Stereospecific Synthesis of Hindered Cis-Disubstituted Cyclopropanones: Fluxional Cyclopropanones

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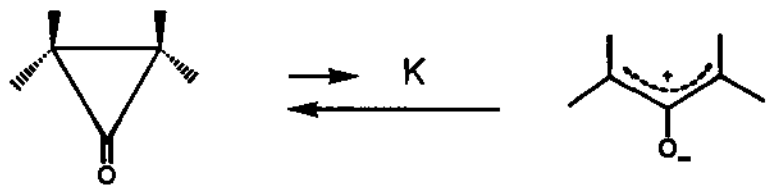
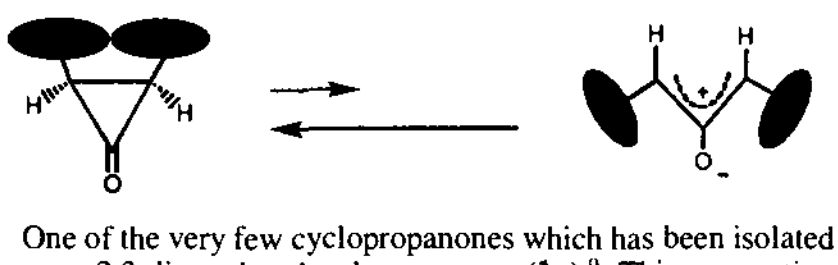
There is continuing interest, both experimental and theoretical, in the chemistry of cyclopropanones **1** and, in particular, their elusive oxyallyl valence bond isomers **3**.[1−5] In "normal"



1 **3**

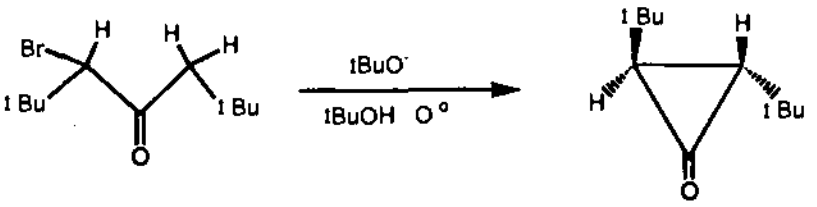
situations, cyclopropanones are much more stable than the oxyallyls, so only extremely miniscule concentrations of the latter are ever present under equilibrium conditions.[6]

Our conceptual aim in this study was to design and then prepare destabilized cyclopropanones with the hope that the oxyallyl partner might then be formed in equilibrium concentrations sufficient for spectroscopic detection. To this end, it appeared that cis-disubstituted cyclopropanones with large bulky substituents[7] might fulfill this purpose since the considerable steric strain in the cyclopropanone could be nearly completely relieved in the oxyallyl.[8] However, there are at present no reported preparations of such cyclopropanones.



One of the very few cyclopropanones which has been isolated is *trans*-2,3-di-*tert*-butylcyclopropanone (**1a**).[9] This preparation used Favorski-type conditions, as shown in Scheme 1. A bromo enolate can be assumed to be the first intermediate, followed by an S_N1 loss of bromide to give an oxyallyl, which can then very rapidly close to the cyclopropanone by a disrotatory process.[10] However, the results in Scheme 1 are difficult to rationalize on the basis of an oxyallyl intermediate since one can confidently predict that the bromo enolate **2b** would be thermodynamically more stable than the alternate **2a**[11] (see Scheme 2). An S_N1 loss of bromide from **2b** would then be expected, also on thermodynamic grounds, to give oxyallyl **3b**

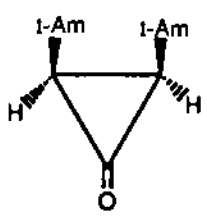
Scheme 1



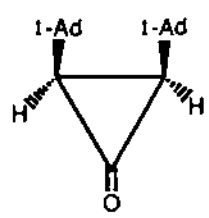
1a

(Scheme 2) as the most stable[12] stereoisomer of **3**, and this in turn should close to *cis*-2,3-di-*tert*-butylcyclopropanone (**1b**). We have now found that the predicted bromo enolate mechanism does indeed produce only the cis cyclopropanone **1b** as the first observable product and that this method also provides a convenient route for the actual isolation of this rather unstable compound.

