

Bleach/Acetic Acid-Promoted Chlorinative Ring Expansion of [2.2.1]- and [2.2.2]-Bicycles

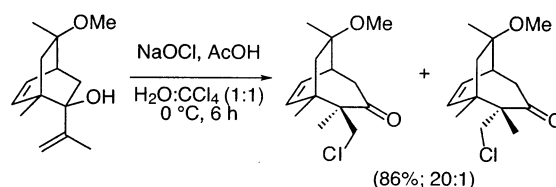
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ABSTRACT



Treatment of vinyl-substituted [2.2.1]- and [2.2.2]-bicyclohexanols with NaOCl and AcOH provides [3.2.1]- and [3.2.2]- β -chloro-bicycloketones, respectively. For [2.2.2]-bicycles, these chlorinative ring expansions are particularly efficient and selective.

Nearly 30 years ago, Johnson¹ described the chlorinative ring homologation of simple cyclobutanes, -pentanes, and -hexanes and isopropenyl [2.2.1]-heptanol (**1**). As reported, treatment of a warm, dark solution of **1** with *t*-BuOCl afforded a mixture of [3.2.1]- β -chloroketones (Scheme 1, conditions a). Despite the relatively mild nature of this chlorinative rearrangement, to the best of our knowledge, its use in the expansion of bicyclic molecules beyond the isopropenyl-containing [2.2.1] framework of **1** has not been studied.²

Due in part to our interest in the ring expansions of bicyclic ketones,³ we wanted to learn more about the regio-, chemo-, and stereoselectivity of this process. Of particular interest was the reaction of [2.2.2]-bicyclic carbinols substituted with different vinyl groups. We also wanted to explore alternative conditions to obviate both the use of potentially explosive *t*-BuOCl⁴ and the reported need to perform these reactions in the dark.

At the start of this investigation, we deemed it prudent to confirm the structural assignments of **2–5** using high-field

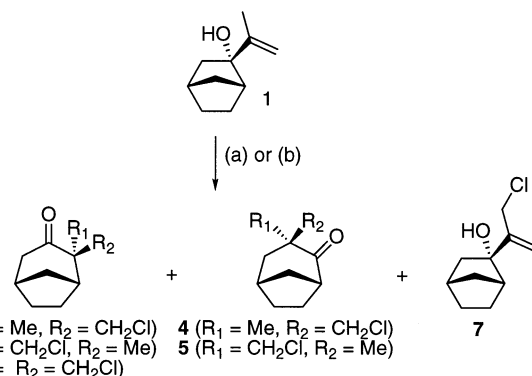
(1) (a) Johnson, C. R.; Herr, R. W. *J. Org. Chem.* **1973**, *38*, 3153–3159. (b) see also Johnson, C. R.; Cheer, C. J.; Goldsmith, D. J. *J. Org. Chem.* **1964**, *29*, 3320–3323.

(2) For a review of one-carbon ring expansions of bridged bicyclic ketones, see: Krow, G. R. *Tetrahedron* **1987**, *43*, 3–38.

(3) Mi, B.; Maleczka, R. E., Jr. *Tetrahedron Lett.* **1999**, *40*, 2053–2056.

(4) Simpkins, N. S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 2, 889–891.

Scheme 1



conditions:	% yields: 2 3 4 5 6 7						
(a) <i>t</i> -BuOCl, dark, 12 hr, 55 °C, CHCl ₃ :	34	23	29	7	2	0	
(b) NaOCl, HOAc, 6 hr, 0 °C, H ₂ O/CCl ₄ (1:1):	36	28	19	6	<1	10	

and NOE NMR methods unavailable at the time of Johnson's original report. Furthermore, as we sought a preparative way to chlorinatively ring-expand bicyclic molecules, the isolated yields of **2–5** needed to be determined.⁵ Isopropenyl [2.2.1]-heptanol **1** was obtained by simple Grignard addition to norcamphor (a 50:1 mixture of diastereomeric carbinols

