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A mild procedure for the oxidative cleavage of substituted indoles catalyzed by plant cell cultures

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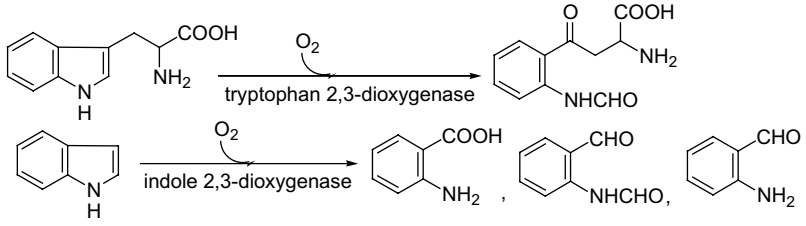
Abstract—We have developed a novel procedure for the oxidative cleavage of indole carbon double bonds in the presence of H_2O_2 using plant cell cultures as a catalytic system. The oxidative procedure has some advantages, such as mild reactions, good yields, easy work-up and safety.

Oxidative cleavage of a carbon–carbon double bond is a widely used method for the preparation of carbonyl compounds in organic synthesis.[1] A number of different reagents have been developed for the oxidative cleavage of the enamine carbon double bonds in the past such as sodium periodate,[2] sodium dichromate in acid,[3] nitrous acid,[4] potassium permanganate[5] and molecular oxygen with copper ion systems.[6,7] On the other hand, the development of the usage of enzymes for oxidation reactions aimed at green chemistry is significant these days. The biocatalytic oxidative cleavage of a carbon–carbon double bond is preferable, because it takes advantage of the mild reaction conditions. Three dioxygenases are known so far: (1) tryptophan 2,3-dioxygenase,[8] (2) indole 2,3-dioxygenase,[9] (3) protocatechuate 3,4-dioxygenase.[10] Tryptophan, at the first step in one of its metabolic pathways, binds molecular oxygen by the catalytic action of tryptophan 2,3-dioxygenase leading to oxidative cleavage of the heterocyclic ring to give formylkynurenin. Indole 2,3-dioxygenase catalyzes the conversion of indole to anthranilic acid. Formylaminobenzaldehyde and *o*-aminobenzaldehyde were detected as intermediates during the overall conversion.

However, only a few attempts have been reported for the oxidative cleavage by enzymes in organic synthesis. Electron-rich alkenes such as enamines and enol ethers are known to react readily with singlet oxygen to yield unstable dioxetanes, which can subsequently cleave to two carbonyl fragments.[11] The coupled oxygenation with peroxidase in the presence of H_2O_2 is analogous to the reaction of singlet oxygen.[12] We have found that plant cell cultures is an efficient source of peroxidase enzymes as 'reagents' in organic synthesis and a huge amount of H_2O_2 is produced in plant cell cultures by the addition of foreign substrates.[13] Then, our attention turned to the subject of whether plant cell cultures have oxidative ability as catalysts to cleave electron-rich carbon double bonds in the presence of H_2O_2. Very recently, we found 2,3-dimethylindole (**1**) was converted into *o*-acetylaminoacetophenone (**2**) with oxidative cleavage of the carbon–carbon double bonds. In this



Keywords: Oxidative cleavage reactions; Enamines; Indoles; Carbazoles; Catalysts; Enzymes and enzyme reaction.
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letter, we would like to present our results of the biocatalytic oxidative cleavage of substituted indoles and enamines with a plant cell culture–H_2O_2 system.

The oxidative cleavage reactions of **1** were performed at 25 °C with H_2O_2 in the medium indicated. These results are shown in Table 1. The suspension-cultured cells, which had originally been isolated from *Camellia sinensis*,[13,14] *Nicotiana tabacum*,[15,16] *Catharanthus roseus*[17,18] and *Daucus carota*[19] were used. Sodium periodate has been used to cleave the indolic double bond of several 2,3-disubstituted indoles to give the corresponding ketoamides.[20] For comparison with such plant cell systems, chemical reagents[21] were also examined.

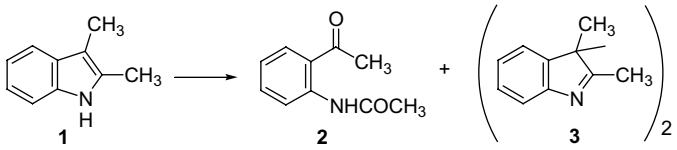
Among the procedures examined, *C. roseus* in the presence of H_2O_2 showed the highest yield of **2** (entry 7). The reaction proceeded much faster with *C. sinensis*, *N. tabacum* or *C. roseus* in the presence of H_2O_2 than with $FeCl_3$, $K_3Fe(CN)_6$ or *D. carota*. In the absence of plant cell cultures, longer reaction time was required with H_2O_2 to complete the reaction (entry 3). In B5 or MS medium, reaction does not proceed (entries 9 and 10). Though reaction with $FeCl_3$or $K_3Fe(CN)_6$ also gave **2** and **3**, the plant cell culture and sodium periodate gave no other products than compound **2** (entries 4–8). Thus, *C. roseus*, *C. sinensis* and *N. tabacum* were proven to be effective catalysts for oxidative cleavage of **1** in satisfactory yields without any side products in short reaction time.

