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Acceleration of the Dess–Martin Oxidation by Water

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The Dess–Martin periodinane (DMP), 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (**2**),[1] is one of the mildest and most convenient reagents available for oxidation of alcohols (Figure 1). DMP enjoys increasing use despite suggestion that its behavior can be capricious.[2] Recently, Ireland has addressed a problem of inconsistency in DMP batch quality by offering an improved procedure for synthesizing the reagent.[2] Important as it is to have a reliable method of preparing pure DMP, we suspect that many D–M (Dess–Martin) oxidations in the literature have been effected not by DMP, but by an impurity commonly present in DMP samples. In our own laboratory, a crucial D-M oxidation in the total synthesis of rapamycin[3] proceeded consistently only with a single 2-year old batch of the reagent, material that was largely insoluble in $CDCl_3$ and that exhibited a complex proton NMR spectrum. Several other samples of DMP, including relatively pure reagent prepared according to the Ireland method,[2] failed to perform the desired transformation. Questions about the composition of the effective sample motivated the present Dess–Martin periodinane study.

In attempts to obtain the impurities present in the effective DMP reagent, we explored Dess and Martin's preparation of the oxidant. However, pure, crystalline DMP was reproducibly obtained using their procedure by adhering to the following details: (1) In order to permit greater ease of stirring during oxidation of iodobenzoic acid, the initially viscous reaction mixture was more dilute than in the D-M preparation, which may ensure that oxidation proceeds to completion.[4] (2) Iodinane oxide **1** was heated at 85 °C in Ac_2O and AcOH at least 1 h beyond the time that dissolution was complete. (3) After acetylation, the mixture was allowed to stand for 1–2 days to permit crystallization of DMP.[5] (4) During isolation of the product, exposure to atmosphere was strictly avoided. The resulting DMP was crystalline and completely soluble in CH_2Cl_2 and $CDCl_3$. The reagent contained a small amount of AcOH, but otherwise its NMR spectra showed no significant (>3%) extraneous peaks.

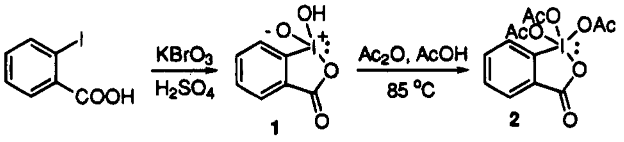

Figure 1.

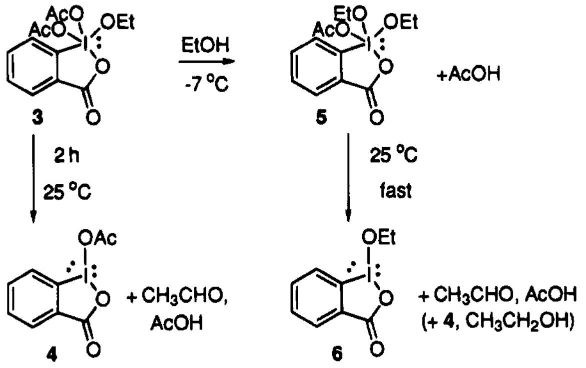

Figure 2.

When pure DMP prepared as above was used under inert conditions (flame-dried glassware, dry solvents, under N_2), oxidation of unactivated alcohols proceeded over several hours. However, small-scale oxidations were significantly accelerated by exposing the stirring mixtures to the atmosphere. Comparing the rates of alcohol oxidation when exposed to air (through a $CaSO_4$ drying tube) to the rate with the use of water-saturated CH_2Cl_2 as solvent (under N_2) demonstrated that water, and not oxygen, accelerated the reaction. A rationale for this rate enhancement follows from the work of Dess and Martin. They observed that the rate of ethanol oxidation was enhanced by the presence of an extra equivalent of alcohol (Figure 2), which causes intermediate periodinane **5** to decompose faster than intermediate **3**. A proposed explanation for this effect was that the increased electron-donating ability of an alkoxy substituent in place of acetyl may enhance the rate of dissociation of the remaining acetate ligand, leading to the production of **6** and the aldehyde. One equivalent of water added to alcohol and DMP would provide an intermediate analogous to **5** with hydroxy in place of the second alkoxy group, and this intermediate, too, may decompose more rapidly than **3**.