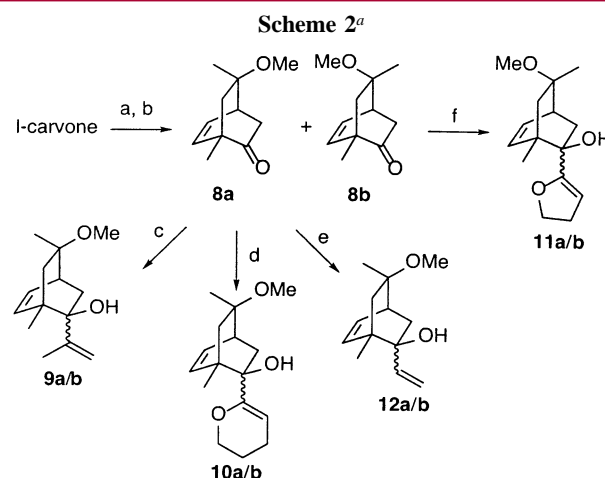
(5) Johnson and Herr (ref 1a) reported GC yields.

resulted). Subjecting **1** to *t*-BuOCl as described by Johnson yielded the expected chloroketones, though complete conversion took 12 h instead of 8 h and a small amount (2%) of dichloroketone **6**⁶ was also observed. ¹H NMR data, including those from one-dimensional NOE experiments, were in good agreement with the original stereo- and regiochemical assignments.⁷

With the foundation for our study secure, we began to experiment with the aim of replacing *t*-BuOCl with NaOCl. These experiments revealed that a combination of ~1.2 equiv of NaOCl⁸ and ~2 equiv AcOH in a 1:1 mixture of water and CCl₄ at 0 °C efficiently afford ring-expanded products **2–5** (Scheme 1, conditions b).⁹ Though the yields of **2–5** were similar to those realized with *t*-BuOCl, the NaOCl/HOAc expansions were slightly faster and afforded an intrusive amount of chlorinated starting material (**7**).

With these conditions in hand, we set out to evaluate NaOCl/HOAc-promoted ring expansions outside the realm of a [2.2.1] to [3.2.1] conversion. Relative to the [2.2.1] systems,^{1,2,10} there is little literature on cationic rearrangements of vinyl-substituted [2.2.2]-bicyclic molecules. To more fully appreciate the selectivity, scope, and mechanism of this chlorinative rearrangement, a series of carvone-derived “vinyl” [2.2.2]-bicyclocarbinols would be subjected to NaOCl and HOAc.

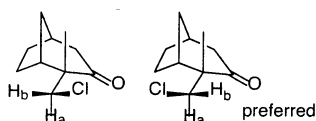
Following the intramolecular alkylation procedure of Srikrishna (Scheme 2), bicyclic ketones **8a** and **8b** were prepared.¹¹ Various vinyl nucleophiles were then introduced as described in Scheme 2. The resultant allylic alcohols (**9–**



^a Reagents and conditions: (a) NBS, CH₂Cl₂, MeOH (3:1), 0 °C, 1.5 h, rt for 10 h (quant). (b) *t*-BuOK, *t*-BuOH, THF, 0 °C, 10 min, rt 18 h (40% **8a**; 28% **8b**). (c) CH₂=C(Me)MgBr, THF, 0 °C, 30 min, 80 °C, 3 h (81%; 4:1 **9a/b**). (d) DHPLi, THF, -78 °C, 15 min, 0 °C, 45 min, -78 °C, 5 h (75%; 10:1 **10a/b**). (e) CH₂=CHMgBr, THF, 0 °C, 30 min, 80 °C, 3 h (87%; 4:1 **12a/b**). (f) DHFLi, THF, -78 °C, 15 min, 0 °C, 45 min, -78 °C, 5 h (60%; 2.5:1 **11a/b**).

(6) Johnson's GLC analysis indicted four major and two unidentified minor peaks. It is likely that one of these unidentified products was **6**.