The synthesis makes use of a recently developed procedure[3] to generate bromo-enolate intermediates such as **2b** under very low temperature and strictly aprotic conditions, starting with α,α′-dibromo ketones and reductively removing one of the bromine atoms with the organometallic salt $PPN^+Cr(CO)_4NO^-$ ($PPN^+ \equiv (PPh_3)_2N^+$). When this reaction was carried out using either of the diastereomeric dibromo ketones **4** or **5** at −78 °C, a quantitative *in situ* yield of **1b** was produced (^1H and ^{13}C NMR detection). For bulky substituents like tBu, which in turn strongly favor the enolate conformer **2b** (and also provide steric hindrance to competing reactions[13]), the synthetic method appears general, and in addition to **1b**, we have also prepared the *cis*-di-*tert*-amyl- and *cis*-di-1-adamantylcyclopropanones **6** and **7**.



6



7

To a considerable extent, this stereospecific cyclopropanone synthesis (Scheme 2) follows the established results and reasoning of Föhlisch *et al.*,[14] who showed that 2-bromo-3-pentanone with methoxide forms *cis*-dimethylcyclopropanone hemiacetal, but such hemiacetals cannot be converted back to cyclopropanones.

Cyclopropanone **1b** was isolated in pure form by sublimation *in vacuo* at *ca.* −10 to 0 °C onto a dry-ice-cooled surface, forming white needles, m.p. *ca.* −22 °C. At room temperature the pure liquid ketone is not stable, forming dimers and insoluble material. Even at −25 °C, dimers and other products are slowly formed. In dilute solution, **1b** and the other cyclopropanones are stable for moderate periods at room temperature (anaerobic, anhydrous inert solvents).

The cis cyclopropanone **1b** is easily distinguished from the trans isomer **1a** by ^1H NMR. In **1b**, the ring hydrogens are

(1) Cordes, M. H. J.; de Gala, S.; Berson, J. *J. Am. Chem. Soc.* **1994,** *116,* 11161.

(2) Cordes, M. H. J.; Berson, J. A., *J. Am. Chem. Soc.* **1992,** *114,* 11010.

(3) Black, C.; Lario, P.; Masters, A. P.; Sorensen, T. S.; Sun, F. *Can. J. Chem.* **1993,** *71,* 1910.

(4) Lim, D.; Hrovat, D. A.; Borden, W. T.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1994,** *116,* 3494.

(5) Coolidge, M. B.; Yamashita, K.; Morokuma, K.; Borden, W. T. *J. Am. Chem. Soc.* **1990,** *112,* 1751.

(6) The $\Delta E^{\ddagger}$ barrier for closure of an oxyallyl to cyclopropanone has been computed at less than 1 kcal/mol.[4] One can assume that equilibrium conditions always exist under our temperature conditions and also that ΔG differences between cyclopropanones and their oxyallyl isomer will be almost identical to the $\Delta G^{\ddagger}$ value.

(7) Besides having steric bulk, it is very important that substituents be tertiary since oxyallyls can otherwise rapidly rearrange to a dienol.[3]

(8) A related approach involves using ring systems to destabilize the cyclopropanone, and in the case of bicyclo[2.1.0]pentan-5-one, the oxyallyl partner is very likely more stable than the cyclopropanone. For a recent study and references to older work, see: Masters, A. P.; Parvez, M.; Sorensen, T. S.; Sun, F. *J. Am. Chem. Soc.* **1994,** *116,* 2804.

(9) (a) Pazos, J. F.; Greene, F. D. *J. Am. Chem. Soc.* **1967,** *89,* 1030. (b) Sclove, D. B.; Pazos, J. F.; Camp, R. L.; Greene, F. D. *J. Am. Chem. Soc.* **1970,** *92,* 7488. (c) Pazos, J. F.; Pacifici, J. G.; Pierson, G. O.; Sclove, D. B.; Greene, F. D. *J. Org. Chem.* **1974,** *39,* 1990.