Access to this short-lived intermediate should be possible either by adding 1 equiv of water to alkoxydiacetoxyperiodinane **3** or by prehydrolyzing DMP with 1 equiv of water before addition of the substrate. Both methods provided enhanced oxidation rates. In the former method (Table 1, method B), optimal results were provided by vigorously stirring a CH_2Cl_2 solution of substrate and DMP while water was added as a dilute solution in CH_2Cl_2 (1 μL of H_2O/mL of CH_2Cl_2) via dropping funnel. The wet CH_2Cl_2 was added slowly enough that the solution remained translucent[6] until nearly 1 equiv of H_2O (relative to substrate) had been added, at which time the oxidation was complete. The latter procedure (Table 1, method C) involved prehydrolyzing DMP by slow addition of 1 or fewer equiv of H_2O

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[1] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

[2] Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

[3] Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906–7907.

[4] A monoacetylated product reported by Ireland (ref 2) to be a common product of the D–M acetylation conditions is 10-*I*-3-acetoxyiodinane (**4** in Figure 2), which would result from incomplete oxidation (Jon Collins, personal communication). A compound matching Ireland's reported spectra for this monoacetate is produced by reducing DMP with 1 equiv of ethanol.

[5] Solid DMP could be obtained immediately by cooling the mixture in an ice bath; however, the crystals thus obtained were smaller and more vulnerable to hydrolysis.

[6] For reaction mixtures involving H_2O and no large excess of DMP, the homogeneity of the reaction mixture was crucial. Insoluble material (presumably polymeric periodinane oxide **1**) seemed to seed precipitation (and thus inactivation) of the reagent at a rate that competed with oxidation of the substrate. Therefore, it was important that the DMP be pure and soluble. (A small amount of precipitate could be dissolved by pyridine.)

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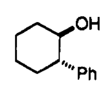
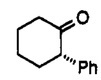
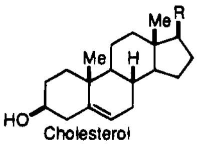
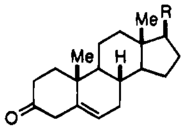
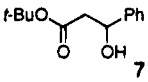
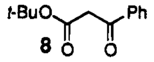
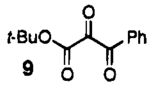
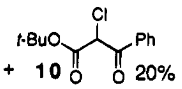
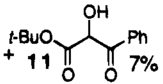
Table 1. Various Methods of Oxidation Using the Dess–Martin Periodinane[a]

Substrate	Entry/ (Method)	DMP	Equiv H_2O	py	Time	Product(s)	Yield
	1 (A)	1.5	--	--	14 h		97%
	2 (B)	1.5	1.1	--	0.5 h		97%
	3 (D)	4.9	excess	--	1.2 h		98%
 Cholesterol	4 (A)	1.6	--	--	8.5 h	 5-Cholesten-3-one	78%
	5 (B)	1.4	1.1	--	0.5 h		91%
	6 (A)	1.2	--	--	5 min		86%
	7 (C)	5.5	3.1	2.3	4 h		80%
	8 (A)	5.5	--	2.3	12 h	"	70%
	9 (A)	5.5	--	--	41 h	9 30% + 	50%
	10 (A)	4.2	4.0	--	1.3 h	9 65% + 	72%

[a] Methods: (A) anhydrous; reaction was under N_2; (B) water in CH_2Cl_2 was added to a stirring solution of substrate and DMP; (C) DMP was prehydrolyzed to a monoacetylated compound; (D) reaction solvent (CH_2Cl_2) was H_2O-saturated.

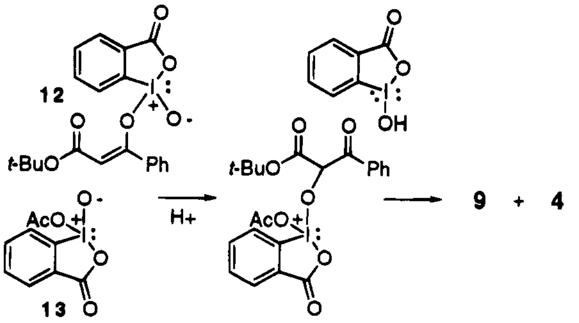


Figure 3.

in CH_2Cl_2. The resulting reagent solution was then transferred to a stirring solution of substrate in CH_2Cl_2. The reagent acetoxyiodinane oxide (**13** in Figure 3)[7] could be isolated in 80% yield by precipitating it from CH_3CN with ether. However, the compound became less soluble over several days (even when sheltered from moisture) and therefore was best used as a freshly-prepared solution.

