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Oxygen Insertion of *o*-Quinone under Catalytic Hydrogenation Conditions

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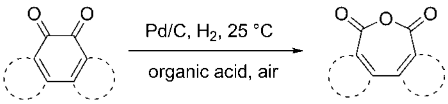
ABSTRACT



An oxygen-insertion reaction that transforms an *o*-quinone and a conjugated α-diketone substrate into an anhydride product or derivative under catalytic hydrogenation conditions is reported. The experiments and computations indicate that the oxygen insertion proceeds via a radical mechanism mediated by an acetoxyl radical.

Chemo- and regioselective oxygen insertion into a C–C bond represents a versatile synthetic strategy of great value in organic chemistry, which includes Baeyer–Villiger oxidation,[1] photooxidation,[2] ozonolysis,[3] and so on. All of these methods generally occur under oxidants, such as peracids in Baeyer–Villiger oxidations, singlet oxygen in photooxidation, and ozone in ozonolysis. However, these methods with common oxidants have several disadvantages. For example, peracids used in Baeyer–Villiger oxidation are costly, intrinsically unstable, toxic, and environmentally unfriendly,[4] while photooxidation and ozonolysis exhibit low reaction selectivity and yield for targeted products. Here we report an oxygen-insertion oxidation that transforms an *o*-quinone and a conjugated α-diketone substrate into an anhydride product or derivative under catalytic hydrogenation conditions.

Tanshinone anhydride-type derivatives are a kind of minor chemical component of *Salvia miltiorrhiza* Bunge, a well-known traditional Chinese medicinal herb.[5] Their syntheses have attracted our efforts due to their potential biological activity. During our study, we surprisingly found that the anhydride-type product **2** of cryptotanshinone (**1**) was obtained under the Pd/C catalytic hydrogenation conditions (Table 1). Compound **2** was characterized by HRMS, 1D NMR,[5a] and 2D NMR spectra and finally confirmed by X-ray single crystal analysis (SFigure 2). The reaction in ethanol gave the oxygen-insertion product **2** and its alcoholytic product **S1** (Supporting Information) in 83% total oxygen-insertion yield (Table 1, entry 4). To our best knowledge, this represents the first case of oxygen insertion into a C–C bond under catalytic hydrogenation conditions,

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(1) (a) Demmin, T. R.; Rogic, M. M. *J. Org. Chem.* **1980**, *45*, 1153. (b) White, L. S.; Hellman, E. J.; Que, L. *J. Org. Chem.* **1982**, *47*, 3766. (c) Jacobs, R. T.; Feutrill, G. I.; Meinwald, J. *J. Org. Chem.* **1990**, *55*, 4051. (d) Yan, J.; Travis, B. R.; Borhan, B. *J. Org. Chem.* **2004**, *69*, 9299. (e) Hitomi, Y.; Yoshida, H.; Tanaka, T.; Funabiki, T. *J. Mol. Catal. A* **2006**, *251*, 239. (f) Langhals, H.; Schonmann, G.; Polborn, K. *Chem.—Eur. J.* **2008**, *14*, 5290. (g) Yang, R. Y.; Kizer, D.; Wu, H.; Volckova, E.; Miao, X. S.; Ali, S. M.; Tandon, M.; Savage, R. E.; Chan, T. C. K.; Ashwell, M. A. *Bioorg. Med. Chem.* **2008**, *16*, 5635. (h) Yao, J. H.; Chi, C.; Wu, J.; Loh, K. P. *Chem.—Eur. J.* **2009**, *15*, 9299. (i) Sun, Z.; Huang, K. W.; Wu, J. *Org. Lett.* **2010**, *12*, 4690. (j) Yin, J.; Zhang, K.; Jiao, C.; Li, J.; Chi, C.; Wu, J. *Tetrahedron Lett.* **2010**, *51*, 6313. (k) Mohebbi, A. R.; Munoz, C.; Wudl, F. *Org. Lett.* **2011**, *13*, 2560.