(7) This analysis also supports Johnson's conclusion of a preferred CH₂-Cl rotamer present in [3.2.1]-ketone **3**. The methyl substituent appears as a doublet (*J* = 0.6 Hz), resultant from W-coupling with the CH₂Cl protons making two conformers possible. Johnson used aromatic solvent-induced shifts of **3** to deduce the preferred conformer shown below. NOE data are consistent with this model. (For aromatic solvent-induced shifts, see: Bhacca, N. S.; Williams, D. H. In *Applications of NMR Spectroscopy in Organic Chemistry*; Holden-Day: San Francisco, 1964; Chapter 7.)



(8) (a) Galvin, J. M.; Jacobsen, E. N. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 7, 4580–4585. (b) This work was carried out with “regular” Clorox, which is ~0.75 M in NaOCl. This product is being replaced by “ultra” Clorox, which is more alkaline and concentrated (~0.83 M).

(9) **Typical Procedure.** After a solution of bicyclocarbinol (1.00 equiv) in CCl₄ (0.6 M) was cooled to 0 °C, AcOH (1.95 equiv) was added rapidly. After 5 min at 0 °C, this solution was added rapidly to a 0 °C solution of NaOCl (0.75 M, 1.19 equiv) in H₂O (same volume as CCl₄). The biphasic reaction was vigorously stirred for 6 h at 0 °C. The reaction was poured into a cold solution of 3% K₂CO₃ in water and then partitioned with room-temperature CH₂Cl₂. The organic layer was washed three times with a cold solution of 3% K₂CO₃ in water. The combined aqueous washes were back-extracted three times with CH₂Cl₂. The combined organics were then dried over MgSO₄, filtered, and concentrated. The residual was purified via flash chromatography (10 g of SiO₂/1 g of compound) with EtOAc/hexane as the eluent. See Supporting Information for additional details.

(10) For examples, see: (a) Filippini, M. H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27–76. (b) Djuardi, E.; Bovonsombat, P.; McNelis, E. *Tetrahedron* **1994**, *50*, 11793–11802. (c) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956–3965.

(11) Srikrishna, A.; Sharma, G. V. R.; Daniellodoss, S.; Hemamalini, P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1305–1311.

12)¹² were then subjected to the bleach and acetic acid chlorinative ring expansion conditions (Table 1).

Rearrangement of isopropenyl [2.2.2] adducts **9a** and **9b** (entries 1 and 2, Table 1) occurred in high isolated yields and proved to be much more selective than those of [2.2.1]-bicycle **1**. For both substrates, the bridgehead carbon migrated exclusively. The new stereogenic center was also formed stereospecifically with NOE experiments indicating that **9a** and **9b** afforded **13** and **14** in 20:1 and 1:12 ratios, respectively.¹² These levels of stereocontrol greatly exceeded the ~1.3:1 ratio observed during the expansion of **1**.

Paquette had shown proton-mediated expansions of dihydrofuran (DHF)-derived [2.2.1]-carbinols to be particularly effective.^{10c} Thus, we examined substrates **10** and **11** to form the chlorofunctionalized [3.2.2] products¹² (entries 3 and 4, Table 1). For the pyranyl derivative (**10a**), rearrangement proceeded in 90% yield with excellent selectivity. Again only the bridgehead carbon migrated. Like the isopropenyl case, the carbinol with the OH exo to the alkene bridge migrated to place the chlorocarbon exo to that bridge. Furthermore, the stereochemistry of that chlorocarbon was such that the chloro group was positioned syn to the ketone.¹² Though rearrangement of the furanyl derivative (**11a**) was less efficient (56%), the regio- and stereocontrol α to the newly formed carbonyl remained total and in accordance with the direction established in entries 1–3.¹²

Finally, simple vinyl derivatives were examined. Substrates **12a** and **12b** mimicked the isopropenyl adducts in both

(12) The structure assigned to each new compound is in accordance with its infrared, 300 or 500 MHz ¹H NMR, and 75 or 125 MHz ¹³C NMR spectral data, as well as appropriate ion identification by high-resolution mass spectrometry. Stereochemical assignments were supported by NOE NMR experiments. See Supporting Information for details.

