Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Development of $Pd(OAc)_2$-catalyzed tandem oxidation of C—N, C—C, and C(sp^3)–H bonds: Concise synthesis of 1-aroylisoquinoline, oxoaporphine, and 8-oxyprotoberberine alkaloids

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ARTICLE INFO

Article history:
Received 10 September 2020
Revised 19 October 2020
Accepted 22 October 2020
Available online xxxx

Keywords:
Catalytic tandem oxidation
Papaveraldine
Pulcheotine A
Liriodenine
8-Oxypseudopalmatine

ABSTRACT

A catalytic tandem oxidation of C—N, C—C, and C(sp^3)–H bonds is developed. This tandem oxidation is applied to two-step total syntheses of papaveraldine and pulcheotine A. Additionally, the total synthesis of liriodenine is achieved in six steps from homopiperonyl alcohol and 2-bromophenylacetonitrile by applying this catalytic tandem oxidation. Moreover, the direct conversion of xylopinine to 8-oxypseudopalmatine in a 76% yield demonstrates the versatility of this catalytic reaction.

Introduction

Nitrogen containing heterocyclic compounds are potential footholds in drug syntheses [1]. Therefore, new synthetic protocols to assemble diverse heterocyclic compounds, including nitrogen atoms, are being developed [2]. Among heterocyclic compounds, bioactive molecules bearing a quinoline or an isoquinoline skeleton have attracted attention as drug candidates [3]. There are roughly two ways to synthesize aromatic heterocyclic compounds: a stepwise approach using multi-components and an oxidation method of saturated multi-cyclic compounds. Our research focuses on the latter methodology, and we searched previous synthetic examples of quinoline and isoquinoline scaffolds for inspiration. Aerobic dehydrogenations of nitrogen heterocycles with or without catalytic transition metals have been studied for many years (Scheme 1, eqs. 1–3) [4]. 1,2,3,4-Tetrahydroquinolines are catalytically transformed into the corresponding quinolines using various transition metals such as Mn, Cu, Fe, Co, or Ru in the presence of oxygen. On the other hand, catalytic dehydrogenations of 1,2,3,4-tetrahydroisoquinolines produce isoquinolines by means of Cu, Co, or Os, etc. Additionally, an oxidation reaction of a benzyl group substituted on an aromatic heterocyclic compound to a benzoyl group has been reported. For instance, 2-benzylpyridines are easily oxidized by Fe, Co, or halogens (Kornblum-type oxidation), etc. to give aryl heteroaryl ketones. However, the tandem catalytic oxidation of C—N, C—C, and C(sp^3)–H bonds is not well researched.

Consequently, we planned a catalytic one-pot conversion of 1-benzyl-1,2,3,4-tetrahydroisoquinolines **1** into 1-aroylisoquinolines **2** (Scheme 1, eq. 4). Namely, we anticipated that 1-aroylisoquinolines such as papaveraldine (**3**) and pulcheotine A (**4**) could be synthesized from easily obtainable precursors such as **1** by a tandem oxidation of the bonds in **1** indicated by the arrows, as shown in Scheme 1 (eq. 4). Additionally, this protocol should assemble oxoaporphines such as liriodenine (**5**) from the corre-sponding perhydrodibenzoquinoline (structure with a dotted line in Scheme 1, eq. 4) by (Fig. 1).

We recently reported a catalytic one-pot preparation of anthranilates from acyclic unsaturated β-enamino esters [5]. During our research, we found that methyl 2-(1H-pyrrol-1-yl)benzoate (**7**) was directly generated from methyl (*E*)-3-(pyrrolidin-1-yl) hepta-2,6-dienoate (**6**) in the presence of a catalytic amount of $Pd(OAc)_2$ (Scheme 2). In this transformation, cycloaromatization was accompanied by sequential dehydrogenation of a pyrrolidine ring in **6** to form pyrrolylbenzoate **7**.

We conducted this study to confirm our hypothesis that the tandem reaction (**6** → **7**) would be applicable to the one-pot transformation (**1** → **2**).

