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Observations on the regioselectivity of some Baeyer–Villiger reactions

Michael Harmata* and Paitoon Rashatasakhon

Department of Chemistry, University of Missouri-Columbia, Columbia, MO 65211, USA

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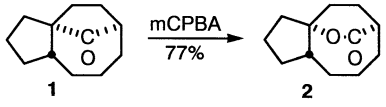
Abstract—The Baeyer–Villiger reaction of a series of compounds related to an intermediate in our synthesis of (+)-dactylol showed a pattern of regioselectivity which could be varied to a small extent as a function of substitution on the precursor. A very unusual Baeyer–Villiger reaction of a methyl ketone resulted in a product from apparent insertion of an oxygen atom into between the carbonyl carbon and the methyl group of the acetyl functionality. © 2002 Elsevier Science Ltd. All rights reserved.

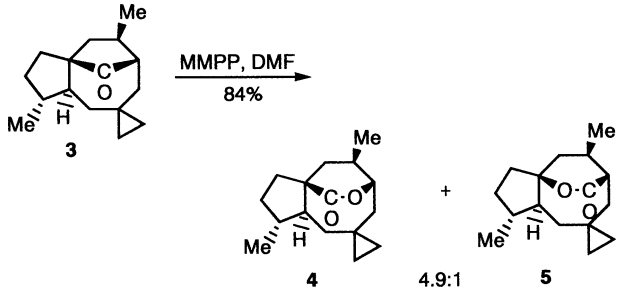
The Baeyer–Villiger (BV) reaction is an important process for the synthesis of lactones and esters from ketones.[1] Usually, the process involves the reaction of a ketone with a peracid. It is commonly understood that this results in the formation of a tetrahedral (Criegee) intermediate which rearranges with elimination of the carboxylic acid fragment corresponding to the peracid used in the oxidation, resulting in the formation of an ester or lactone. In general, the regiochemical outcome of the reaction involves migration of the more-substituted side of the ketone to afford, in the case shown in Scheme 1, a lactone such as **2**.[2] In addition to this inherent kinetic preference for bond migration, both a primary and secondary stereoelectronic effect are considered important in determining the regiochemistry of the reaction.[3,4] Exceptions to the common regiochemical outcome shown are known.[5] This letter reports a case of a BV reaction proceeding with the 'wrong' regiochemistry and studies conducted in order to understand the structural features of the molecule responsible for the result. It also presents a very unusual BV reaction in which an acetyl group flanked by a tertiary carbon apparently experiences oxygen insertion into the carbonyl carbon–methyl group bond.

As part of our recent total synthesis of (+)-dactylol, we carried out the BV reaction shown in Scheme 2.[6] Treatment of ketone **3** with magnesium monoperoxyphthalate (MMPP) in DMF at room temperature for 2 days afforded a mixture of ketones. We were surprised to find that the reaction favored the formation of the regioisomer **4** by a ratio of 4.9:1.[6,7] We thus decided to examine Baeyer–Villiger reactions of compounds related to **3** to gain further understanding of the regioselectivity.

We hypothesized that the peracid would attack the carbonyl of ketone **3** from the face *cis* to the methyl group on the cyclopentanone ring, a conclusion based on the examination of molecular models. The primary electronic effect associated with the BV reaction requires that the migrating bond be antiperiplanar to the oxygen–oxygen bond of the perester functionality in the Criegee intermediate. We thought that the methyl group on the cyclopentanone would sterically disfavor the conformation necessary to produce lactone **5**. In the absence of reactivity differences between the two con-



Scheme 1.



Scheme 2.