(2) (a) Kusurni, T.; Kishi, T.; Kakisawa, H.; Kinoshita, T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1716. (b) Sawaki, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3464. (c) Hall, C. A., III; Cuppett, S. L.; Dussault, P. *J. Am. Oil Chem. Soc.* **1998**, *75*, 1147. (d) Ji, S. J.; Lu, J.; Lang, J. P.; Horiuchi, C. A. *Synth. Commun.* **2002**, *32*, 1659. (e) Higashida, S.; Harada, A.; Kawakatsu, R.; Fujiwara, N.; Matsumura, M. *Chem. Commun.* **2006**, 2804.

(3) (a) Crandall, J. K.; Schuster, T. *J. Org. Chem.* **1990**, *55*, 1973. (b) Tabuchi, T.; Nojima, M. *J. Org. Chem.* **1991**, *56*, 6591.

(4) For reviews, see: (a) Strukul, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1198. (b) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.

(5) (a) Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P. *J. Org. Chem.* **1990**, *55*, 3537. (b) Chang, H. M.; Choang, T. F.; Chui, K. Y.; Hon, P. M.; Lee, C. M.; Mak, T. C. W.; Wong, H. N. C. *J. Chem. Res. (S)* **1990**, 114.

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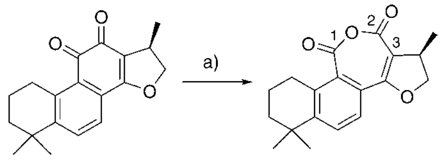
Table 1. Optimization of Oxygen Insertion of Cryptotanshinone



1 **2**

entry	cat.	solvent	acid	atm	yield (%)
1	Pd/C	C_6H_6	AcOH	H_2	30
2	Pd/C	AcOEt	AcOH	H_2	16
3	Pd/C	CH_2Cl_2	AcOH	H_2	18
4	Pd/C	EtOH	AcOH	H_2	50 (33)[b]
5	Pd/C	AcOEt	AcOH	N_2	0
6	Pd/C	AcOEt	AcOH	air	0
7	Pd/C	AcOEt	HCO_2H	H_2	8
8	Pd/C	AcOEt	$PhCO_2H$	H_2	21
9	Pd/C	AcOEt	CF_3CO_2H	H_2	11
10	Pd/C	AcOEt	H_2SO_4	H_2	0
11	Pd/C	AcOEt	HCl	H_2	0
12	Pd/C	AcOEt+H_2O[c]	AcOH	H_2	46
13	Pd/C	EtOH+H_2O[c]	AcOH	H_2	55 (32)[b]
14[d]	Pd/C	C_6H_6+H_2O[c]	AcOH	H_2+air	88
15[d]	Pd/C	AcOEt+H_2O[c]	AcOH	H_2+air	66
16[e]	R-Ni	AcOEt	AcOH	Air	71
17[e]	R-Ni	EtOH	AcOH	Air	44 (42)[b]
18[e]	R-Ni	AcOEt	AcOH	N_2	61

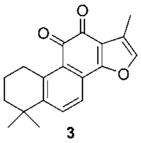
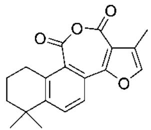
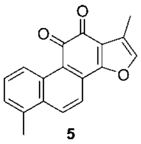
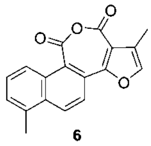
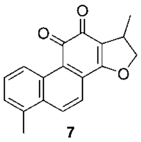
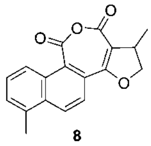
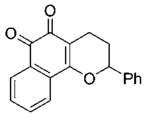
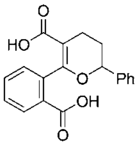
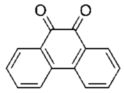
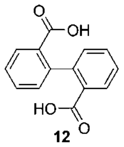
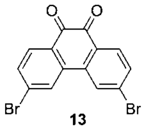
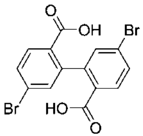
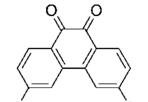
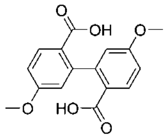
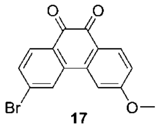
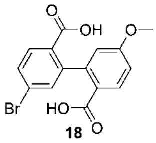
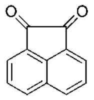
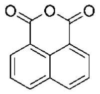
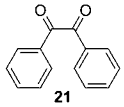
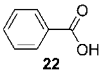
[a] Reagents and conditions: catalyst, H_2, organic acid, 25 °C, 0.5–1 h. [b] Values in parentheses are the yields of alcoholytic product **S1** of compound **2**. [c] The solvent contains 0.3% water. [d] The reaction was carried out under a 1:9 air/H_2 mixture. [e] Raney Ni slurry 50% in water was used.