(10) For a review of the mechanism of the "normal" Favorski reaction, see: Chenier, P. J. *J. Chem. Educ.* **1978,** *55,* 286.

(11) The two enolates were computed using molecular mechanics and also AM1 semiempirical MO methods. The energy difference with the latter was 4.4 kcal/mol. Both procedures were implemented using the Spartan program (Wavefunction Inc., Irvine, CA).

(12) Oxyallyls are notoriously difficult to compute by MO methods, but since we are only interested in relative energies caused mainly by steric effects, the AM1 calculations used here should be reliable. These give a 7.60 kcal/mol energy difference between **3b** and **3a**. The computed oxyallyl bond lengths are reasonably similar to those obtained for the parent oxyallyl obtained from high-level computations.[4]

(13) This cis-disubstituted cyclopropanone synthesis fails when used with small substitutents such as methyl groups (2,4-dibromo-3-pentanone), apparently because of competing bimolecular reactions, although tri- and tetra-substituted methyl analogs can be prepared *in situ* at subambient temperatures.[3]

(14) Föhlisch, B.; Gehrlach, E.; Stezowski, J. J.; Kollat, P.; Martin, E.; Gottstein, W. *Chem. Ber.* **1986,** *119,* 1661.

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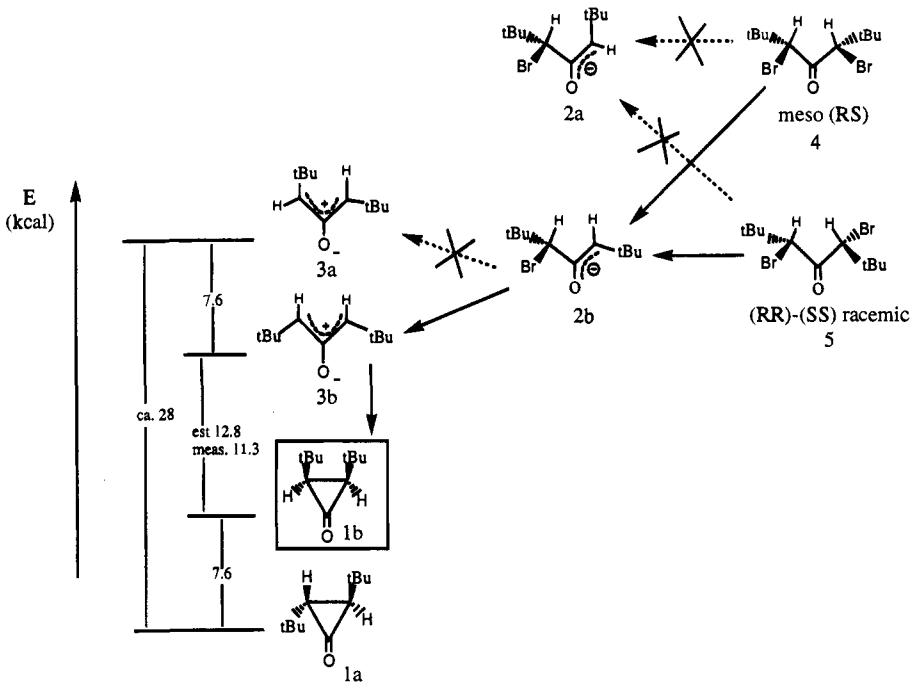
Scheme 2



found at δ 3.04 *vs* 1.67 in **1a**, almost 1.5 ppm to lower field. Similar low-field positions are found for **6** (δ 3.03) and **7** (δ 2.88). A related result is observed for the $^{13}C-H$ peak, δ 47.1 in **1b** *vs* 30.8 in **1a**. The >C=O stretch in **1b** is found at 1792 (s) and 1819 (m) cm^{-1} *vs* 1819 cm^{-1} for **1a**, again a very distinctive difference which appears to be general for these cis cyclopropanones.

