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Oxidation of Indole Substrates by Oxodiperoxomolybdenum·Trialkyl(aryl)-phosphine Oxide Complexes

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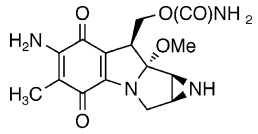
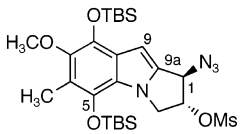
Abstract: A series of oxodiperoxo molybdenum complexes MoO_5·O=PR_3·L, where R = Me, Et, Pr, Bu, or Ph, have been synthesized. The X-ray crystal structures for the complexes with triethylphosphine oxide and tripropylphosphine oxide as ligands were obtained. These complexes oxidize indoles to various indolone products depending on the substitution pattern of the indole substrate.

From the onset of their discovery in the late 1960s, oxodiperoxo molybdenum complexes have been used for the oxidation of various functional groups.[1,2] First characterized by Mimoun and therefore referred to as Mimoun-type complexes, their most common use is as epoxidation reagents for alkenes. However, an added versatility of these compounds is their ability to oxidize the C2−C3 double bond of indoles.[3] Other reagents which oxidize the indole C2−C3 double bond to various products depending on the indole substitution pattern are dimethyldioxirane,[4] singlet oxygen,[5] *m*-CPBA or MMPP,[6] Co(salen),[7] thallium(III) acetate,[8] thallium(III) nitrate,[9] *N*-chlorobenzotriazole,[10] and DDQ.[11] During the course of developing a synthesis of the natural product, mitomycin C (Figure 1), we discovered that use of MoO_5·HMPA oxidizes the C9−9a double bond of azidomitosene **1** to give a ∼2:1 mixture of the diastereomeric methoxy ketones **7a** and **7b** in one step.[12] Furthermore, the HMPA ligand can be replaced by a trialkyl (or aryl) phosphine oxide to form MoO_5·O=PR_3·L (L = H_2O or MeOH or O=PR_3) complexes which also convert **1** into a ∼2:1 mixture of **7a/7b**. In comparison to the MoO_5·HMPA complex,[1,12] complexes **2**−**6** are more stable to room temperature and moisture and do not decompose as readily upon exposure to light. Herein we report the synthesis of a series of oxodiperoxo molybdenum complexes where R = Me, Et, Pr, Bu, or Ph, the X-ray crystal structures for complexes with triethylphosphine oxide and tripropylphosphine oxide ligands, and their oxidation of **1** and several simple indole substrates.



Mitomycin C



azidomitosene
1

FIGURE 1. Structure of mitomycin C and azidomitosene **1**.

The oxodiperoxo molybdenum complexes were synthesized by a modification of the method of Mimoun et al.[1] and Vedejs and Larsen.[13] Elemental analysis indicated that MoO_5·O=PR_3·MeOH is formed for R = Me (**2**) or Et (**3**), MoO_5·O=PR_3·H_2O for R = n-Pr (**4**),[14] and MoO_5·[O=PR_3]$_2$ for R = *n*-Bu (**5**) or Ph (**6**).[14]

All of these complexes oxidize **1** to a ∼2:1 mixture of the diastereomers **7a**/**7b** in a 60−75% combined yield along with 10−25% of an undesired benzopyrrole byproduct **12**, except for **2** which is not soluble in the dichloromethane/methanol solvent system used to run these reactions. It is likely that oxodiperoxo molybdenum complexes oxidize azidomitosene **1** through transient formation of the epoxide **8**, followed by formation of the iminium ion **9**. A second oxidation at C9 takes place leading to the formation of intermediate **10** as outlined in Scheme 1. The oxodiperoxo complexes of molybdenum and tungsten (including MoO_5·HMPA·H_2O) have been previously shown to oxidize secondary alcohols to the corresponding ketones in modest yields.[2e] Methanolysis of **10** then results in the diastereomeric mixture of products **7a** and **7b** in 60−75% combined yield. When the second oxidation at C9 does not take place, then loss of a proton leads to the enolate **11**, which is then converted into the undesired benzopyrrole **12** by loss of

