1 mL at 0 °C in an open tube for 30 s. [b]Gram-scale reaction; all reactants and solvents are scaled up; reaction time is 60 s. [c]Reaction temperature is 60 °C. [d]Reaction temperature is 90 °C. [e]Reaction time is 10 min. [f]The amount of solvents is 5 times.

of cyclobutanol were conducted (Scheme 3, eq 5). The results show that the transformation is nearly completely blocked by

Scheme 3. Experiments for Mechanistic Studies



adding 1−1.5 equiv of TEMPO. Subsequently, in determining the rate-limiting step of this transformation, the deuterium isotope effect was measured (Scheme 3, eq 6). Therefore, substrate d7-**1a** was synthesized[8] and submitted together with **1a** to the Ce^{4+}-mediated ring-opening/cyclization reaction. After 5 s, the reaction was stopped and the mixture was determined by GC-MS. An intermolecular competitive product isotope effect (PIE) of 3.0 indicates that deprotonation is probably the rate-determining step in the reaction (Scheme 3, eq 7).

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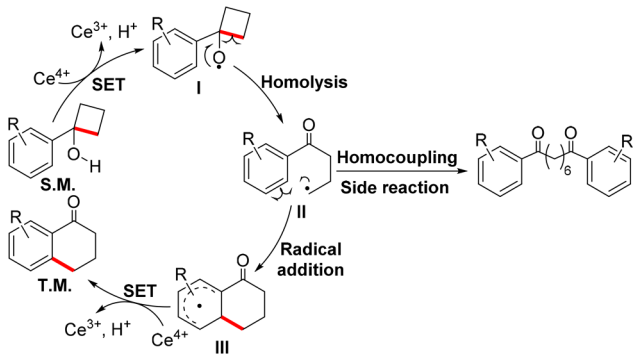
On the basis of these results, a tentative mechanism was proposed in Scheme 4. Initially, the oxygen free radical

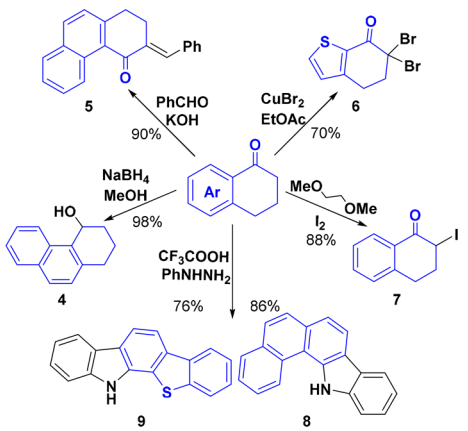
Scheme 4. Tentative Mechanism for the Tandem Oxidative Ring-Opening/Cyclization Reaction of 1-Substituted-Cyclobutanol



intermediate **I** was formed by a single electron transfer (SET) process mediated by CAN. Immediately, with the ring tension release as the driving force, hemolysis of C−C occurred and the carbon free radical **II** was generated. Subsequently, the free radical addition reaction was conducted, and the delocalized radical intermediate **III** formed. Then, another SET process mediated by CAN occurred such that the aromatization product was achieved.

Finally, the derivatization of synthesized products is shown in Scheme 5 (see Supporting Information for details). The

Scheme 5. Derivatization of the Cyclization Product



reduction of 1-tetralone using $NaBH_4$ as the reductant was performed; an excellent yield of 98% is achieved (**4**).[9] The aldol condensation of the 1-tetralone derivative with benzaldehyde produces a good yield of α,β-unsaturated ketone **5**.[10] Treatment of the synthetic ketones with different halogen reagents leads to the α-halogenated ketones **6** and **7** in 70% and 88% yields, respectively.[11,12] Finally, carbazole derivatives **8** and **9** were also achieved via Fischer indole synthesis with high yields of 86% and 76%, respectively.[13]

In summary, a practical method for the catalyst-free tandem oxidative ring-opening/cyclization reaction mediated by Ce^{4+} for the synthesis of 1-tetralones was described. The success of this transformation is attributed to control of the reaction time and temperature. This strategy possesses the advantages of rapid transformation, operation simplicity, and mild reaction conditions. In addition, this strategy can be easily scaled up to gram-scale, and the desired products can further undergo diverse transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03246.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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