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# CONFORMATIONAL BIASING IN 1,3-OXIDATIVE REARRANGEMENTS OF DIENOLS§

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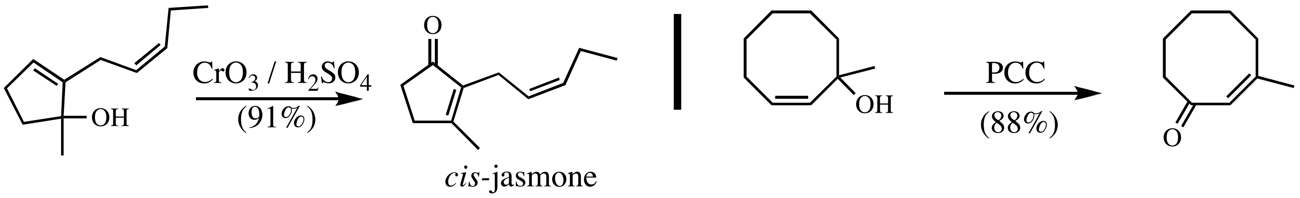
**Abstract** – 1-Vinyl-2-cycloalkenols are oxidized to form conjugated dienones in useful yields. Although this oxidative rearrangement is general, severe steric interactions can favor the formation of a conjugated dienal instead of a conjugated dienone. Several heterocyclic analogues were also studied.

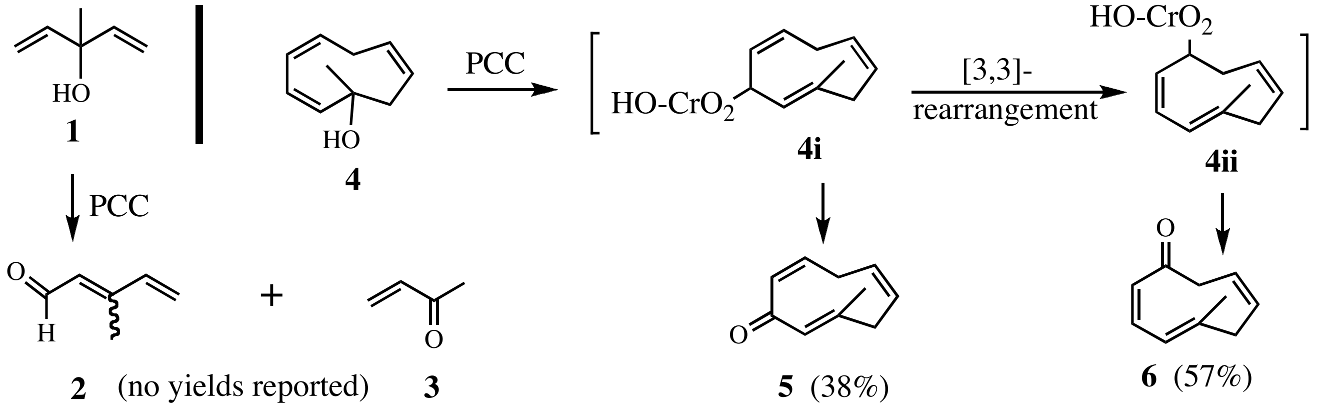
Since its discovery in the early seventies by Büchi and Egger,[1] the oxidative rearrangement of tertiary allylic alcohols to α,β-unsaturated ketones or aldehydes using chromium trioxide in aqueous 2.6 *M* sulfuric acid (Jones reagent) has been widely used in synthesis (Scheme 1).[2] Following the development of less acidic oxidants, such as pyridinium chlorochromate (PCC)[3] or pyridinium dichlorochromate (PDC),[4] Dauben and Michno reexamined the oxidation of tertiary allylic alcohols for the synthesis of a variety of cyclic and acyclic enones.[5] In contrast to the use of Jones reagent, the reaction conditions using PCC are mild enough to tolerate the presence of sensitive functional groups such as silyl ethers, esters, and isolated double bonds.