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SCHEME 1

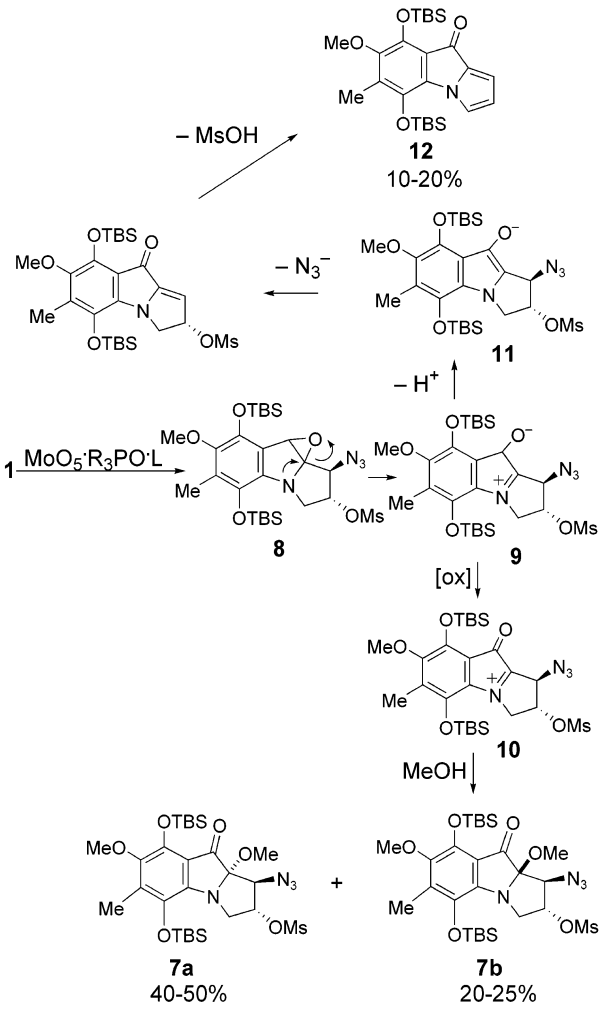


TABLE 1. Oxidation of the C9−9a Double Bond of 1

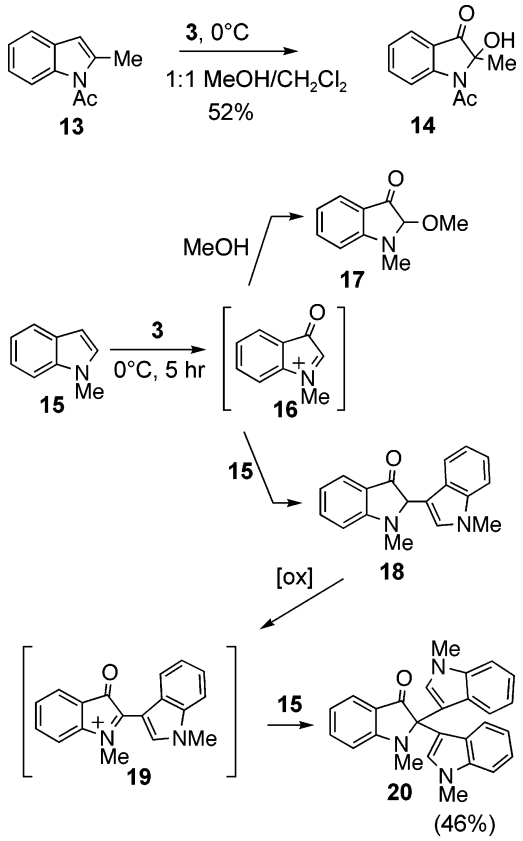
oxidant	% yield of **7a** + **7b**	% yield of **12**
MoO_5·R_3P=O·L		
R = Me; L = MeOH[a] (**2**) (unrecryst)	10	80
R = Me; L = MeOH[a] (**2**) (recryst from MeOH)		major
R = Et; L = MeOH (**3**) (recryst from MeOH)	72	25
R = n-Pr; L = H_2O (**4**) (unrecryst)	75	15
R = n-Pr; L = H_2O (**4**) (recryst from MeOH)	65	12
R =n-Bu; L = O=P(n-Bu)$_3$ (unrecryst)[b](**5**)	71	10
R= Ph; L = O=PPh_3 (**6**) (unrecryst)[c]	62	22

[a] Crystalline and crude material were insoluble in the CH_2Cl_2/MeOH solvent system. [b] Unable to obtain crystals due to the waxy nature of **5**. [c] Unable to obtain crystals and oxidant not very soluble in the CH_2Cl_2/MeOH solvent system.

azide and methanesulfonic acid. Table 1 shows the yields of the diastereomers **7a** and **b** and the benzopyrrole byproduct **12** obtained when **1** was oxidized with 6−8 equiv of the oxodiperoxo molybdenum complexes **2**−**6** in a 1:1 mixture of CH_2Cl_2/MeOH at 0−2 °C for about 12 h.

