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LETTERS

Carbonyl groups at positions C2 and C3 enhance stereochemical inversion at C7 in norbornane compounds

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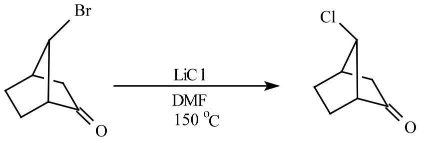
Abstract—It is known that the presence of a carbonyl group at C2 in norbornane compounds aids in the S_N2 displacement of substituents at C7. In this study, we report a significant enhancement in reactivity at C7 by a second carbonyl group at C3. These diketones undergo rapid inversion at 80°C, while the monoketone does not exhibit any reactivity at this temperature. The increase in reactivity is attributed to electric field effects. © 2002 Elsevier Science Ltd. All rights reserved.

S_N2 displacement at the C7 position of a norbornane compound is difficult to achieve for two reasons. First, the angular constraints of the C1–C7–C4 bond angle, ca. 93°, make it difficult to form the trigonal bipyramidal transition state, which is optimal when the bond angles are 120°.[1] Second, the *exo*-hydrogens at C5 and C6 hinder the approach of an incoming nucleophile.[1a]

In a previous study, Lumb and Whitham synthesized *anti*-7-chloro-2-norbornanone (**2**) from *syn*-7-bromo-2-norbornanone (**1**) using LiCl in refluxing DMF (Eq. (1)).[1a]

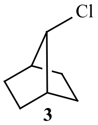


1 2

(1)

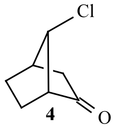
The authors suggested that the carbonyl group aids the displacement of bromide ion at the C7 position. The complete inversion of configuration at the C7 position was later experimentally verified by Nash et al.[2]

Molecular orbital (MO) calculations were used to estimate activation enthalpies ($\Delta H^{\ddagger}$) for displacement of Cl^- (using Cl^- as a nucleophile) for compounds **3**–**5**.[2] The MO calculations showed that the presence of one carbonyl group (**4** versus **3**) decreases $\Delta H^{\ddagger}$ by 4.2 kcal/mol, whereas the presence of a second carbonyl group (at C3) has a much larger effect, i.e. $\Delta H^{\ddagger}$ is decreased by 8.1 kcal/mol (**5** versus **4**).



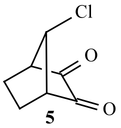
3

($\Delta H^{\ddagger}$ = 22.4 kcal/mol)



4

($\Delta H^{\ddagger}$ = 18.2 kcal/mol)

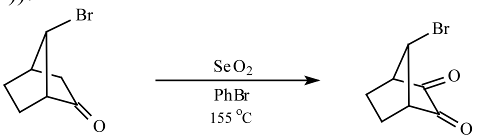


5

($\Delta H^{\ddagger}$ = 10.1 kcal/mol)

Based on the results of natural bond order (NBO) calculations, the lowering of the activation enthalpies in **4** and **5** (relative to **3**) was attributed primarily to electric field effects[3] (through-space and through-bond interactions were negligible) produced by the introduction of the carbonyl group(s) at the C2 and/or C3 position(s).[2]

In order to test the predicted large enhancement in reactivity of 7-halo-2,3-norbornadiones, we have synthesized *syn*-7-bromo-2,3-norbornadione (**6**) from **1** (Eq. (2)).[4]



1 6

(2)

Keywords: S_N2 displacement; norbornanes; electric field effect.

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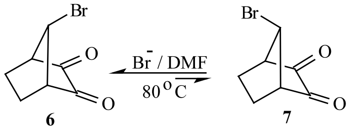
Compound **6** (7.42×10^{-2} M) was then subjected to nucleophilic displacement using a general procedure involving dissolution in anhydrous DMF containing either LiBr (9.2×10^{-2} M) or LiCl (1.25×10^{-1} M). The solutions were heated and the reactions were monitored by GC. The products were analyzed by GC/MS and ^{1}H NMR spectroscopy. Table 1 contains a summary of the results when the reactions were conducted at 80°C.[5]

It is clear from Table 1 that the anticipated enhancement of inversion chemistry by the presence of the diketone moiety is indeed observed. No reaction was observed when compound **1** was reacted with LiCl at 80°C for 24 h, whereas compound **6** was completely converted to its chloro substitution products in 2 h. In fact, the reaction between **6** and LiCl is so facile, that even at room temperature a 4% conversion can be observed within 24 h (the product at this point is entirely compound **8**).