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https://doi.org/10.1016/j.tetlet.2020.152599
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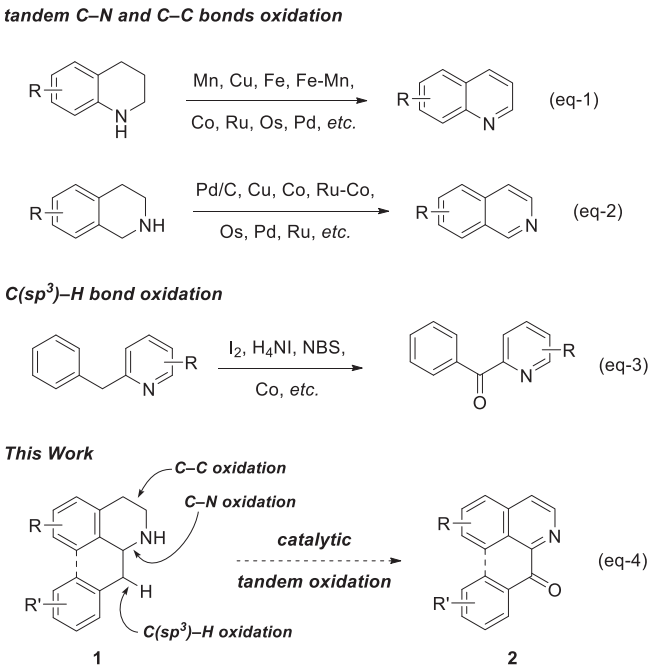


Scheme 1. Various aerobic oxidation of *N*-heterocycles.

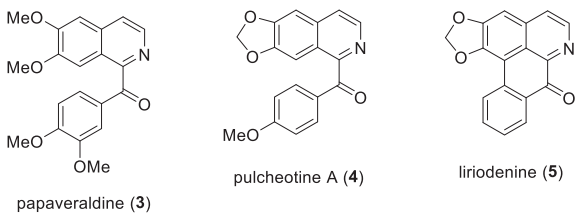
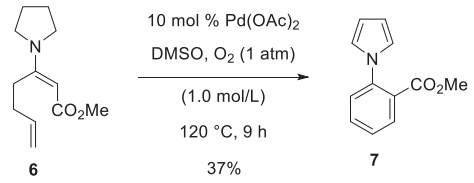


Fig. 1. Structures of papaveraldine (**3**), pulcheotine A (**4**), and liriodenine (**5**).

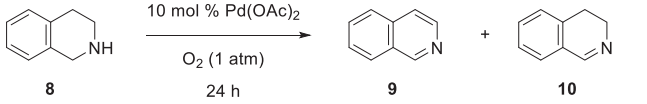


Scheme 2. $Pd(OAc)_2$-catalyzed tandem cycloaromatization-dehydrogenation.

Results and discussion

As the first step, we examined the tandem oxidation of C—N and C—C bonds using 1,2,3,4-tetrahydroisoquinoline (**8**) as a model compound. Applying the reaction conditions in Scheme 2 to the tandem oxidation of **8** gave 3,4-dihydroisoquinoline (**10**) in 9% yield (Table 1, entry 1). Extending the reaction time to 36 h did not improve the chemical yield of **10**. However, increasing the reaction temperature to 120 °C provided desired **9** in 21% yield together with **10** (26%) (Table 1, entry 2). This result suggested that imine **10** is a precursor of isoquinoline (**9**). Next we investigated the solvent effect. The reaction did not proceed when THF, MeCN, or dichloromethane (DCM) was used as a solvent. However, in the case of toluene, a small amount of **9** was obtained even at 60 °C (Table 1, entry 3). It should be noted that compared to using DMSO as the solvent, the reaction in toluene was clearer, and the crude ^1H NMR spectrum did not show any byproducts. Increasing the reaction temperature to 120 °C improved the total yield of **9** and **10**

Table 1
Catalytic tandem oxidation of C—N and C—C bonds in **8**.[2]



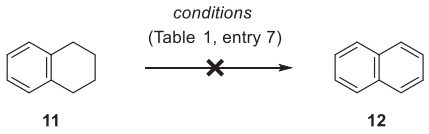
Entry	Oxidant (equiv)	Conc (mol/L)	Solvent	Temp (°C)	Yield (%)	
					9	**10**
1	none	1.0	DMSO	60	0	9
2	none	1.0	DMSO	120	21	26
3	none	1.0	toluene	60	trace	12
4	none	1.0	toluene	120	26	52
5	$CuCl_2$ (2.0)	1.0	toluene	120	trace	27[a]
6	$Cu(OAc)_2{\cdot}H_2O$ (0.2)	1.0	toluene	120	60	15
7[b,c]	$Cu(OAc)_2$ (0.2)	1.0	toluene	120	70	9
8	$Cu(OAc)_2$ (1.0)	1.0	toluene	120	22	45
9	$Cu(OAc)_2$ (0.2)	1.0	toluene	180	39	0
10	$Cu(OAc)_2$ (0.2)	2.5	toluene	120	46	9
11	$Cu(OAc)_2$ (0.2)	0.3	toluene	120	47	33

[a] Starting material 8 was also isolated in a 67% yield.
[b] When the reaction was conducted under N_2 instead of O_2, only *N*-acetyl-1,2,3,4-tetrahydroisoquinoline was obtained in a 27% yield.
[c] When the reaction was conducted only using 10 mol % $Cu(OAc)_2$, **10** was isolated in a 66% yield together with 9 (3%).

