OXIDATION OF 1,3-DIMETHYLTHYMINE AND 1,3-DIMETHYLURACIL WITH OXONE® IN THE SOLID TO SOLID STATE[1]

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Abstract - The oxidation of the title substrates with Oxone® in the presence of camphor in the solid to solid state afforded a simple and efficient method for epoxidation under mild reaction condition.

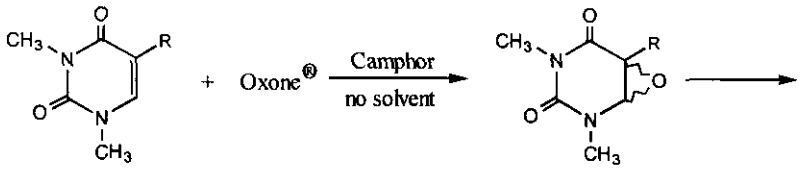
Organic reactions have been generally carried out in solution. It was, however, found that not only photochemical reactions, but also ground state organic reactions take place efficiently in the solid to solid state.[2]

Because of the oxidation of nucleic acid bases has been of interest in connection with the damage of nucleic acids by γ-irradiation and by active oxygen species,[3] and because most of the biological reactions proceed in the solid to solid like states rather than in solutions,[2] we tested this solid to solid state reaction methodology on the oxidation of 1,3-dimethylthymine (**1a**) and of 1,3-dimethyluracil (**1b**) with Oxone® in the presence of camphor as an oxygen transfer catalyst. Herein, we report the preliminary observed results of these oxidation reactions.

In this study, oxidation was simply performed by grinding the solid mixture of **1a** or **1b**, Oxone® and camphor with mortar and pestle for 10 min under a N_2 atmosphere in a glove box, then the resulting mixture was further ground in a ball mill for additional 5 days. The results of the oxidation of **1a** or **1b** obtained from the comparison experiments of the solution method in the presence of acetone and the present method are summarized in Table 1. Oxidation of **1a** by potassium peroxomonosulfate(Oxone®)[4] in water and by dimethyldioxirane in CH_2Cl_2[5] has been reported. In accord with previously reported results, we have isolated *cis*-5,6-dihydroxy-5,6-dihydro-1,3-dimethylthymine (**3a**)[6] and 5-hydroxy-1,3,5-trimethylbarbituric acid (**4**)[7] from the reaction of **1a** with Oxone® in the solid to solid state. No oxidation products were detected in the absence of camphor. Moreover, oxidation of **1a** with Oxone® in the presence of camphor and Molecular sieves 4Å gave (2,3),(5,6)-1,3-dimethylthymine-1,4-dioxane (**8**),[8] which is a dimeric product of **2a** and is analogous to the commonly known formation of 1,4-dioxan from ethylene oxide.

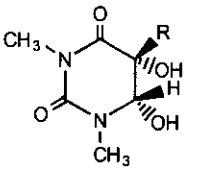
Postreaction treatment of the reaction mixture of **1a** with methanol gave **7a**[9] but such a treatment of **3a** resulted in no reaction. These findings could be readily explained by assuming that **2a** was also formed as an initial product in this oxidation reaction.

It has been reported that **2a** and **2b** were postulated to be the initial product when **1a** and **1b**, respectively, treated with dimethyldioxirane,[5] in the oxidation of 1,3-dimethylpyrimidine derivatives with peracids,[10] and in the α-diketone sensitized photooxidation of pyrimidine bases.[8] Oxidation of olefines with Oxone® in solution required the presence of carbonyl compounds such as acetone to create initially an oxygen transfer reagent, dimethyldioxiranes, which epoxidize olefine to form epoxides in situ.[11] Thus, it could be assumed that reaction of Oxone® with camphor in the solid to solid state, similarly, create camphordioxirane (**12**) or its equivalent, camphoroxide (**13**), as an oxygen transfer reagent which epoxidize (**1a**) or (**1b**) to form **2a** or **2b** in situ.



1a, R = CH_3
b, R = H

2a, R = CH_3
b, R = H



3a, R = CH_3
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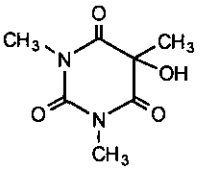

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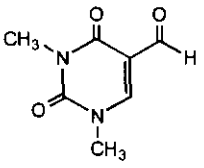

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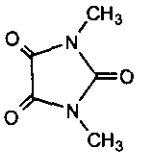

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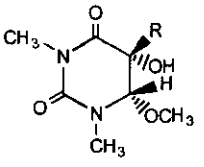
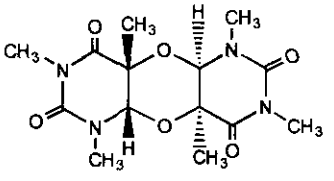


