## Communications to the Editor

[Chem. Pharm. Bull. 34(9)3945—3948(1986)]

# MILD OXIDATION OF ALLYLIC AND BENZYLIC ALCOHOLS WITH 5-ARYLIDENE BARBITURIC ACID DERIVATIVES AS A MODEL OF REDOX COENZYMES

Kiyoshi Tanaka, Xing Cheng, Teiji Kimura and Fumio Yoneda*
Faculty of Pharmaceutical Sciences, Kyoto University,
Sakyo-ku, Kyoto 606, Japan

Under neutral conditions 5-arylidene 1,3-dimethylbarbituric acid effectively oxidizes allylic and benzylic alcohols to the corresponding carbonyl compounds. There is a close relationship between oxidizing ability and electron density on the aromatic ring. The mechanism of this oxidation involves hydride transfer from the alcohol.

KEYWORDS——— 5-arylidene 1,3-dimethylbarbituric acid; coenzyme model; oxidation; allylic and benzylic alcohol; oxidation mechanism; hydride transfer; primary isotope effect

NAD and FAD are essential redox coenzymes which play important roles in the energy metabolism of organisms. 5-Deazaflavins have been exploited and shown to have a pattern of redox potential similar to NAD and FAD.[1] During the course of our investigation of models of functional coenzymes, we chose 5-arylidene barbituric acid derivatives[2] as a coenzyme model and used it to oxidize some alcohols under neutral and mild conditions. Since this simple model compound preserves the electron-deficient conjugated double dond found as a common and characteristic structural feature in all of above mentioned redox coenzymes, a considerable degree of oxidation ability expected. 5-Arylidene 1,3-dimethylbarbituric acid derivatives were readily prepared quantitatively as beautifully crystallized compounds by heating 1,3-dimethylbarbituric acid and an appropriate aromatic aldehyde in ethanol.[2,3] This simple procedure makes it possible to get various kinds of compounds which differ in electronic density and the steric situation of the carbon-carbon double bond (Chart 1).

Incidentally, benzylic alcohols were oxidized with aromatic alcohol oxidase isolated from the microorganism *Polystictus versicolor*,[4] but the structure of this flavin-dependent enzyme is uncertain.

Thus, we synthesized several 5-arylidene 1,3-dimethylbarbituric acid derivatives which were subjected to oxidation in dioxane. These results are summarized in Table I.
As can be seen, there is a good correlation of oxidation yield with Hammetts' substituent constant ($\sigma^-$ or $\sigma$). The oxidation with compound 1a was not good, but the yields (62 and 70 %) with the electron-deficient compound 1f and 1g were satisfactory.

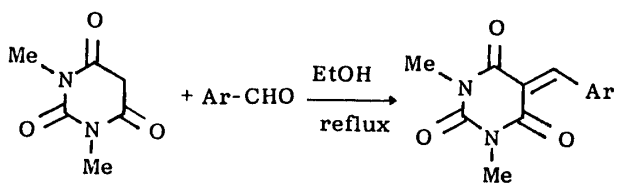
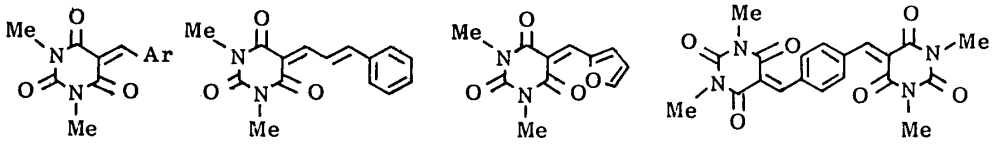



Chart 1

Table I. Oxidation[a] of Cinnamyl Alcohol with Compounds 1~4

| 5-Arylidene 1,3-dimethyl-barbituric acid derivative | None | 1 Ar = OMe (1a) | (1b) | OAc (1c) | OAc (1d) | Cl (1e) | Cl | $NO_2$ (1f) | $NO_2$ (1g) | 2 | 3 | 4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Isolated yield of cinnamyl aldehyde (%)[b] | <2 | 4 | 30 | 33 | 38 | 55 | 62 | 70 | | <2 | <2 | 40 |

a) Refluxed in dioxane for 3 days.
b) Isolated product other than cinnamaldehyde is recovered cinnamyl alcohol.