Some representative oxidations on indoles with various substitution patterns at C2 and C3 were carried out in 1:1 CH_2Cl_2/MeOH at 0 °C with the oxodiperoxo molybdenum complexes **3** and **4** (Scheme 2). Oxidation of 1-acetyl-2-methylindole **13** with **3** resulted in a 52% yield of the hydroxy ketone **14**. A similar result had been

SCHEME 2



reported previously for oxidation of **13** with MoO_5·HMPA.[3] Oxidation of 1-methylindole **15** gives a mixture of three products. Intermediate **16** gives rise to a methanolysis product **17** and an electrophilic aromatic substitution (EAS) product **18**. Ketone **17** is obtained as a ∼10:1 **17**/**20** mixture (∼19%), while **18** is obtained as a ∼1:2 **17**/**18** mixture (∼12%). As attempts to completely separate these compounds were not successful, tentative structural assignments were made based on the ^{1}H and ^{13}C NMR and mass spectral data. Further oxidation of **18** by loss of a hydride equivalent would result in the formation of intermediate **19**, which gives rise to an EAS product **20** (46%).[15] Oxidation of 1,2-dimethylindole **21** results in the formation of an EAS product **22**[16] exclusively in a 90% yield, while 1-methyl-2-phenylindole **23** gives both a methanolysis product **24**[17] (33%) and an EAS product **25**[18] (54%) (Scheme 3). The greater steric hindrance invoked by the phenyl group at the 2 position may slow the EAS reaction and allow the solvolysis reaction to become competitive. The mitosene **1**, which is also an indole substituted at the 1 and 2 positions, is apparently too sterically hindered to produce an EAS product, and thus only the methanolysis products **7a** and **b** are observed.

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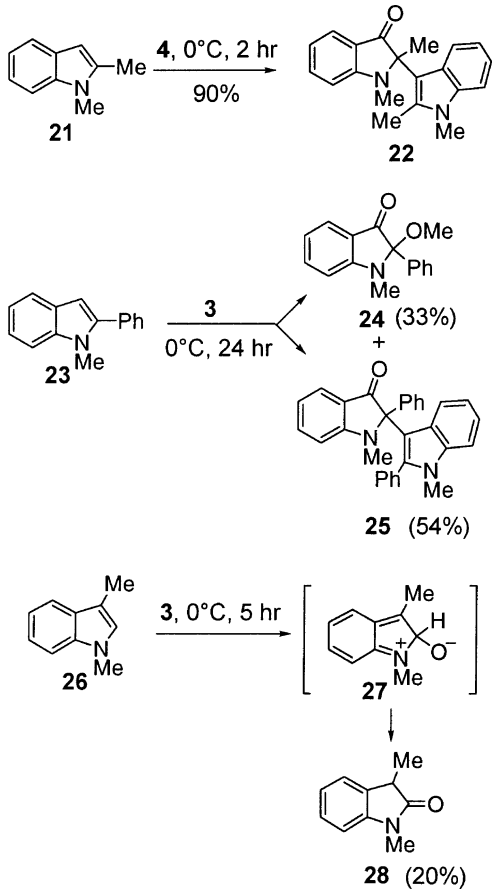
SCHEME 3



When indoles are substituted at the 1 and 3 positions as in 1,3-dimethylindole **26**, oxidation apparently occurs at C2 to give an intermediate **27** which tautomerizes to the indolone product **28**[19] in a low yield (20%).

The oxodiperoxo molybdenum complexes are useful in their ability to oxidize the C2−C3 double bond of indoles to indolone iminium species such as **10**, **16**, or **19**. The isolated products can be predicted to occur via solvolysis or EAS of these intermediates. In contrast, the oxidant dimethyldioxirane (DMDO) is unable to effect oxidation of **1** to **10** and results in a different product, the C9a hydroxy analogue of **7a**.[4b] DMDO appears to oxidize the enol form of **11** (Scheme 1) while the oxodiperoxo molybdenum complexes seem unable to effect this type of oxidation, losing azide and MsOH to form the benzopyrrole byproduct **12** instead. Thus these two different classes of reagents appear to oxidize indoles by complimentary reaction pathways.

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Supporting Information Available: X-ray crystal data, oxodiperoxomolybdenum complex preparation, and experimental procedures and compound characterization for the oxidations of indoles **1**, **15**, **21**, **23**, and **26** are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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