Next, to explore the catalytic abilities of the plant cell cultures–H_2O_2 system, the oxidative cleavages of substituted indoles and enamines such as 3-methylindole (**4**), 2-methylindole (**7**), 2,3-dimethyl-5-methoxyindole (**9**), 2,3-cyclopentenoindole (**11**), 2,3-cyclopenteno-5-methoxyindole (**13**), 1,2,3,4-tetrahydrocarbazole (**15**), 6-methoxy-1,2,3,4-tetrahydrocarbazole (**17**), 2,3-cycloheptenoindole (**19**), *N*-methyl-2,3-cyclopentenoindole (**21**), 1-(4-morpholino)-2,2-diphenylethene (**23**) and 1-(4-morpholino)-2-phenylpropene (**25**) using *C. roseus*, *C. sinensis*, *N. tabacum* or *D. carota* were investigated, and these results are shown in Table 2. The carbon–carbon double bonds of all indoles (**4**, **7**, **9**, **13**, **15**, **17**, **19, 21**) were cleaved to give the corresponding amides (entries 1–3) and cyclic lactam (entries 5–9) in the presence of H_2O_2. A huge amount of H_2O_2 was produced in the plant cell culture by the addition of foreign substrates.[13] In the absence of foreign H_2O_2, **11**, **23** and **25** were cleaved to give **12**, **24** and **26** in the plant cell culture with produced H_2O_2 (entry 4, 10, 11). For comparison with such plant cell cultures–H_2O_2 system, sodium periodate[20] was also examined. The reaction of **4**, **7**, **9**, **11**, **13**, **15**, **17**, **19**, **21, 23** and **25** with $NaIO_4$ in 50% aqueous MeOH afforded **5** (Y. 47%), **8** (Y. 16%), **10** (Y. 68%), **12** (Y. 28%), **14** (Y. 55%), **16** (Y. 99%), **18** (Y. 19%), **20** (Y. 40%), **22** (Y. 8%), **24** (Y. 70%) and **26** (Y. 15%). The yields with $NaIO_4$ decreased in the case of highly reactive indoles having an electron-donating substituent into the indole ring (e.g., compounds **7**, **9**, **11**, **17** and **21**). But, the yields with the plant cell culture were much higher than that with $NaIO_4$ (entries 2, 3, 4, 7 and 9).

The representative experimental procedure is as follows: the suspension-cultured cells, which had originally been derived from *C. roseus*, *N. tabacum*, *C. sinensis* or *D. carota* as described in our previous papers[13–19] were used. A substrate (1 mmol) was added to the freely suspended plant cell cultures (42 g cells and 200 mL broth). After the mixture was shaken at 25 °C on a rotary shaker (110 rpm) in the dark for 10 min, 30% H_2O_2 (1.0 mL) was added to the mixture. After 0.5 h of incubation, the incubation mixture was filtered, the filtered cells were washed with AcOEt and the filtrates were combined. The combined mixture was extracted with AcOEt and the organic layer was dried over anhydrous $MgSO_4$. A substrate (10 mmol) was added to the freely suspended plant cell culture (420 g cells and 2000 mL broth) with 30% H_2O_2 (10 mL) in a bioreactor.

The structures of **2**,[21] **3**,[21] **5**,[24] **6**,[25] **10**,[26] **12**,[27] **16**[27] and **20**[27] were confirmed by a comparison of the proton nuclear magnetic resonance (^{1}H NMR) data with those