**Scheme 1**



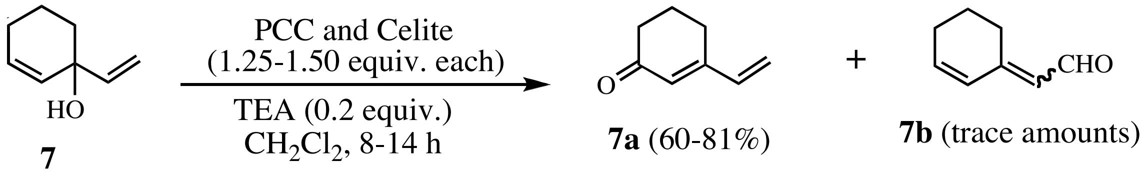
Prior to 1989, the study of the 1,3-oxidative rearrangement of substrates in which competing allylic rearrangements are possible was limited to only two examples (Scheme 2). In 1976, Babler and Coghlin noted that treatment of 3-methyl-1,4-pentadien-3-ol (**1**) with PCC afforded a mixture of the stereoisomeric 3-methyl-2,4-pentadienals (**2**),[6] and methyl vinyl ketone (**3**), the result of oxidative cleavage. In the second example, the oxidation of trienol **4** using PCC produces dienone **5** in 38% yield through the oxidation of intermediate **4i**, whereas dienone **6** is produced in 57% yield from intermediate **4ii**, the result of a second allylic transposition.[7]

**Scheme 2**



These observations prompted us to oxidize a series of *bis*-allylic alcohols in order to address the regioselectivity in analogues of **7** (Scheme 3).[8] In general, simple vinyl cyclohexenols and vinyl cyclopentenols rearrange exclusively involving the endocyclic double bond to give good yields of the β-vinylic cyclohexenone or cyclopentenone;[9] however, small amounts (< 5%) of the isomeric dienals were occasionally isolated. Our recent findings regarding the scope and limitations of this oxidative rearrangement, as well as additional insight into its mechanism, are reported herein.[10]