1a - 1g 2 3 4

Alternatively, another type of compounds, 2 - 4, was prepared to explore the oxidation-structure relationship, but no significant results or information were obtained. Using the compound 1f, oxidation of various kinds of alcohols was undertaken with the results shown in Table II. The aliphatic alcohols are poorly oxidized in contrast to the allylic and benzylic alcohols.

Table II. Oxidation[a] of Various Alcohols with Compound 1f

| Alcohol | Octyl alcohol | Menthol | Cholesterol | *p*-Anisalcohol | Carveol | Cinnamyl alcohol |
|---|---|---|---|---|---|---|
| Oxidation yield[b] (%) | < 2 | < 2 | < 2 | 25 | 28 | 62 |

a) Refluxed in dioxane for 3 days.
b) Isolated yield.
The isolated product other than carbonyl compounds is the starting alcohol.

A typical experimental procedure is as follows: A mixture of 5-(4'-nitrobenzylidene) 1,3-dimethylbarbituric acid 1f (219 mg, 0.75 mM), cinnamyl alcohol (100 mg, 0.75 mM) and dioxane (8 ml) was refluxed for 3 days. The progress of oxidation was monitored by HPLC (μ-Porasil, *n*-hexane/ethyl acetate 8/1, UV 254 nm). The reaction mixture was concentrated and the residue was subjected to preparative TLC ($SiO_2$, *n*-hexane/ethyl acetate 5/1) to give 62 mg of cinnamaldehyde and 21 mg of the recovered cinnamyl alcohol.

This oxidation can be performed also in other solvents such as chloroform, toluene and ethyl acetate resulting in a comparable or less satisfactory yield. It also turned out that the oxidation runs well even when atmospheric oxygen is strictly excluded under an atmosphere of argon. Furthermore, it is interesting that pyridodipyrimidine[5] and 5-deazaflavin[6] derivatives,

having high oxidizing potential, fail to oxidize *p*-anisalcohol under the neutral condition as described above.

Next, we turned our attention to the interpretation of the oxidation mechanism with 5-arylidene barbituric acid derivatives. To explore the mechanism, *p*-anisalcohol-$d_2$ was prepared by the lithium aluminum deuteride reduction of ethyl *p*-methoxybenzoate and oxidized with 1f. The reaction products of this oxidation were examined in some detail. Beside *p*-anisaldehyde-$d_1$, compounds 5 and 6[7,8] were isolated together with trace amount of an unidentified compound (Chart 2). In this case the rate of oxidation was retarded in comparison with unlabelled *p*-anisalcohol and this may be an isotope effect. In a kinetic study, normal and primary isotope effects in this oxidation were observed and the value of $k_H/k_D$ was 3.3 suggesting that a bond to the isotopically substituted atom is broken in the rate-determining step.