A third procedure (Table 1, method D) involved use of a large excess of DMP with H_2O-saturated CH_2Cl_2 as solvent. The reaction mixture with this method appeared to be similar to that with use of an old or incompletely-acetylated batch of DMP. In both cases, oxidation rates were accelerated relative to reactions employing pure DMP under anhydrous conditions. Also, the mixtures were heterogeneous and became increasingly cloudy as the reagents precipitated out of solution. The danger of a heterogeneous reaction mixture is underscored by Dess and Martin's observation that, in an oxidation reaction where there are 2 equiv of alcohol relative to DMP, some of the alcohol may remain on the reduced iodine species (Figure 2); the resulting alkoxyperiodinane is not hydrolyzed under the standard $NaHCO_3/Na_2S_2O_3$ workup conditions.[1b]

Table 1 compares results of some D-M oxidations using the methods above with corresponding anhydrous conditions. Oxidation of *trans*-2-phenylcyclohexanol and cholesterol with DMP under anhydrous conditions took several hours (Table 1, entries 1 and 4). When wet CH_2Cl_2 was added dropwise to the alcohol–DMP complexes, the reactions were finished in 30 min. (Table 1, entries 2 and 5). For cholesterol, the reaction involving water was cleaner as well, because the product, 5-cholesten-3-one, was unstable to prolonged exposure to the reaction conditions.[8] Thus, whereas the yield of the anhydrous oxidation (78%) is good, the better results in the wet D–M reaction suggest that the latter method should be ideal for many sensitive substrates.

An application of DMP relevant to our synthesis of rapamycin is Golec's oxidation of β-dicarbonyl compounds to their corresponding tricarbonyl derivatives.[9] When β-hydroxy ester **7** was exposed to DMP in the absence of water or pyridine, the methylene oxidation required days and the yield was low (Table 1, entry 9). A significant

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[7] This material gave the following ^1H NMR ($CDCl_3$, 500 MHz) data: 8.29 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 7.1 Hz, 1H), 7.97 (t, J = 7.4 Hz, 1H), 7.90–7.83 (m, 1H), 2.27 (br s, 3H). Dess and Martin obtained acetoxyiodinane oxide in 36% yield while attempting to isolate *tert*-butoxydiacetoxyperiodinane, and this material oxidized less than 1 equiv of ethanol almost instantly (ref 1b). Acetoxyiodinane oxide obtained through their method (though we found heating to be necessary to promote formation of the monoacetate compound) exhibited a slightly different ^1H NMR spectrum than the one above. However, a co-NMR experiment established that the reagents were identical. The differences between spectra may be due to aggregation or oligomerization.

[8] Anhydrous oxidations of cholesterol left to stir just a few hours past probable completion suffered extensive decomposition (including some double-bond migration); with pyridine present, the destruction was worse.

[9] Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett.* **1993**, *34*, 167–170.

side product, identified as α-chloro derivative **10**,[10] was also formed; its chlorine atom is believed to have come from CH_2Cl_2 solvent. Greater efficiency in the methylene oxidation was provided by the addition of pyridine[11] or H_2O (entries 8 and 10). When wet CH_2Cl_2 was added directly to a stirring DMP–substrate mixture (entry 10), however, there resulted some incompletely oxidized α-OH compound **11**[12] as well as unidentified polar side products. Therefore, the optimum method of methylene oxidation involved prehydrolyzing the DMP (with added pyridine for solubility) before reaction with substrate **7** (entry 7).

A working mechanism for methylene oxidation is shown in Figure 3. Acetoxyiodinane oxide **13** (or DMP) may react with the enol form of β-dicarbonyl **8** to form iodinane enol ether **12** (or its diacetate analog). Attack of iodinane oxide **13** via an allylic substitution followed by a β-elimination would provide a direct route to tricarbonyl compound **9**.[13] Other potential nucleophiles that could react with an iodinane enol ether are water (to form α-OH compound **11**), acetate ion, and chloride (from decomposing CH_2Cl_2 solvent). Two consecutive additions of such nucleophiles could provide alternate routes to tricarbonyl **9**. In entry **8**, for example, the presence of pyridine permits tricarbonyl **9** to be obtained in good yield despite the absence of H_2O or acetoxyiodinane oxide **13**. One might propose an intermediate diacetoxy acetal whose formation and decomposition to a carbonyl would be facilitated by pyridine; however, no direct evidence for such an intermediate has been found.