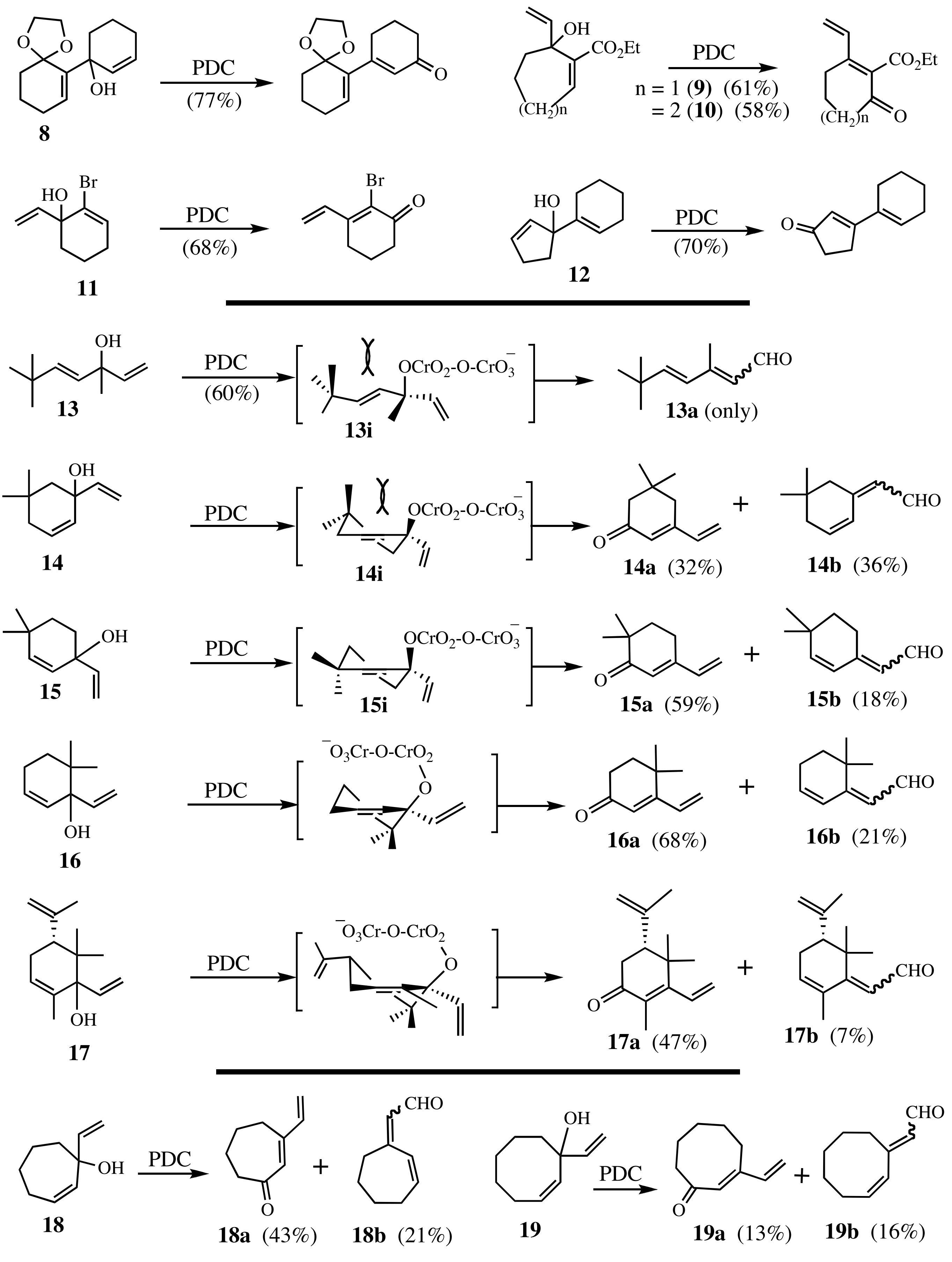
**Scheme 3**



Scheme 4 presents twelve dienols which were treated with PDC.[11,12] The oxidation of dienols **8-12** confirmed that acetals (cf. **8**), vinyl bromides (cf. **11**), and esters (cf. **9** and **10**) can tolerate the mild reaction conditions employed. Cyclic dienols **13-17** demonstrated that the introduction of nonbonded steric interactions increases dienal formation whereas the oxidation of dienols **11**, **12**, **18** and **19** revealed that the size of the ring containing the endocyclic double bond influenced the product distribution.

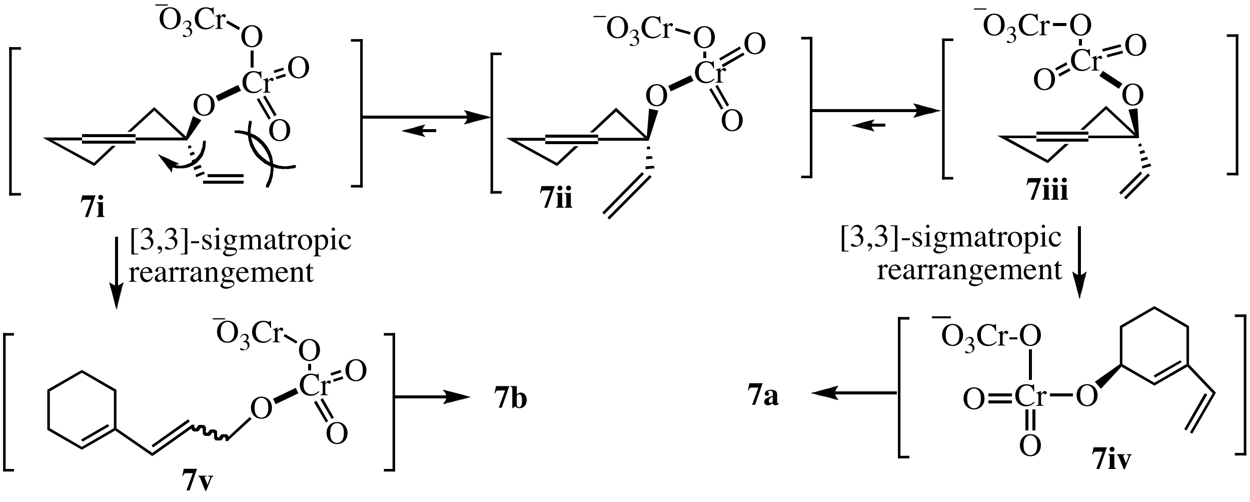
Although a solvolysis mechanism can be envisioned for each of these transformations, we believe these results are best explained in terms of a [3,3]-sigmatropic mechanism, and that the regioselectivity