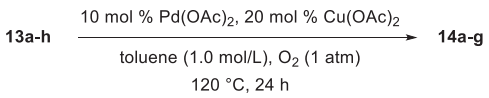
(Table 1, entry 4). Then we evaluated the efficient conversion of **10** into **9** using different oxidants. Employing 2 equivalents of DDQ as an oxidizing agent did not form **9** or **10**. Similarly, the addition of $CuCl_2$ did not improve the yield (Table 1, entry 5). On the other hand, the presence of $Cu(OAc)_2{\cdot}H_2O$ drastically enhanced the yield (Table 1, entry 6) [6]. The best isolated yield (70%) was obtained when the reaction was performed at 120 °C in toluene in the presence of 10 mol% $Pd(OAc)_2$ using 20 mol% $Cu(OAc)_2$ as an oxidant (Table 1, entry 7). Conducting the reaction in an atmosphere of nitrogen instead of oxygen gave only *N*-acetyl-1,2,3,4-tetrahydroisoquinoline in a 27% yield. In addition, using 10 mol% $Cu(OAc)_2$ provided mostly **10**. Increasing $Cu(OAc)_2$ to 1 equivalent decreased the production ratio of **9** (Table 1, entry 8). Raising the reaction temperature to 180 °C produced only **9**, but the isolated yield was 39% (Table 1, entry 9). The yield of product **9** was not affected by the concentration of substrate **8** (Table 1, entries 10 and 11).

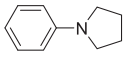
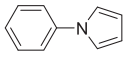
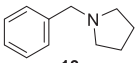
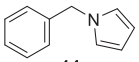
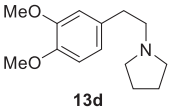
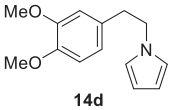
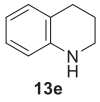
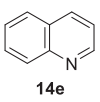
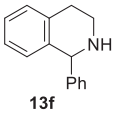
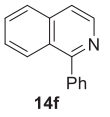
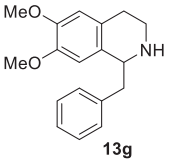
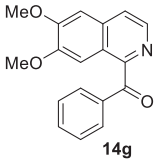
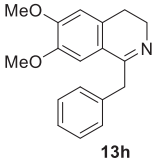
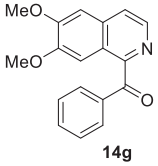
The reaction conditions shown in Table 1, entry 7 were applied to the oxidative conversion of 1,2,3,4-tetrahydronaphthalene (**11**) to naphthalene (**12**). The reaction did not proceed at all, and **11** was recovered intact. Hence, this oxidation reaction cannot be used for dehydrogenation of hydrocarbon compounds (Scheme 3).

To investigate the versatility of the catalytic tandem oxidation, a C—C bond oxidation and a tandem C—N and C—C bonds oxidation in *N*-containing heterocycles were examined (Scheme 4). Indoline (**13a**) was converted to indole (**14a**) in a 68% yield, and 1-phenylpyrrolidine (**13b**) was successively oxidized to afford 1-phenyl-1H-pyrrole (**14b**) in a 76% yield. To complete oxidation reactions of **13c** and **13d** in 24 h, 99.98% pure $Pd(OAc)_2$ was used in both oxidations to give **14c** and **14d** in isolated yields of 70% and 74%, respectively. The tandem oxidation reaction of C—N and C—C bonds in the same molecule does not depend on the substrates and tends to proceed smoothly. For example, 1,2,3,4-tetrahydroquinoline (**13e**) was transformed into quinoline (**14e**) in a 76% yield. 1-Phenylperhydroisoquinoline **13f** was also oxidized to furnish 1-phenylquinoline (**14f**) in a 62% yield. In the case of **13f**, the reaction was completed by changing the solvent to DMF and increasing the reaction temperature to 150 °C. We applied the above-mentioned catalytic oxidation to a tandem oxidation of C—N, C—C, and C(sp^3)-H bonds built-in the same molecule. When



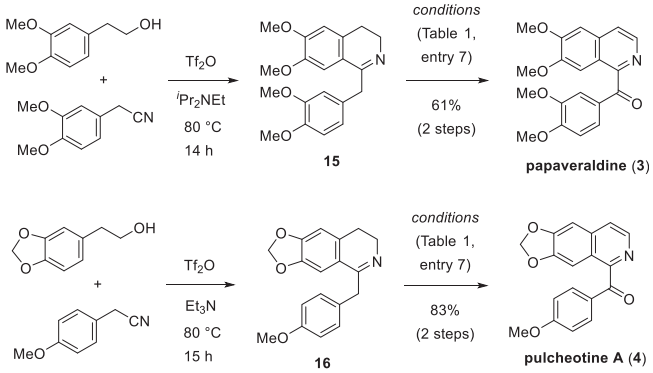
Scheme 3. Transformational examination of **11**.