* Corresponding author. Tel.: 573-882-1097; fax: 573-882-2754; e-mail: harmatam@missouri.edu

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formations, this should result in the increased formation of **4**, as observed. Further, the secondary stereoelectronic effect in the BV reaction[4] suggests that bond migration is favored for that bond which is antiperiplanar to a lone pair of electrons of the hydroxy group of the Criegee intermediate. This is illustrated by the Newman projection shown in Fig. 1. Models suggest that the favored conformation of the hydroxy group in the Criegee intermediate should place the hydrogen in the least sterically encumbered region of space. This puts a lone pair of electrons antiperiplanar to the less-substituted carbon–carbon bond and thus kinetically favors the formation of **4**. Other factors, including torsional and steric strain effects, could also contribute to the regiochemistry observed.[9]

As a test of the effect of the methyl group on the cyclopentanone ring of **3** on the regiochemical outcome of the BV reaction, ketone **6** was subjected to treatment with MMPP in DMF (rt, 24 h). The lactones **7** and **8** were isolated in 89% yield in a ratio of 1:3.9 (Scheme 3). While this is not an exceptionally high regioselectivity, the outcome is in accord with what is expected based on standard mechanistic considerations for the reaction and supports the idea that the methyl group on the five-membered ring in **3** helps direct the migration of the less-substituted group, in support of our analysis.

In order to see if the cyclopropane ring exerted any effect on the reaction,[10] **6** was subjected to hydrogenolysis and the resulting ketone **9** oxidized under BV conditions as described previously (Scheme 4). Lactones **10** and **11** were isolated in 78% yield in a ratio of 1:3.3. It appears that presence of the cyclopropane ring slightly favors the formation of the normal regioisomer relative to the dimethyl substituents. It is possible that this is due to a small change in the populations of the hydroxy group in the Criegee intermediate, but the effect is not very large.

Based on these data, one would predict that the ketone **12** should react with a slightly higher regioselectivity than its cyclopropyl congener **3** to afford a mixture of lactones in which the product derived from migration of the less-substituted group predominates to an extent greater than 4.9:1. This is not the case. Treatment of **12** with MMPP gave a mixture of lactones **13** and **14** but in a ratio of only 1.7:1 (Scheme 5).

It appears likely that the regiochemical outcome of BV reactions in this class of compounds is determined by several effects, none of which have an overriding influence on the reaction course. Primary and secondary electronic effects operate and their directional effects are dictated by conformational preferences of the Criegee intermediate. Structural variables that are playing a role in determining these conformational preferences no doubt make an important contribution. This is most clearly indicated by the regiochemical differences in the oxidation of **3** and **12**. Effects associated with torsional strain and other steric influences are probably also important. The bottom line is that syntheses dependent on high levels of regiocontrol in this reaction need to consider the possible causes of lack of regiocontrol.

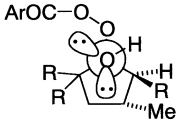
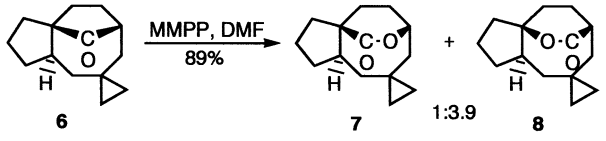


Figure 1.

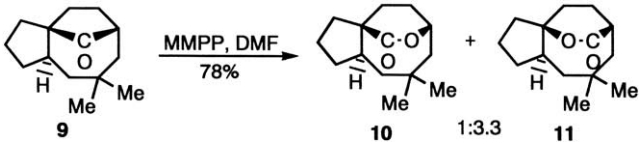
Another interesting BV reaction took place in our attempts to make use of the lactone **15** for the synthesis of (+)-dactylol.[6] We envisaged conversion of the lactone **15** to an enol ether using the Tebbe reagent. Hydrolysis would then afford the ketone **16**. A BV reaction on this compound would then give the acetate **17**.

The reaction of **15** with the Tebbe reagent and subsequent hydrolysis gave the ketone **16** in 60% yield for two steps. This compound was identified by spectroscopic means and the data strongly support the structure shown.[11] Reaction of hydroxyketone **16** with MMPP afforded not the expected acetate **17** but the starting lactone **15** (Scheme 6). This reaction has been repeated four times with no change in the outcome.