which stimulates our further investigation on the potential mechanism and also the optimal reaction conditions for such a novel oxygen-insertion reaction.

Hydrogen plays an important role in the reaction. As we replaced H_2 with the nitrogen or air atmosphere, no oxygen-insertion product was obtained with Pd/C as the catalyst (Table 1, entries 5 and 6). Interestingly, when we carried out the experiment with the Raney Ni (R-Ni) catalyst in the absence of hydrogen except that contained in the catalyst,[6] the yield of the oxygen-insertion product (Table 1, entries 16–18) was comparable to that obtained under Pd/C and mixed H_2/air conditions.

On the other hand, the yield of the oxygen-insertion product increased as the hydrogen gas was replaced by the mixture of hydrogen and air (9/1 ratio), indicating the oxygen-insertion reaction involving molecular oxygen (Table 1, entry 14). To study whether oxygen gas was the direct oxygen source for the oxygen-insertion reaction, the reaction was carried out under the gas mixture of hydrogen and $^{18}O_2$.[7] An ESI/MS study showed that the ^{18}O atom was not incorporated into the oxygen-insertion product, indicating oxygen gas was not the oxygen source for the oxygen-insertion reaction.

Table 2. Oxygen Insertion of *o*-Quinone and α-Diketone Substrates

entry	substrate	product	yield[a]
1[b]	 **3**	 **4**	86%
2[b]	 **5**	 **6**	68%
3[b]	 **7**	 **8**	81%
4[c]	 **9**	 **10**	66%
5[c]	 **11**	 **12**	71%
6[c]	 **13**	 **14**	16%
7[c]	 **15**	 **16**	70%
8[c]	 **17**	 **18**	40%
9[c]	 **19**	 **20**	65%[d]
10[c]	 **21**	 **22**	13%[d]

[a] Isolated yield unless mentioned. [b] Reaction conditions: Pd/C, benzene with 3% water, AcOH, 1:9 air/H_2, 25 °C, 1–8 h. [c] Reaction conditions: Raney Ni, organic solvent, AcOH, 25 °C, 1–8 h. [d] HPLC yield.

An organic acid is also essential for the reaction, since inorganic acids, such as concentrated sulfuric acid and hydrochloric acid, cannot facilitate the formation of the