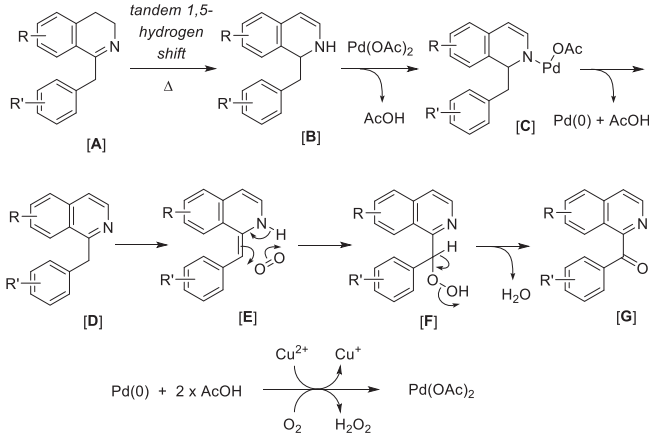
substrate	product	isolated yield (%)
C–C bond oxidation		
 **13a**	 **14a**	68
 **13b**	 **14b**	76
 **13c**	 **14c**	70[a]
 **13d**	 **14d**	74[a]
tandem C–N and C–C bonds oxidation		
 **13e**	 **14e**	76
 **13f**	 **14f**	62[b]
tandem C–N, C–N, and C(sp³)–H bonds oxidation		
 **13g**	 **14g**	42[a]
tandem C–C and C(sp³)–H bonds oxidation		
 **13h**	 **14g**	78

Scheme 4. Catalytic C—N, C—C, and C(sp^3)–H bonds oxidation of **13a–h**.

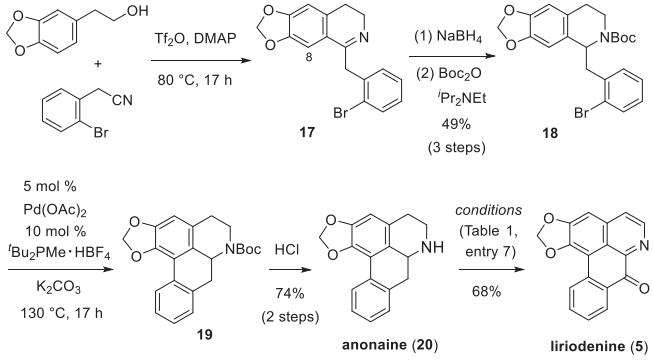
1-benzylperhydroisoquinoline **13g** was subjected to the tandem oxidation, desired 1-benzoylisoquinoline **14g** was obtained in a 42% yield. Changing the reaction substrate to 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**13h**) increased the chemical yield of the tandem oxidation to 78%. Although there is not experimental evidence that the relatively bulky benzyl group in the case



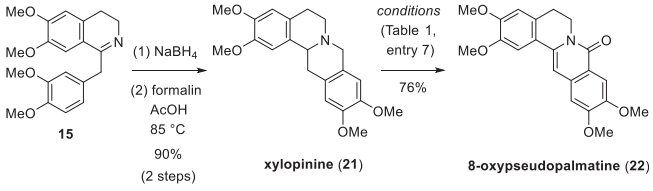
Scheme 5. Two-step total synthesis of natural alkaloids **3** and **4**.



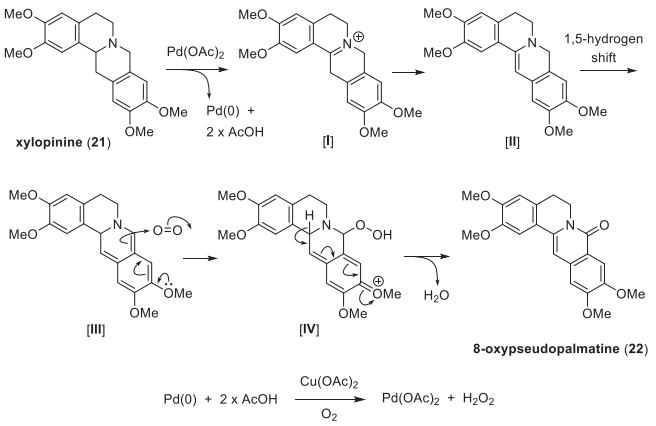
Scheme 6. Plausible reaction mechanism.