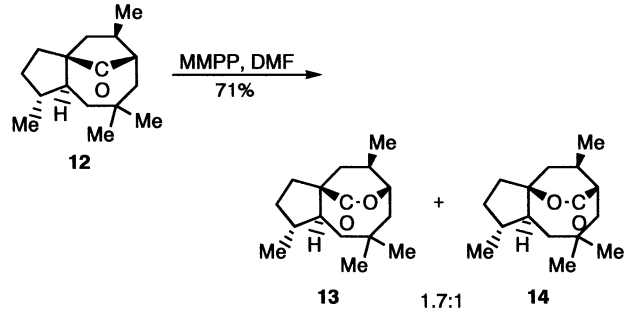
We presume that during the course of the reaction an intermediate such as **18** forms and the methyl migration take place in preference to alkyl group migration (Scheme 7). Methyl migration relieves transannular interactions; migration of the other bond would give a



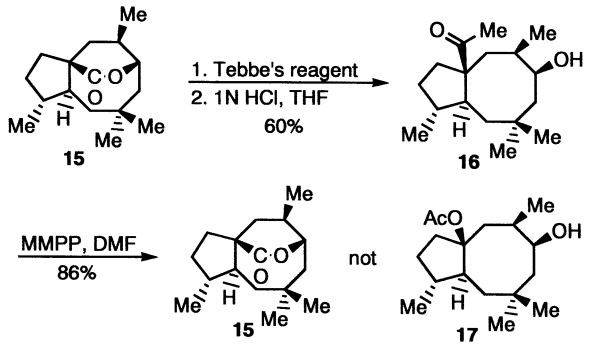
Scheme 3.



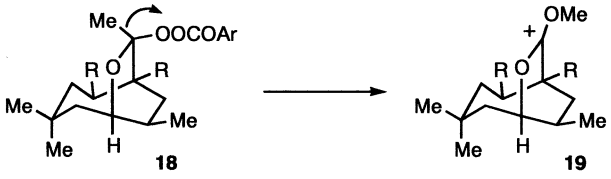
Scheme 4.



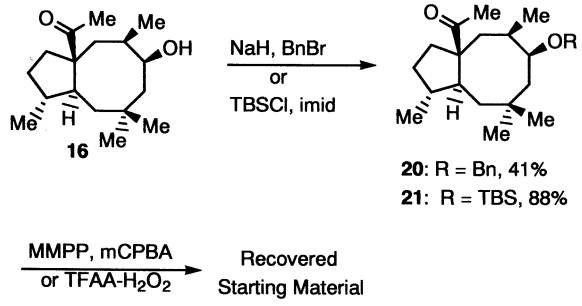
Scheme 5.



Scheme 6.



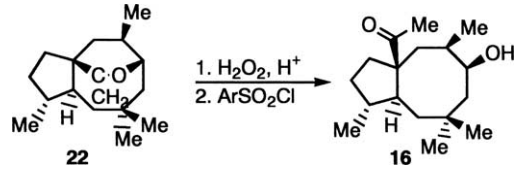
Scheme 7.



Scheme 8.

strained seven-membered ring. Hydrolysis then gives the lactone **15**. To the best of our knowledge a reaction such as this is without precedent. Attempts to protect the hydroxy group in **16** and carry out the BV reaction have not been successful, as shown in Scheme 8. Attempts to prepare a hydroperoxide from the enol ether **22** and carry out a subsequent Criegee rearrangement have met with failure.[12] Only hydrolysis to the ketone **16** was observed (Scheme 9).

In summary, we have examined several Baeyer–Villiger oxidations in a series of polycyclic ketones. The regiochemical outcomes of the reactions are unexpected based on simple expectations. It is important to remember that such reactions are controlled by steric, electronic and substituent effects but that at least some control over regiochemistry can be exerted by appropriate structural changes in the molecule and presumably the reagent as well. However, based on our studies with **3**, the direction of the regiochemical outcomes in these reactions do not appear to be affected by the reagents or reaction conditions.[8] The conversion of **16** to **15** appears to be without precedent and we are currently attempting to understand the mechanistic basis of the result. Further results will be reported in due course.[13]



Scheme 9.