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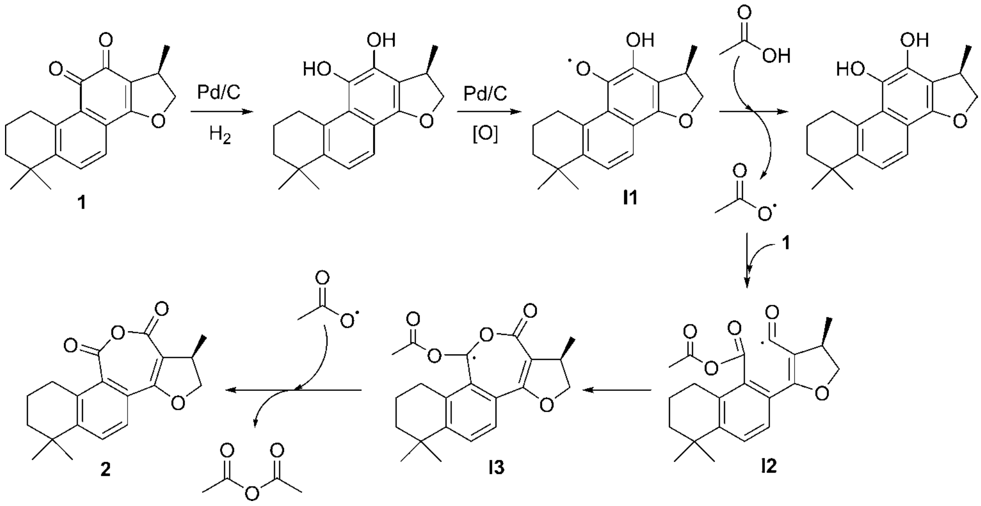
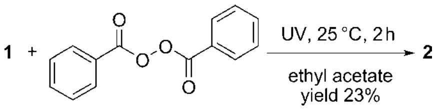
(6) Kokes, R. J.; Emmett, P. H. *J. Am. Chem. Soc.* **1959**, *81*, 5032.

(7) Reaction conditions: compound **1**, Pd/C, H_2/$^{18}O_2$ gas (96:4), benzene, 1 h.

Scheme 1. Proposed Mechanism of the Oxygen Insertion



Scheme 2. Oxygen Insertion of **1** with Benzoyl Peroxide



oxygen-insertion product (Table 1, entries 10 and 11). Detailed inspection of the reaction conditions suggests that the organic acid is the key species involved in the oxygen-insertion reaction. To clarify this question, the reaction was carried out in the presence of the ^{18}O-labeled acetic acid. ^{13}C NMR and ESI/MS^2 studies showed that the isotopic ^{18}O atom substituted into the carbonyl group at the C-1 position of the oxygen-insertion product (Supporting Information), indicating that acetic acid was the oxygen source of the oxygen-insertion product.

Based on the above-mentioned observations, we proposed a plausible mechanism for the oxygen-insertion reaction as shown in Scheme 1. Tanshinone is first hydrogenated to the hydroquinone product under catalytic hydrogenation conditions, and the hydroquinone product is then oxidized to the radical intermediate **I1** by oxygen gas catalyzed by the metal catalyst. Proton-coupled electron transfer from acetic acid to the radical intermediate **I1** generates an acetoxyl radical. The generated acetoxyl radical then attacks the carbonyl carbon of the *o*-quinone, leading to the bond breaking of the *o*-quinone to form a ring-opening acyl radical intermediate (**I2**). Subsequently, a seven-member-ring intermediate (**I3**) is formed by the attack of the carbonyl oxygen of the neighboring anhydride group to the acyl radical. The oxygen-insertion product is formed by the attack of another acetoxyl radical to the carbonyl carbon of the acetate group, accompanied by the release of an acetic anhydride.

To verify the involvement of the acetoxyl radical in the oxygen-insertion reaction, the reaction was carried out in the presence of benzoyl peroxide under UV irradiation, in which benzoyl peroxide could generate a benzoyl radical that was thought to have properties similar to those of the acetoxyl radical reacting with compound **1** (Scheme 2).[8] As expected, the oxygen-insertion product **2** of cryptotanshinone was observed, indicating the reliability of the proposed radical mechanism. Moreover, the presence of water would promote the oxygen-insertion reaction (Table 1, entries 12−15) because water can form hydrogen bonds with the acetoxyl radical, which stabilize the acetoxyl radical and furnish a higher acetoxyl radical concentration.[9]

To further verify the radical characteristics of the proposed mechanism, radical scavengers, such as 2,2,6,6-tetramethylpiperidinooxyl (TEMPO)[10] and 2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl (DPPH),[11] were employed in the oxygen-insertion reaction catalyzed by Raney Ni (Scheme 3). As expected, the reaction was completely suppressed by TEMPO and DPPH with all of material **1** remaining in the reaction solution, highlighting that the radical is the key species in the oxygen insertion reaction under the catalytic hydrogenation conditions.