**Scheme 4**


8
PDC
(77%)
n = 1 (9) (61%)
= 2 (10) (58%)
11
PDC
(68%)
12
PDC
(70%)
13
PDC
(60%)
13i
13a (only)
14
PDC
14i
14a (32%)
14b (36%)
15
PDC
15i
15a (59%)
15b (18%)
16
PDC
16a (68%)
16b (21%)
17
PDC
17a (47%)
17b (7%)
18
PDC
18a (43%)
18b (21%)
19
PDC
19a (13%)
19b (16%)

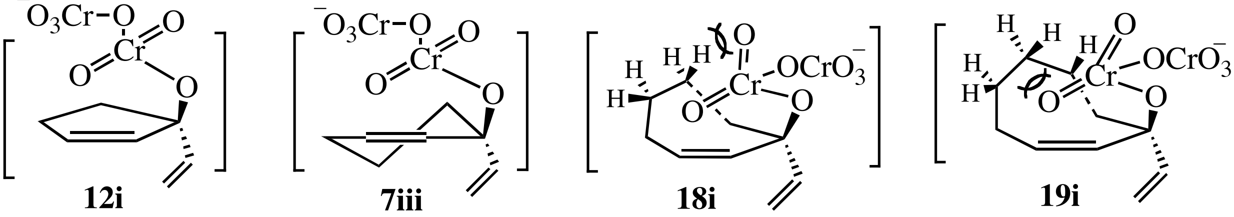
observed is the result of conformational biasing. For example, the chromate ester derived from the *bis*-allylic alcohol **7**, the simplest substrate studied, should adopt a conformation in which the chromate group resides in a pseudoequatorial position (cf. **7i**, Scheme 5). However, in this conformation nonbonded steric interactions between the chromate ester and the vinyl group would cause the vinyl susbstituent to rotate away from the chromate moiety (cf. **7ii**). Once the chromate ester adopts a rotamer in which it is above the endocyclic double bond (cf. **7iii**), a [3,3]-sigmatropic rearrangement produces intermediate **7iv**, the further oxidation of which irreversibly produces conjugated dienone **7a**. In the case of the acyclic dienol **13**, the disubstituted double bond of chromate ester **13i** is much more hindered than the vinyl group, hence only dienal formation is observed. Similarly, significant steric interactions between the chromate ester and the indicated methyl group of **14i** disfavors the sigmatropic rearrangement with the endocyclic double bond and dienal **14a** is the major product. In contrast, the geminal dimethyl groups present in substrates **15**, **16**, and **17** do not interact with the chromate ester resulting in the preferred formation of the conjugated dienones.

**Scheme 5**



Conformational biasing also accounts for the trend that larger cyclic dienols produce more dienals. In particular, the nearly planar, rigid conformer **12i** has few non-bonded steric interactions between the carbocyclic methylene units and the chromate ester to destabilize this conformation (Scheme 6).

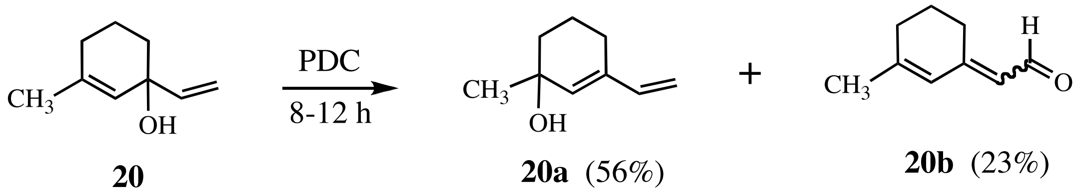
**Scheme 6**



A chair-like conformation of **7iii** also has few significant nonbonded steric interactions. In contrast, the more flexible cycloheptenol and cyclooctenol rings can adopt multiple conformations, several of which introduce significant steric congestion (e.g. **18i** and **19i**), thereby favoring the formation of the dienal.