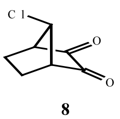
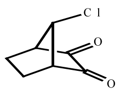
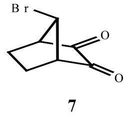
As seen in Table 1, the Br^- anion (a much weaker nucleophile than Cl^- under these conditions) also exhibits displacement chemistry with compound **6**. There is a gradual build-up of the *anti* isomer (**7**) until an 80:20 ratio of **6**:**7** is reached at 24 h. Interestingly, this ratio of **6**:**7** persisted for several additional days. One may conclude that the 80:20 ratio for **6**:**7** represents the thermodynamic equilibrium distribution at this temperature (Eq. (3)). The addition of excess Br^- to this reaction had no effect on this ratio.



6 (80%) **7** (20%) (3)

A calculation of ΔG for the two isomers, using the equilibrium constant from Eq. (3), $K=4.0$ (*syn*/*anti*), gives a difference in energy between the *syn* and *anti* isomers of 0.97 kcal/mol.

Table 1. Results of S_N2 reactions at 80°C in DMF compound LiX products

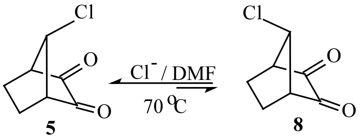
compound	LiX	products
1[a]	X=Cl	no reaction
6[b]	X=Cl	 +  **8** **5**
6[c]	X=Br	 **7**

[a] 24 h

[b] 2 h; 100% yield

[c] 24 h; 20% yield

The complete conversion of **6** to a 25:75 mixture of **5:8** occurs within 2 h at 80°C. Compounds **5** and **8** also appear to equilibrate. When a large excess (8 equiv.) of LiCl was then added to the reaction mixture and the solution maintained at 70°C for 24 h, an equilibrium mixture of 82:18 for **5:8** was observed (Eq. (4)).



5 (82%) **8** (18%) (4)

This equilibrium distribution also persisted for several days, suggesting that this is the thermodynamic equilibrium distribution. The ΔG value calculated from the observed equilibrium constant, $K=4.6$ (*syn*/*anti*), indicates that the *syn* isomer is more stable by about 1.0 kcal/mol.

MO calculations at the HF/6-31+G* level qualitatively support these observations. The *syn*-7-chloro isomer (**5**) is calculated to be 0.34 kcal/mol lower in energy than the *anti*-7-chloro isomer (**8**). The slightly higher energy of the *anti* compound relative to its *syn* isomer may be a consequence of steric interactions between the halogen and the *exo*-hydrogens at positions C5 and C6.

Because **7** could not be isolated free of **6**, it was not possible to obtain accurate rate data for the conversions of these isomers to the chloronorbornadione products. We did, however, subject an equilibrium mixture of **6** and **7** to an excess of LiCl (8 equiv.) at 70°C and monitored their disappearance by GC. The pseudo first-order rate constants were determined from analyses within 4 min and were found to be within 90% of one another. Such comparable rates were also predicted in previous MO calculations for the reaction of **5** and **8** with chloride ion. $\Delta H^\ddagger$ values for *anti* attack on **5** versus **8** were calculated (HF/6-31+G*) to be 9.7 and 10.1 kcal/mol, respectively.

In summary, we have shown that nucleophilic displacement chemistry on the 7-halo-2,3-norbornadiones is quite facile, and is observable at temperatures as low as 25°C. The dione is clearly much more reactive than the monoketone, *syn*-7-bromo-2-norbornanone, which requires much higher temperatures for reaction to occur. The *syn*-7 and *anti*-7 bromo isomers appear to react with chloride at comparable rates. The increased reactivity of the diones is attributed to an increased electric field effect that lowers the enthalpy of activation for the S_N2 transition state. Initial nucleophilic attack with inversion on either the *syn*-7 or *anti*-7-halonorbornadiones is followed by equilibration to a mixture that favors the *syn* isomer in both the chloro and bromo series.

This chemistry may be more broadly applicable as a means of inverting stereochemistry in rigid ring systems.

Supplementary material

Analytical and spectroscopic data for compound **6** and spectroscopic data for mixtures of **5** and **8**, and **6** and **7** are available.

Acknowledgements

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References

1. (a) Lumb, J. T.; Whitham, G. H. *Chem. Commun.* **1966**, 400; (b) Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 3887.
2. Nash, J. J.; Waugh, T.; Morrison, H. A. *Tetrahedron Lett.* **1998**, *39*, 6449.
3. For a discussion of inductive and electric field effects, see: Stock, L. M. *J. Chem. Educ.* **1972**, *49*, 400.
4. Meinwald, J. *J. Org. Chem.* **1964**, *29*, 3649–3473. This reference contains the procedure to make the chloro analogue of this molecule.
5. Satisfactory analytical and spectroscopic data were obtained for compound **6**. Compounds **5** and **8** were isolated as a mixture and identified using ^{1}H NMR and GC/MS. Likewise, compound **7** was isolated as a mixture with compound **6** and identified spectroscopically.