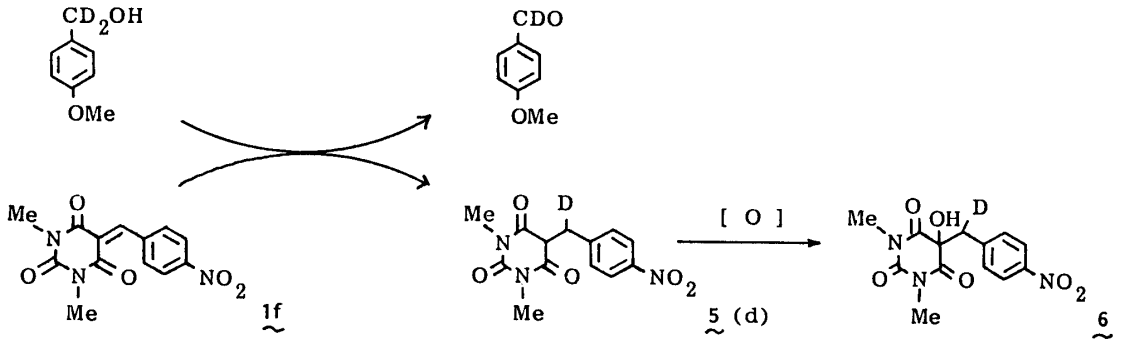



Chart 2. Oxidation of *p*-Anisaldehyde-$d_2$ with 1f

From this, it is deduced that the oxidation must be an Oppennauer type of reaction including hydride transfer and not a chromic acid type of oxidation involving proton shift of the intermediate chromate ester. This is also consistent with the proposed oxidation mechanisms for NAD[9] and 5-deazaflavin.[10] The transition state may be as shown in Chart 3, but so far no evidence of the termolecular mechanism has been found.

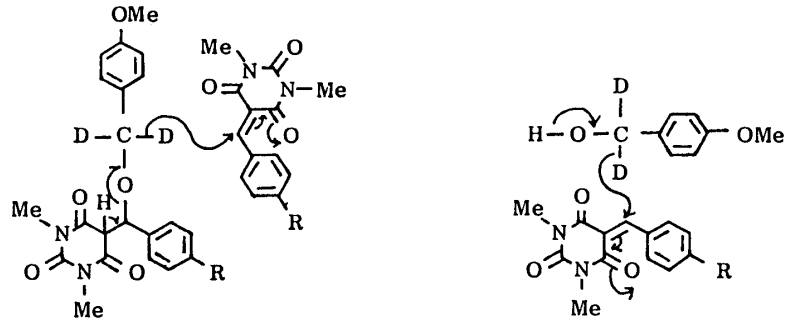



Chart 3. Probable Mechanism of the Oxidation with the Compound 1

Both flavin and deazaflavin function as catalysts in the oxidation of various substrates in the presence of oxygen. We attempted to oxidize compound 5 in order to examine its ability as a turn-over catalyst for oxidation. Although the 5-position of 5 was readily accessible to electrophiles including molecular oxygen[8] and diethyl azodicarboxylate,[11] reoxidized compound

1f was not formed in the oxidation.

In conclusion, the present study reveals that the readily available 5-arylidene 1,3-dimethylbarbituric acids, especially compounds 1f and 1g, are good stoichiometric organic oxidants for allylic and benzylic alcohols under neutral conditions.

Further studies in progress are concerned with the activation of molecular oxygen with nucleophilic compounds such as 5, the oxidation of other types of substrate such as thiols, and the preparation of analogues of 1 having optical activity.

## REFERENCES AND NOTES


1) P. Hemmerich, V. Massey and H. Fenner, *FEBS Lett.*, 84, 5 (1977) and references cited therein.
2) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Jpn.*, 48, 1484 (1975).
3) All new compounds in this paper were fully characterized spectroscopically and by combustion.
4) V. C. Farmer, M. E. K. Henderson and J. D. Dussell, *Biochem. J.*, 74, 257 (1960).
5) F. Yoneda, H. Yamato and M. Ono, *J. Am. Chem. Soc.*, 103, 5943 (1981).
6) F. Yoneda, K. Mori, S. Matsuo, Y. Kadokawa and Y. Sakuma, *J. Chem. Soc., Perkin Trans.* 1, 1981, 1837.
7) F. Yoneda, K. Tanaka, Y. Sakuma, H. Yoshino and M. Takomoto, *Chem. Pharm. Bull.*, 32, 3761 (1984).
8) The 5-hydroxy compound 6 was probably derived from the compound 5 during the work up and separation ($SiO_2$, $O_2$) procedure. Compound 5 was transformed into 6 in quantitative yield by *m*-cpba oxidation.
9) F. H. Westheimer, H. F. Fisher, E. E. Conn and B. Vennesland, *J. Am. Chem. Soc.*, 73, 2403 (1951).
10) M. Brüstlein and T. Bruice, *J. Am. Chem. Soc.*, 94, 6548 (1972).
11) F. Yoneda, K. Suzuki and Y. Nitta, *J. Am. Chem. Soc.*, 88, 2328 (1966).


(Received June 18, 1986)