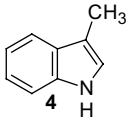
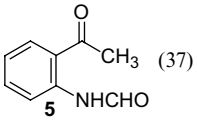
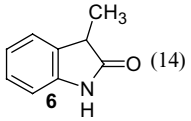
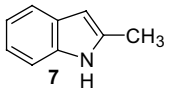
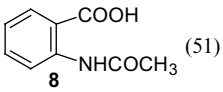
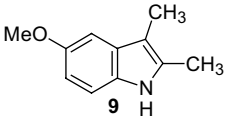
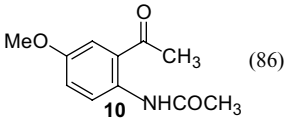
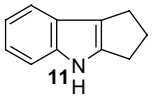
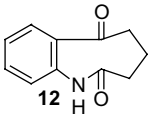
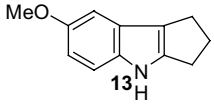
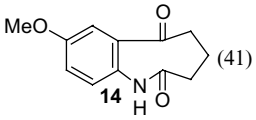
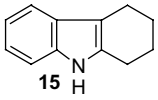
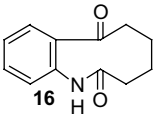
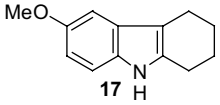
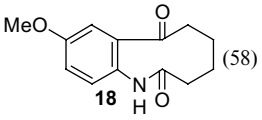
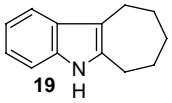
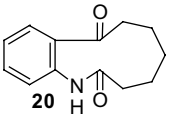
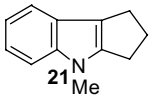
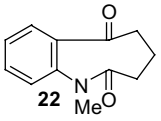
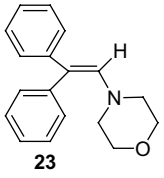
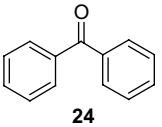
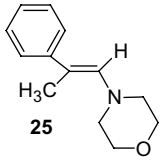
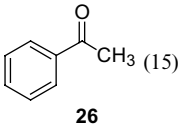
Table 1. Oxidative cleavage of **1** with plant cell cultures or chemical reagents



Entry	Method	Medium	Time (h)	**2**[a] Y. (%)	**3**[a] Y. (%)
1	$FeCl_3$	EtOH	24	8	4
2	$K_3Fe(CN)_6$	H_2O–acetone	24	19	2
3	H_2O_2	MS medium[22]	168	16	0
4	$NaIO_4$	H_2O–CH_3OH	0.5	85	0
5	*C. sinensis*, H_2O_2	B5 medium[23]	0.5	49	0
6	*N. tabacum*, H_2O_2	MS medium	0.5	53	0
7	*C. roseus*, H_2O_2	B5 medium	0.5	95	0
8	*D. carota*, H_2O_2	MS medium	168	53	0
9		B5 medium	168	0	0
10		MS medium	168	0	0

[a] All are isolated yields.

Table 2. Oxidative cleavage of indoles and enamines with plant cell cultures

Entry	Indole, enamine	Plant[a]	Time (h)	Product (Y. %)[b]
1	 **4**	*C. sinensis* (H_2O_2)	24	 **5** (37)  **6** (14)
2	 **7**	*C. roseus* (H_2O_2)	24	 **8** (51)
3	 **9**	*N. tabacum* (H_2O_2)	24	 **10** (86)
4	 **11**	*C. roseus*	12	 **12** (46)
5	 **13**	*N. tabacum* (H_2O_2)	12	 **14** (41)
6	 **15**	*N. tabacum* (H_2O_2)	72	 **16** (44)
7	 **17**	*N. tabacum* (H_2O_2)	12	 **18** (58)
8	 **19**	*C. sinensis* (H_2O_2)	96	 **20** (15)
9	 **21**	*C. sinensis* H_2O_2	24	 **22** (28)
10	 **23**	*D. carota*	0.2	 **24** (76)
11	 **25**	*C. sinensis*	0.2	 **26** (15)

[a] 30% H_2O_2 was added to the freely suspended plant cell cultures (entries 1–3, 5–9).
[b] All are isolated yields.

reported. The products **8**, **24** and **26** were confirmed by a comparison of ^{1}H NMR data, mp and TLC with a commercially available sample. The structures of **14**,[28] **18**[28] and **22**[28] were supported by MS spectra data and confirmed by analysis of their ^{1}H NMR data. Indole **9** and cyclic indoles **13, 17** and **21** were synthesized by the synthetic route of Rogerts and Corson.[29]

In summary, a novel oxidative cleavage of substituted indoles and enamines was developed by using plant cell

cultures of *C. roseus*, *C. sinensis*, *D. carota* and *N. tabacum* with or without H_2O_2. This procedure has some advantageous features such as mild reactions, good yields, easy work-up and safety; therefore, it is a valuable alternative to the cleavage of indoles by sodium periodate.