7a, R = CH_3
b , R = H



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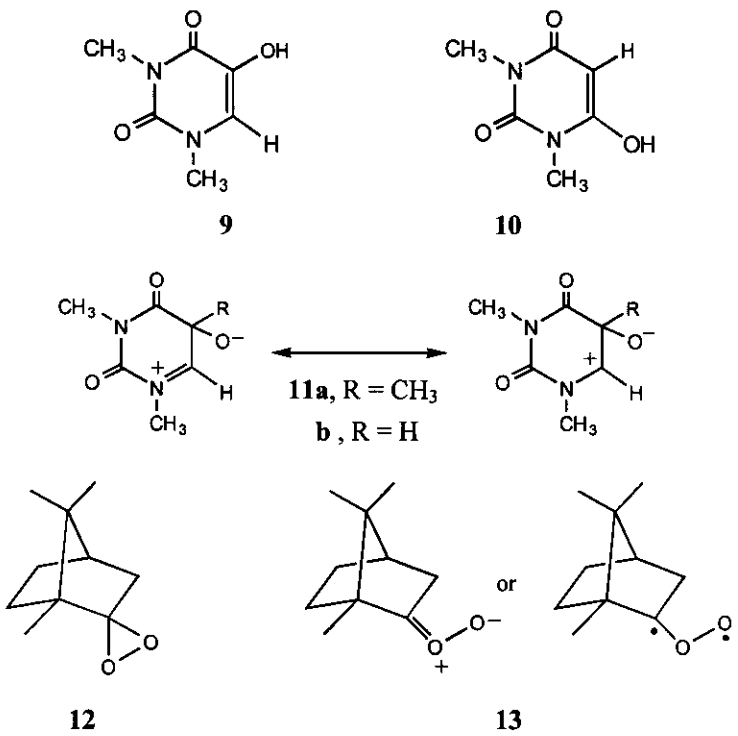

Table 1. Oxidation of 1,3-dimethylthymine and 1,3-dimethyluracil by Oxone® in the solid to solid state and in solution

Substrate (mmol)	Oxone®	Ketone; (mmol) A=Acetone C=Camphor	Reaction Time(day)	Temp (°C)	Product (isolated yield %)
1a[a]	2	5.5(A)	2	2	**3a**(21.4), **4**(64.1), **5**(1.8), **6**(1.8).
1a	5	5(C)	5	rt	**3a**(34), **4**(41).
1a[b]	5	5(C)	5	rt	**3a**(24), **4**(32), **7a**(9).
1a[c]	5	5(C)	6	rt	**3a**(12), **8**(10).
1b[a]	2	5.5(A)	2.4	2	**6**(41), **9**(10), **10**(6).
1b	5	5(C)	5	rt	**6**(57), **9**(5).
1b[b]	5	5(C)	5	rt	**6**(50), **9**(3), **7b**(trace).

[a] The reaction was performed in the presence of acetone in water. [b] Methanol was added to solid reaction mixture after grinding for 3 days. [c] The reaction was performed in the presence of Molecular Sieves 4 Å.

The direct epoxy ring opening of **2a** by the attacking of moisture present and/or the addition of moisture on **11a**, an α-stabilized nitrogen cationic intermediate, may be resulted the formation of **3a**, and **4**. The formation of a dimeric product (**8**) could be also explained by direct coupling of **2a** or **11a** under the anhydrous condition in the presence of Molecular Sieves 4 Å. An explanation for the formation of *cis*-

diol (**3a**) but it's *trans* isomer from **2a** or **12** was given in terms of an energetically favorable cisoid (gauche) stereochemistry.[4,5,8a] Different from oxidation of **1a** in solution, neither 5-formyl-1,3-dimethyluracil (**5**)[12] nor 1,3-dimethylprabanic acid (**6**)[13] was detected in the solid to solid state oxidation.
In contrast to the oxidation of **1a**, when oxidation of **1b** with Oxone® in solution or in the solid to solid state was performed, 1,3-dimethylparabanic acid (**6**) was always found as major product along with 1,3-dimethylisobarbituric acid (**9**)[14] or 6-hydroxy-1,3-dimethyluracil (**10**)[15] as minor products. Neither of *cis*-5,6-dihydroxy-5,6-dihydro-1,3-dimethyluracil (**3b**) nor it's stable *trans* isomer was presented in the products. The latter compounds were probably produced either directly from **2b** by a hydride transfer[16] or through unstable *cis*-diol (**3b**) by E2 type elimination of water.[17] Postreaction treatment of the reaction mixture of **1b** with methanol afforded trace amount of *cis*-5,6-dihydro-5-hydroxy-6-methoxy-1,3-dimethyluracil (**7b**).[18]
These findings could be also postulated the oxidation products of **1b** were derived from the initial product, (**2b**) or (**11b**), as it was the case in the oxidation of **1a**. 1,3-Dimethylparabanic acid (**6**) considered to be formed from either of **3b**, **9** or **10** by attacking of water present followed by decarboxylation accompanying with ring contraction process.
A typical experimental procedure is as follow: A mixture of 1,3-dimethylthymine [(**1a**), 1.7g, 12 mmol], Oxone® (36.8g, 60 mmol) and camphor (8.2g, 60 mmol) was ground with mortar and pestle at room temperature for 10 min under N_2 atmosphere in a glove box and further ground in a ball mill for 5 days. After quenching the reaction mixture by the addition of water, $CHCl_3$ was added and the mixture was filtered. Extraction with $CHCl_3$ and evaporation of the solvent, and the products, separated by tlc on silica gel with eluent EtOAc: n-Hexane(3:1), were found to be 5-hydroxy-1,3,5-trimethylbarbituric acid [(**4**), 41%] and *cis*-diol [(**3a**), 34%].

In conclusion, the solid to solid state reaction of Oxone® in the presence of camphor, though the reaction is slower, could serve as a simple and efficient method for epoxidation of 1,3-dimethylthymine and 1,3-dimethyluracil under mild reaction conditions.

ACKNOWLEDGEMENT
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