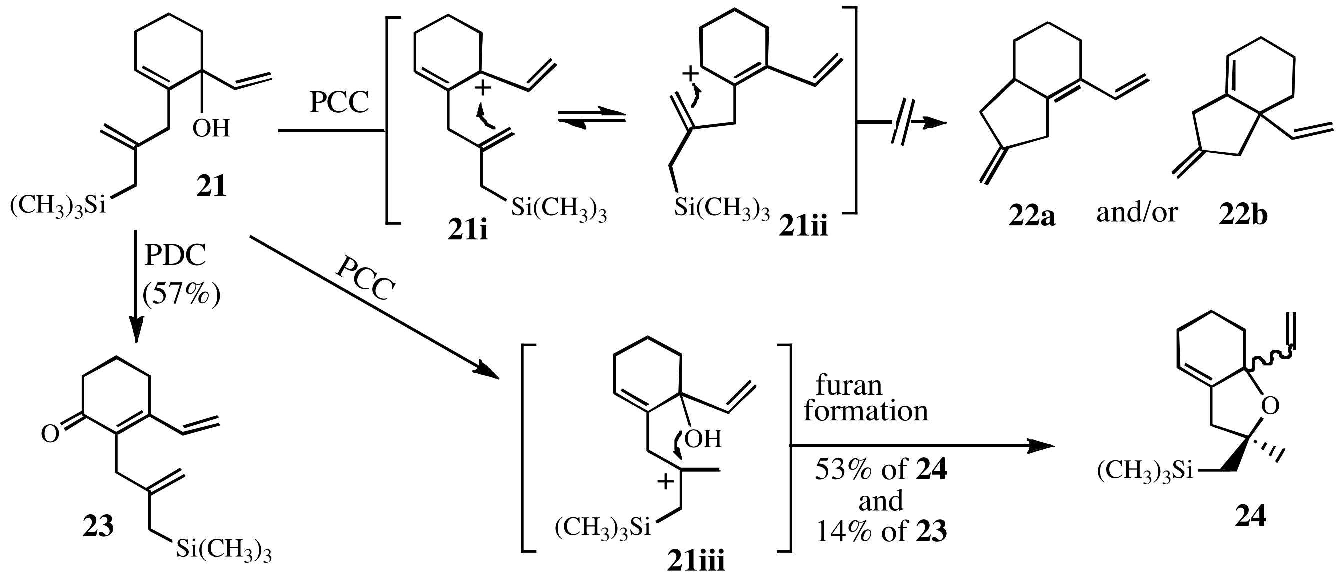
Additional support for endocyclic selectivity in the [3,3]-sigmatropic rearrangement can be found in the oxidation of 3-methyl-1-vinyl-2-cyclohexenol (**20**) which can only undergo irreversible oxidation at the terminal carbon of the vinyl substituent (Scheme 7). Although a 23% yield of the *E* and *Z* isomers of acetaldehyde **20b** is produced, tertiary alcohol **20a** nevertheless predominates (56%).

Scheme 7



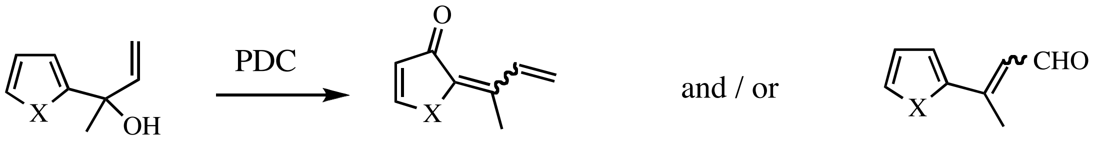
The oxidation of allylsilane **21** could form annulation products **22a** and **22b** if discrete carbocation intermediates (cf. **21i** and **21ii**) were involved. However, treatment of allylsilane **21** with two equivalents of PCC gave a mixture of products from which dienone **23** was isolated in only 14% yield and heterocycle **24** was isolated in 53% yield (Scheme 8). In contrast, treatment of **21** with PDC cleanly afforded dienone **23** in 57% yield. We believe that bicyclic heterocycle **24** is the result of the protonation of the allylsilane moiety by capricious acid present in the PCC (cf. **21iii**). When PDC was employed, the buffered reaction medium prevented furan formation and the dienone was produced in good yield.