References and notes

1. For recent reviews and leading citations, see: (a) Hudlicky, M. In *Oxidation in Organic Chemistry*; ACS Monograph 186; American Chemical Society: Washington, DC, 1990; p 77; Lee, D. G.; Chen, T. Cleavage Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, p 541. See also: (b) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643.
2. Vetelino, M. G.; Coe, J. W. *Tetrahedron Lett.* **1994**, *35*, 219.
3. Slomp, G.; Shealy, Y. F.; Johnson, J. L.; Donia, R. A.; Johnson, B. A.; Holysz, R. P.; Pederson, R. L.; Jensen, A. O.; Ott, A. C. *J. Am. Chem. Soc.* **1955**, *77*, 1216.
4. Mahajan, J. R.; Nunes, B. J.; Aravjo, H. C.; Ferreira, G. A. L. *J. Chem. Res. (S)* **1979**, 284.
5. Sreekumar, R.; Padmakumar, R. *Tetrahedron Lett.* **1997**, *38*, 5143.
6. Rheenan, V. V. *J. Chem. Soc., Chem. Commun.* **1969**, 314.
7. Ebitani, K.; Nagashima, K.; Mizugaki, T.; Kaneda, K. *J. Chem. Soc., Chem. Commun.* **2000**, 869.
8. Schutz, G.; Feigelson, P. *J. Biol. Chem.* **1972**, *247*, 5327.
9. Msdhusudanan, N. P.; Vaidyanathan, C. S. *Biochim. Biophys. Acta* **1964**, *81*, 496.
10. Saeki, Y.; Nozaki, M.; Senoh, S. *J. Biol. Chem.* **1980**, *255*, 8465.
11. For reviews see: (a) Foote, C. S. *Acc. Chem. Res.* **1968**, *1*, 104; (b) Kearns, D. R. *Chem. Rev.* **1971**, *71*, 395; (c) Schaap, A. P.; Zaklika, K. A. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic: New York, 1979; p 173.
12. Chan, H. W.-S. *J. Am. Chem. Soc.* **1971**, *93*, 4632.
13. Takemoto, M.; Aoshima, Y.; Stoynov, N.; Kutney, J. P. *Tetrahedron Lett.* **2002**, *43*, 6915.
14. Takemoto, M.; Suzuki, Y.; Tanaka, K. *Tetrahedron Lett.* **2002**, *43*, 8499.
15. Takemoto, M.; Moriyasu, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1995**, *43*, 1458.
16. Takemoto, M.; Achiwa, K. *Tetrahedron Lett.* **1999**, *40*, 6595.
17. Takemoto, M.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2925.
18. Takemoto, M.; Matsuoka, Y.; Achiwa, K.; Kutney, J. P. *Tetrahedron Lett.* **2000**, *41*, 499.
19. Takemoto, M.; Yamamoto, Y.; Achiwa, K. *Chem. Pharm. Bull.* **1998**, *46*, 419.
20. Dolby, L. J.; Booth, D. L. *J. Am. Chem. Soc.* **1966**, *88*, 1049.
21. Takizawa, Y.; Matsuyama, C.; Katayose, R.; Urabe, T. *Abstract*, The 34th Symposium on Chemical and Biochemical Oxidation, 2001; p 17.
22. Murashige, T.; Skoog, F. *Physiol. Plant* **1962**, *15*, 473–497.
23. Gamborg, O. L.; Miller, R. A.; Ojima, K. *Exp. Cell Res.* **1968**, *50*, 151.
24. Nishinaga, A. *Chem. Lett.* **1975**, 273.
25. Bourdais, J. *Bull. Soc. Chim. Fr.* **1968**, 1506.
26. Duchstein, H. J. *Arch. Pharm.* **1985**, *318*, 127.
27. Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, *73*, 2641.
28. Compound **14**: ^{1}H NMR ($CDCl_3$): δ, ppm 2.18 (2H, m), 2.50 (2H, m), 3.06 (2H, m), 3.86 (3H, s), 7.06 (2H, m), 7.65 (1H, d, $J = 2.3$ Hz), 8.26 (1H, s). MS *m/e*: 219 (M^+). Compound **18**: ^{1}H NMR ($CDCl_3$): δ, ppm 1.84 (4H, m), 2.25 (2H, m), 2.91 (2H, m), 3.86 (3H, s), 7.04 (2H, m), 7.17 (1H, d, $J = 8.5$ Hz), 7.38 (1H, s). MS *m/e*: 234 (M^+). Compound **22**: ^{1}H NMR ($CDCl_3$): δ, ppm 2.40 (2H, m), 2.61 (2H, m), 2.90 (2H, m), 3.40 (3H, s), 7.20–7.65 (3H, m), 8.05 (1H, d, $J = 5.8$ Hz). MS *m/e*: 203 (M^+).
29. Rogerts, C. U.; Corson, B. B. *Org. Synth. Collect. Vol.* **1963**, *4*, 884.