Scheme 7. Total synthesis of liriodenine (**5**).



Scheme 8. Total synthesis of two 8-oxoprotoberberine alkaloids.



Scheme 9. Plausible reaction mechanism.

of **13g** prevented the initial bond formation between the nitrogen atom in the substrate and $Pd(OAc)_2$, the isolated yield of **14g** dropped to 42%. Since imines such as **13h** can be synthesized in a single step using a Bischler-Napieralski type reaction, the total synthesis of various of 1-aroylisoquinolines should be assembled in two steps according to the present protocol.

Next we employed the present catalytic tandem oxidation to realize the two-step syntheses of papaveraldine (**3**) and pulcheotine A (**4**). For the key reaction, requisite imine **15** was prepared from 2-(3,4-dimethoxyphenyl)ethanol and 2-(3,4-dimethoxyphenyl)acetonitrile using Hu's protocol [7]. Crude imine **15** was subjected to the catalytic tandem oxidation to give papaveraldine (**3**) in a 61% overall yield. Pulcheotine A (**4**) was similarly synthesized from 2-(3,4-dimethoxyphenyl)ethanol and 2-(4-methoxyphenyl)acetonitrile *via* imine **16** with a total yield of 83% (Scheme 5). The spectral data of synthetic papaveraldine (**3**) [8] and pulcheotine A (**4**) [8] were identical with those reported.

Although we did not attempt to experimentally verify the reaction mechanism, Scheme 6 depicts a plausible reaction pathway. Under thermal conditions, imine **A** was isomerized to **B** *via* sequential 1,5-hydrogen shift (tautomerization). Amine **B** was oxidized to afford 1-benzylisoquinoline **D** by $Pd(OAc)_2$ through intermediate **C**. After isomerization of **D** to enamine **E**, oxygen was caught to produce peroxide **F**. Finally, dehydration from peroxide **F** produced 1-aroylisoquinoline **G**. The Pd(0) species could be oxidized to Pd $(OAc)_2$ by oxygen in the presence of $Cu(OAc)_2$ (Scheme 6) [9].

Then we aimed for the total synthesis of liriodenine (**5**) utilizing this catalytic tandem oxidation. Imine **17** was prepared from homopiperonyl alcohol and 2-bromophenylacetonitrile as previously reported. At this point, an intramolecular coupling reaction between the 8-position carbon and a bromobenzene on the side chain was conducted. However, the desired product was not obtained. Therefore, we decided to carry out an intramolecular coupling reaction after protecting the nitrogen atom. Hydride reduction of **17** and subsequent protection with di-*tert*-butyl dicarbonate (Boc_2O) furnished **18** (total yield of 49% in 3 steps), which was converted to pentacyclic compound **19** by means of an intramolecular coupling reaction. After deprotection of **19** with hydrogen chloride, resulting amine **20** was isolated in two steps with 74% yield. The key catalytic tandem oxidation was performed using anonaine (**20**) to give rise to liriodenine (**5**) in a 68% yield (Scheme 7). The spectral properties of synthetic **5** were identical with those previously reported [10].

To expand the versatility of the catalytic tandem oxidation, the conversion of protoberberines to 8-oxoprotoberberines [11] was attempted. Xylopinine (**21**), which is a biological precursor for 8-oxypseudopalmatine (**22**), was synthesized (Scheme 8). Specifically, hydride reduction of imine **15** followed by a Mannich reaction provided xylopinine (**21**) [11] with a total yield of 64%. The key catalytic tandem oxidation was performed using **21** under the reaction conditions described in Table 1, entry 7 to afford 8-oxypseudopalmatine (**22**) in a 75% yield. It is noteworthy that the reaction was clean and byproducts were not detected in the crude ^1H NMR spectrum. The ^1H and ^{13}C NMR spectra of synthetic **22** were identical to those previously reported [12].

Although we did not attempt to experimentally verify the reaction mechanism of this oxidative transformation of **21** into **22**, Scheme 9 depicts a plausible reaction pathway. Namely, the catalytic oxidation of **21** gave enamine **II** through ammonium ion **I**. Under thermal conditions, a 1,5-hydrogen shift of **II** produced intermediate **III**, which reacted with oxygen to give hydroperoxide **IV**. Recovery of the aromaticity of **IV** followed by dehydration produced **22**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152599.

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