In summary, our observations (following from those of Dess and Martin) may explain why impure samples of DMP in many cases provide better results than the pure reagent. Such heterogeneous samples contain acetoxyiodinane oxide **13** from partial hydrolysis of DMP (or incomplete acetylation), and this partially-hydrolyzed reagent is a more effective oxidant. However, these samples of DMP also contain varying amounts of fully-hydrolyzed material, iodinane oxide **1**, a polymer that seems to effect the precipitation of acetoxyiodinane oxide **13**. In practice, therefore, heterogeneous D–M oxidations require multiple equivalents of reagent, and they have a finite lifetime. For consistency, it is probably best in most cases to employ pure DMP. When rate enhancement is desired, the oxidant may be decomposed with an equivalent of water immediately before or during its use. Given such control over the reagent species present, the Dess–Martin oxidation can be as reliable as it is convenient.

Experimental Section

The following experiments were performed during dry, Cambridge, MA, winter months (with relative humidities of 30% or less). During limited summertime use of the Dess–Martin periodinane reagent (with laboratory humidities of 65–75%), greater care to avoid adventitious moisture was necessary. As an illustration, exposure of a D–M reaction mixture to an atmosphere with 20% humidity would provide enough moisture to cause some rate acceleration; however, brief exposure of a similar reaction solution to 75% humidity would quickly destroy the reagent. During humid conditions, the following modifications were useful: (1) DMP was weighed into a dry, N_2-purged vessel in a glove box. (2) To the neat DMP under N_2 was added 2,6-lutidine or pyridine (0.5 equiv or more) before dilution with CH_2Cl_2 (this order of solvent addition ensured reagent solubility). (3) Transfer operations and preparation of dilute H_2O solutions in CH_2Cl_2 (10 μL/20 mL) were performed in closed systems under N_2.

Caution! Iodinane oxide 1 was reported to be explosive under impact or heating to >200 °C.[14] **1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (2).** To 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**1**)[15] (19.6 g, 70.0 mmol) was added Ac_2O (61 mL, 0.64 mol) and AcOH (52 mL, 0.91 mol) under N_2. The vigorously stirring mixture was gradually heated to 85 °C over 1 h; 10 min later dissolution was complete. The clear solution was stirred an additional 1.3 h at 85 °C and then allowed to cool to rt under N^2. The solution was tightly sealed, wrapped in aluminum foil, and allowed to crystallize over 2 days.[5] The crystals were transferred under N_2 through a male–male adapter to a sintered-glass filter. A positive N_2 pressure was maintained during brief and intermittent applications of vacuum as the crystals were filtered and then washed with 5 × 30 mL ether (freshly distilled from Na-benzophenone ketyl). N_2 was passed through the reagent for 30 min before the pure, crystalline **2** (23.3 g, 78%) was directly transferred into several dry, N_2-purged amber vials.

Method B: **2-Phenylcyclohexanone.** Ten μL of H_2O (0.55 mmol) was solvated in 10 mL of CH_2Cl_2 by drawing the solvent mixture into and expelling it from a disposable pipet several times.[16] The wet CH_2Cl_2 was added slowly via dropping funnel to a vigorously stirring solution of *trans*-2-phenylcyclohexanol (88.4 mg, 0.502 mmol) and DMP (321 mg, 0.502 mmol) in 3 mL of dry CH_2Cl_2. The clear solution grew cloudy toward the end of wet CH_2Cl_2 addition, which required 30 min. The mixture was diluted with ether, then concentrated into a few mL of solvent by rotary evaporator. The residue was taken up in 30 mL of ether and then washed with 15 mL of 1:1 10% $Na_2S_2O_3$: saturated aqueous $NaHCO_3$, followed by 10 mL of H_2O and 10 mL of brine. The aqueous washings were back-extracted with 20 mL of Et_2O, and this organic layer was washed with H_2O and brine. The combined organic layers were dried with Na_2SO_4 and concentrated. Flash chromatography (20:1 to 10:1 hexane-ethyl acetate) provided 2-phenylcyclohexanone (84.7 g, 97%) as a crystalline solid.