Table 1. NaOCl/HOAc-Promoted Ring Expansion Results^a

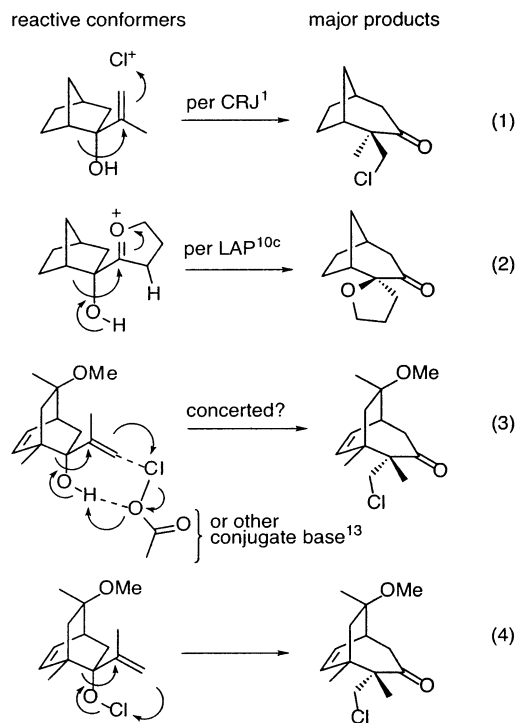
entry	substrate	products (isolated yield; ratio)
1		 (86%; 20:1)
2		13 + 14 (82%; 1:12)
3		 15 (90%)
4		 (56%; 7:1)
5		 18 (32%) 19 (48%)
6		 19 (47%) 20 (36%)

^a Conditions: NaOCl, HOAc, 6 h, 0 °C, H₂O/CCl₄ (1:1); for experimental details, see ref 9 and Supporting Information.

regioselectivity and stereospecificity (entries 5 and 6, Table 1). The *exo*-carbinol (relative to the alkene bridge) again produced the *exo*-chloroketone, while the *endo*-carbinol yielded the *endo*-chloroketone.¹² A key difference in the rearrangement of these substrates was that the β -chloroketone products were quick to eliminate HCl as can be seen from enone production. Such an elimination is in itself useful because it represents a direct way of carrying out a ring expansion/*exo*-olefin insertion process on bicyclic ketones. Further studies on the generality of this sequence will be reported in due course.

Whether these reactions are carried out in the light or in the dark, the product composition is not affected by the addition of radical scavenger di-*tert*-butylhydroxytoluene

(BHT). Given these observations and earlier works,^{1,7,10,13} these ring expansions appear to be best described as cationic. Capture of Cl⁺ by the vinylic portion of the molecule followed by a Wagner–Meerwein shift of the more nucleophilic bridgehead carbon² and loss of a proton would afford the observed products (Figure 1).

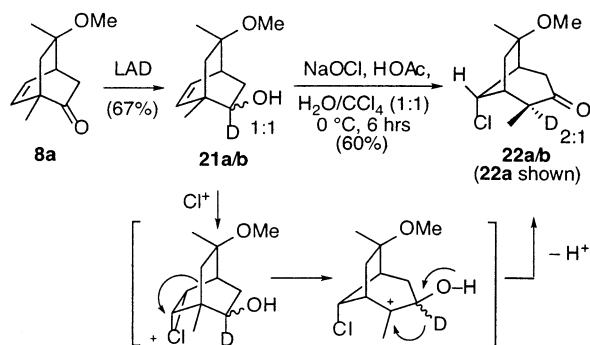
**Figure 1.**

As for stereocontrol, the [2.2.1] and [2.2.2] systems behave differently. For rearrangement of the [2.2.1] molecule (**1**), the conformer that places the alkene and the hydroxyl in opposing directions appears to be slightly preferred. Johnson argued that this is the result of a steric bias with the reacting conformer being the lowest energy rotamer (Figure 1, eq 1).