Scheme 8



It is well known that pyrroles are more reactive than furans, which in turn are more reactive than thiophenes. We were curious whether the tertiary alcohols **24**-**26** would oxidize the C(3) positions of the aromatic rings or produce the corresponding functionalized enals (Scheme 9). Treatment of pyrrole derivative **24** with PDC (and buffer) might have produced 2-alkylidenepyrrolinone **24a** or enal **24b**, but these products rapidly decomposed.[13] Treatment of furan derivative **25** with PDC did not produce furanone **25a;** instead enal **25b** was isolated in 60% yield. Finally, since thiophenes are the most aromatic in character of these three heterocycles, it was not surprising that oxidation of thiophene derivative **26** only produces enal **26a** in 70% yield.

**Scheme 9**



x = NH (**24**)
= O (**25**)
= S (**26**)

x = NH (**24a**) decomposes
= O (**25a**) (0%)
= S (**26a**) (0%)

x = NH (**24b**) decomposes
= O (**25b**) (60%)
= S (**26b**) (70%)

In conclusion, the above results are most consistent with this type of oxidation occurring via a [3,3]-sigmatropic rearrangement mechanism whereby the formation of the conjugated dienone predominates unless there are severe steric interactions present in the transition state, which leads to the formation of significant quantities of the conjugated dienal.

## ACKNOWLEDGEMENTS

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## REFERENCES AND NOTES

§ In honor and celebration of the 75th birthday of Professor Ekkehard Winterfeldt of the *University of Hannover*.

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9. For other oxidative routes for the preparation of β-vinylic cycloalkeneones, see: Z. Jin and P. Fuchs, *J. Am. Chem. Soc.,* 1994, **116**, 599; B. M. Trost and T. Schmidt, *J. Am. Chem. Soc.*, 1988, **110**, 2301-2303.
10. All yields are isolated yields. The spectroscopic data obtained for all new compounds were fully consistent with the assigned structures.
11. The optimum conditions for these oxidations consist of using 1.25 to 1.50 equivalents of pyridinium dichromate (PDC) with an amount of dry Celite equal to the number of equivalents of the oxidant and 0.20 equivalents of triethylamine as an acid scavenger. The reagents were added to dry $CH_2Cl_2$ and stirred at rt for 8 to 14. Standard ethereal workup, followed by chromatography, provided the yields cited.
12. The preparation of 3-ethenyl-2-cyclohexen-1-one is a representative example of this oxidative protocol: A 50-mL flame-dried two-neck round-bottom flask under a positive pressure of dry nitrogen was charged with 4.54 g of PDC (12.09 mmol), 4.50 g of Celite, 225 mL of dry triethylamine (1.61 mmol) and 15 mL of anhydrous $CH_2Cl_2$. To this mixture was added a solution containing 1.00 g of ethenyl-2-cyclohexen-1-ol (8.00 mmol) in 10 mL of anhydrous $CH_2Cl_2$. The resulting mixture was stirred at ambient temperature and monitored by TLC analysis until the starting material was completely consumed (~12 h). The reaction mixture was diluted with $Et_2O$ (100 mL) and filtered through a plug of glass wool. The solids were washed with $Et_2O$ (20 mL). The filtrate was washed once with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The crude residue was chromatographed on silica gel 60 (230-400 mesh ASTM) using freshly distilled reagent grade solvents (elution with hexanes/ $Et_2O$, 4:1) to provide 803 mg (81% yield) of 3-ethenyl-2-cyclohexenone which was homogeneous by TLC.
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