To verify the proposed role of hydroquinone in the reaction, the reaction was carried out using the hydroquinone form of compound **1** as the starting material in the presence of Pd/C and acetic acid but not including

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(8) (a) Brown, D. J. *J. Am. Chem. Soc.* **1940**, *62*, 2657. (b) Cass, W. E. *J. Am. Chem. Soc.* **1946**, *68*, 1976. (c) Brown, D. J. *J. Am. Chem. Soc.* **1948**, *70*, 1208. (c) Rao, T. S. S.; Pritzkow, W. *J. Prakt. Chem.* **1988**, *330*, 748.

(9) (a) Ukegawa, K.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1632. (b) Csanyi, L. J.; Jaky, K. *J. Catal.* **1993**, *141*, 721.

(10) (a) Beckwith, A. L. J.; Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4983. (b) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1992**, *114*, 4992. (c) Sobek, J.; Martschke, R.; Fischer, H. *J. Am. Chem. Soc.* **2001**, *123*, 2849.

(11) Foti, M. C.; Daquino, C.; Geraci, C. *J. Org. Chem.* **2004**, *69*, 2309.

(12) Reaction procedure: Comopund **1** was hydrogenized into hydroquinone catalyzed by Pd/C in EtOH. The solvent was removed in vacuo. And then, a solution of AcOH in benzene was added to the residue by syringe.

Scheme 3. Radical Trapping Experiments

$$\mathbf{1} \xrightarrow[\text{air, AcOEt, 2 h}]{\text{R-Ni, acetic acid}} \mathbf{2}$$

no scavenger	71% (HPLC)
TEMPO (100%)	0
DPPH (100%)	0

hydrogen gas. The oxygen-insertion product **2** was observed.[12] In contrast, no oxygen-insertion product was observed if there was no Pd/C or acetic acid in the reaction solution. This result implied that the hydroquinone was the key intermediate of the oxygen-insertion reaction, and Pd/C has additional roles in the reaction besides the catalyst for the hydrogenation.

In addition, the proposed mechanism suggests that the formation of the oxygen-insertion product is accompanied by the release of acetic anhydride. Evidence was obtained by using aniline to trap the anhydride formed in the oxygen-insertion reaction. Acetylaniline was detected in the reaction solution by HPLC analysis (Supporting Information). As a comparison, no acetylaniline was detected under similar conditions without cryptotanshinone. Furthermore, no acetylaniline was detected after the oxygen-insertion reaction solution in DMF with 3% water was treated with aniline, which indicated that acetic anhydride could be spontaneously hydrolyzed to regenerate the acetic acid for the next catalytic cycle *in situ* in the presence of water.

The proposed mechanism was confirmed by a density functional theory (DFT) study, which indicated that once the acetoxyl radical is generated, the overall process is a fast process as predicted by the low activation energy barriers along the reaction pathway. The energy profile for the reaction pathway is shown in SFigure 3 (Supporting Information).

The scope of this reaction was preliminarily explored by studying the oxygen-insertion reaction of several *o*-quinones and a conjugated α-diketone as depicted in Table 2. The oxygen-insertion products or their derivatives were obtained using both *o*-quinone and conjugated α-diketone (Table 2, entry 10) as a substrate, thus validating the versatility and efficiency of this method to some extent.

In summary, we have discovered a novel oxygen-insertion reaction that transforms an *o*-quinone and a conjugated α-diketone substrate into an anhydride product or derivative under catalytic hydrogenation conditions in combination with an organic acid. Combined computations and experiments revealed that the oxygen-insertion reaction proceeds via a radical mechanism. Therefore, this finding might provide important insights into discovering novel reactions for oxygen insertion into a C–C bond and also provide an atom-economic and environmentally benign method to synthesize carboxylic derivatives.

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Supporting Information Available. Experimental procedures, compounds' characterization data and spectra, crystallographic data of compound **2**, ^{13}C NMR and MS/MS spectra of ^{18}O-labeled **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.