Data on the rearrangements of **9–12** suggest that, in contrast to **1**, the [2.2.2]-bicycles rearrange via conformers that place the olefin and the hydroxyl syn to each other. Paquette has described a similar relationship during proton-mediated ring expansions of dihydrofuran-substituted [2.2.1]-carbinols,^{10c} pointing to a preferred anti relationship between the ring oxygen and the hydroxyl (Figure 1, eq 2). However, entries 1, 2, 5, and 6 suggest that, in our reactions, the heteroatom may not be the primary stereocontrol element. Furthermore, the resultant stereochemistry of the chlorine bearing carbons in **15** and **16** indicates that the same conformer undergoes both chlorination and ring expansion. These observations, in combination with the lack of reactivity at the bridging olefin (vide infra), open up the possibility of

(13) Anbar, M.; Ginsburg, D. *Chem. Rev.* **1954**, *54*, 925–958.

Scheme 3



a concerted mechanism (Figure 1, eq 3), which Johnson ruled¹ out for **1**. It is also possible that in contrast to the rearrangement of **1**,¹ the [2.2.2] systems are converted to their hypochlorites prior to rearrangement (Figure 1, eq 4). However, when hypochlorites are reacted in light, at least trace amounts of oxy-radical-derived products^{14,15} are expected. We saw none. Furthermore, attempts to purposely prepare hypochlorites of **12** by alternative methods never afforded **18** (or other halo analogues) or **19**.

In terms of chemoselectivity, ether oxygens did not interfere with the expansion. Moreover, no reaction with the bridging olefin was observed during the rearrangement of the vinyl carbinols. This is not to say that such olefins are completely inert to the reaction conditions. Reaction of [2.2.2] secondary alcohols (**21a/b**) gave γ -chloro[3.2.1]-ketones **22a/b**¹² in good yield and in a ratio of 2:1 (Scheme 3). A putative cationic mechanism involving reaction of Cl^+ with the internal olefin, bond migration, 1,2-deuterium shift,

(14) (a) Greene, F. D.; Savitz, M. L.; Osterholtz, F. D.; Lau, H. H.; Smith, W. N.; Zanet, P. M. *J. Org. Chem.* **1963**, *28*, 55–64. (b) Walling, C.; Thaler, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877–3884. (c) Walling, C.; Clark, R, T. *J. Am. Chem. Soc.* **1974**, *96*, 4530–4534.

(15) Galatsis, P.; Millan, S. D.; Faber, T. *J. Org. Chem.* **1993**, *58*, 1215–1220.

and loss of a proton can be drawn.¹⁶ However, data suggest that here there may be some radical involvement because the reaction is somewhat hindered by BHT (45% yield with BHT vs 60% yield without BHT). Furthermore, the stereochemistry about the methyl group α to the ketone goes from a 2:1 to a 1.2:1 mixture when the reaction is run dark. Thus, the exact mechanism of this rearrangement remains under investigation.

In summary, bleach and acetic acid are effective promoters of chlorinative one-carbon ring expansions of [2.2.1]- and [2.2.2]-bicyclic molecules. Rearrangement of vinyl-, *iso*-propenyl-, DHF-, and DHP-substituted [2.2.2]-bicyclocarbinols are chemo-, regio-, and stereoselective, affording β -chloro-[3.2.2]-bicycloketones¹⁷ in respectable yields. The selectivity of these rearrangements appears to be derived from reaction of a preferred conformer in which the hydroxyl and the reacting vinyl groups are in a *syn* orientation. In addition, nonvinylic [2.2.2]-bicyclocarbinols undergo their own unique chlorinative rearrangements upon exposure to NaOCl/HOAc.

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Supporting Information Available: Spectral data for all new compounds pictured, as well as general experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) (a) Kwart, H.; Irvine, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 5541–5546. (b) Smith, W. B. *J. Org. Chem.* **2001**, *66*, 376–380.

(17) For examples of β -chloroketones in organic synthesis, see: (a) Zoretic, P. A.; Bendiksen, B.; Branchaud, B. *J. Org. Chem.* **1976**, *41*, 3767. (b) Krause, H.-J. DE Patent 29 25 521, 1981. (c) Miller, J. A.; Ullah, G. M.; Welsh, G. M.; Mallon, P. *Tetrahedron Lett.* **2001**, *42*, 2729–2731.