Method C: ***tert*-Butyl 2,3-Dioxo-3-phenylpropionate (9).** DMP (630 mg, 1.48 mmol) was dissolved in 5 mL of dry CH_2Cl_2 with py (50 μL, 0.62 mmol). The solution was stirred vigorously as H_2O (15 μL, 0.83 mmol) in 15 mL of CH_2Cl_2 was added via dropping funnel over 1 h. The faintly milky but translucent reagent solution was poured into a stirring solution of β-hydroxy ester **7** (59.3 mg, 0.267 mmol) in 2 mL of dry CH_2Cl_2. The resultant mixture was stirred vigorously under N_2 for 4 h before dilution with ether and partial concentration by rotary evaporator. The residue was taken up in 40 mL of ether, and precipitates were removed by extraction with 2 × 20 mL of 1:1 10% $Na_2S_2O_3$:saturated aqueous $NaHCO_3$. The organic layer was washed with H_2O and brine. The combined aqueous washings were back-extracted with 20 mL of ether, and this organic layer was washed with H_2O and brine. The combined organic extracts were dried with Na_2SO_4 and concentrated. Flash chromatography (10:1–5:1 petroleum ether:ether) pro-

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[10] This α-chloro compound **10** could be oxidized with DMP in the presence of pyridine to form tricarbonyl compound **9**. Spectral data for *tert*-butyl 2-chloro-3-oxo-3-phenylpropionate (**10**): ^1H NMR ($CDCl_3$, 500 MHz), 4.4:1 keto:enol tautomers, data for major tautomer 8.00–7.96 (m, 2H), 7.62–7.59 (m, 1H), 7.50–7.46 (m, 2H), 5.46 (s, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 188.5, 164.0, 134.1, 133.6, 129.2, 128.8, 84.5, 59.2, 27.6; HRMS calcd for $C_{13}H_{15}O_3Cl$ $(M + NH_4^+)$ = 272.1041, found 272.1053.

[11] Golec's oxidation procedure involved pyridine (ref 9). In our application (ref 3), pyridine worsened decomposition and therefore was not added.

[12] Spectral data for *tert*-butyl 2-hydroxy-3-oxo-3-phenylpropionate (**11**): ^1H NMR ($CDCl_3$, 300 MHz) 8.05–8.02 (m, 2H), 7.65–7.59 (m, 1H), 7.51–7.46 (m, 2H), 5.47 (br d, J = 6.4 Hz, 1H), 4.11 (br d, J = 6.4 Hz, 1H), 1.31 (*S*, 9H); HRMS calcd for $C_{13}H_{16}O_4$ $(M + Na)^+$ = 259.0951, found 259.0946.

[13] Spectra data for tricarbonyl **9**: Wasserman, H. H.; Ennis, D. S.; Vu, C. B.; Schulte, G. *Heterocycles* **1993**, *35*, 975–995.

[14] Plumb, J. B.; Harper, D. *J. Chem. Eng. News* **1990**, July 16, 3.

[15] This material was prepared according to the Dess–Martin procedure (ref 1a) but at greater dilution (2-iodobenzoic acid was 0.18 M in 0.73 M H_2SO_4) to facilitate stirring. Also, the iodinane oxide was further rinsed with anhydrous ether following the ethanol washings as suggested by Ireland (ref 2).

[16] In practice it may be more efficient to water-saturate the CH_2Cl_2 using a separatory funnel; the wet CH_2Cl_2 may then be titrated into the reaction mixture based on progress of the oxidation by TLC.

vided **9**[13] (51.8 mg, 80%) as a yellow oil that by NMR was roughly a 1:1 ratio of tricarbonyl and hydrate.

Method D: **2-Phenylcyclohexanone.** *trans*-2-Phenylcyclohexanol (83.3 mg, 0.472 mmol) was dissolved in 12 mL of H_2O-saturated CH_2Cl_2. (Using a separatory funnel, the CH_2Cl_2 had been shaken with several milliliters of H_2O and then separated from the water layer). DMP was added (989 mg, 2.33 mmol), and the resultant cloudy reaction mixture was vigorously stirred for 1.2 h. 2-Phenylcyclohexanone (81.1 mg, 98%) was isolated from the reaction mixture by the procedure in method B.

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