Acknowledgements

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2. Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860–2871.
3. For an example and leading references pertaining to the existence of the primary stereoelectronic effect, see: Crudden, C. M.; Chen, A. C.; Calhoun, L. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2852–2855.
4. For experimental evidence in support of a secondary stereoelectronic effect, see: (a) Noyori, R.; Kobayashi, H.; Sato, T. *Tetrahedron Lett.* **1980**, *21*, 2573–2576; (b) Noyori, R.; Sato, T.; Kobayashi, H. *Tetrahedron Lett.* **1980**, *21*, 2569–2572.
5. See Ref. 1 and for examples in polycyclic systems, see: Krow, G. R. *Tetrahedron* **1981**, *37*, 2697–2724.
6. Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913–2915.
7. We initially reported the ratio of **4**:**5** as being 4:1.[5] This was determined by isolation of the individual products. The ratio reported here was determined by GC analysis of a crude reaction mixture. The regiochemistry of each lactone isomer was assigned based on NMR spectral data. For example, the bridgehead proton in lactone **4** (-COO-CH) resonates at 4.36–4.31 ppm, whereas that in lactone **5** (-OOC-CH) appears at 2.66–2.38 ppm. Also, in a DEPT 135 experiment, the ^{13}C signal of the carbon adjacent to the oxygen in lactone **4** (85.4 ppm) corresponds to a -CH- group, while that in lactone **5** (90.6 ppm) corresponds to a quaternary carbon. For **4** and **5**, the assignment was confirmed by X-ray analysis. Structural assignments for other lactones were made in a similar fashion.
8. Other reagents also favored the formation of **5**: reagent, ratio **4**:**5**, solvent, temperature, time, yield: (a) mCPBA/$NaHCO_3$, 6:1, CH_2Cl_2, rt, 5 days, 67%; (b) TFAA/H_2O_2, 5:1, CH_2Cl_2, 0°C–rt, 3 days, 36%; (c) mCPBA/TFA, 4:1, CH_2Cl_2, 0°C–rt, 48 h, 53%; (d) peracetic acid/NaOAc, 9:1, AcOH, rt, 48 h, 31%. The ratios in these experiments were determined by isolation of the individual products.
9. See Ref. 5 and Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611–4613.
10. To the best of our knowledge, no systematic study of the directing effect of a cyclopropyl substituent beta or gamma to a ketone has been conducted for the BV

reaction. However, see: Marshall, J. A.; Ellison, R. H. *J. Org. Chem.* **1975**, *40*, 2070–2073.

11. Data for **16**: $[\alpha]_D^{20} = +33.33$ ($c = 1.0$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.20$–3.71 (m, 1H), 2.15 (s, 3H), 2.09–1.96 (m, 2H), 1.89–1.71 (m, 4H), 1.66–1.30 (m, 5H), 1.28–1.13 (m, 3H), 1.07 (d, $J = 6.7$ Hz, 3H), 0.98–0.90 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 213.7$, 72.4, 60.8, 49.4, 41.2, 41.3, 39.0, 36.8, 36.6, 34.7, 32.0, 31.8, 30.8, 27.6, 23.8, 20.6, 19.9; IR (KBr) 3465w, 2953s, 2875m, 1700s, 1466m, 1359m, 1266m cm^{-1}. Anal. calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35. Found: C, 76.70; H, 11.48.
12. (a) Menges, M.; Brückner, R. *Synlett* **1993**, 901–905; (b) Schreiber, S.; Liew, W. *Tetrahedron Lett.* **1983**, *24*, 2363–2366; (c) Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1984**, *25*, 617–620.
13. All new compounds exhibited satisfactory ^1H and ^{13}C NMR data as well as satisfactory combustion analysis or high resolution exact mass data.