The equilibration of **1b** with the oxyallyl **3b** is an NMR "hidden" reaction with the *tert*-butyl substituents but becomes detectable in the *tert*-amyl case (**6**). Indeed, variable temperature ^1H NMR spectra of this cyclopropanone already show line broadening of the diastereotopic methyls of the *tert*-amyl group at −70 °C in $CDCl_3$, and by 0 °C, only a single sharp peak is observed (room temperature fluxionality). From a coalescence temperature of −45 °C, $\Delta G^{\ddagger}$ was calculated to be 11.3 kcal/mol. One might assume that a similar rate would apply to **1b**. In the case of the 1-adamantyl derivative **7**, we have seen only a single peak down to −95 °C for the diastereotopic methylene protons,[15] an indication that the cyclopropanone−oxyallyl barrier (energy difference) is smaller still.

Greene *et al.*[9] were able to resolve **1a** and then to subsequently measure the thermal racemization rate, assuming oxyallyl **3a** as the achiral intermediate. This rate translates into an activation energy of ~28 kcal/mol, and this value has been incorporated into Scheme 2. Using the calculated steric strains present in **1b** *vs* **1a**[16] and in **3a** *vs* **3b**[12] (also shown in Scheme 2), one can then set the approximate energy levels for all of these species. The actual experimental energy separation of **1b**−**3b** (11.3 kcal/mol minus a small $\Delta G^{\ddagger}$ component[6]) is in relatively good agreement with the calculated value (12.8 kcal/mol), and this lends further credence to the whole Scheme 2 proposal.

Assuming the 11.3 kcal/mol ΔG difference between **1b** and **3b**, then at 298 K, a 0.1 M solution of **1b** would correspond to a ~1 nM concentration of **3b**. This is still very dilute, but as previously discussed, the 1-adamantyl analog **7** appears qualitatively to have an even more favorable equilibrium constant. The design, in a controllable way, of even less stable cyclopropanones can be envisaged, given that a synthetic methodology now exists.

Rearrangement of 1b into 1a. Cyclopropanone **1b** can be converted to **1a** by a thermal process. For example, GLC analysis of **1b** under split-mode capillary conditions gives a peak which is identical in retention time to that of the trans **1a**. Preparative GLC of **1b** gives pure **1a**. In solution, the rearrangement appears slower, since at least some **1b** survives at room temperature for several days in $CDCl_3$. As mentioned, the pure liquid is unstable at room temperature, but essentially no trans isomer is formed in these reactions.

One mechanism for the **1b** → **1a** rearrangement involves interconversion of oxyallyls **3b** and **3a** by 180° rotation about the C1−C2 bond.[17] From Scheme 2, the minimum activation barrier from **1b** to **3a** can be estimated at 20.4 kcal/mol. Although the rearrangement kinetics for **1b** → **1a** have not yet been studied in detail, the experimental barrier is clearly somewhat higher than this, an indication that a small $\Delta G^{\ddagger}$ barrier would be required above the oxyallyl **3a** energy level.

The preparation of **1a** by Greene *et al.*[9] can be rationalized as initial *cis*-**1b** formation followed by base-catalyzed isomerization to **1a**. These authors showed that $tBuO^-$/tBuOD solution was able to exchange H for D in **1a** by an enolate mechanism, but only in competition with an irreversible Favorski rearrangement. Using the data in Scheme 2, one can estimate that **1b** at 0 °C is 1×10^6 times more acidic than **1a** (they form a common conjugate base). Furthermore, **1b** is less hindered than **1a**, so an epimerization reaction should be virtually instantaneous under their reaction conditions (0 °C).

In conclusion, a high-yield stereospecific synthesis of cis-disubstituted cyclopropanones (bulky substituents) has been developed, and in suitable cases these compounds show room temperature fluxional behavior as measured by ^1H NMR spectroscopy.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for generous support.

Supplementary Material Available: Experimental description of the preparation of **1b** and **6** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) This same result has been found in three different solvents (toluene-d_8, $CDCl_3$ (to −70 °C), and CD_2Cl_2), so it is unlikely that we are observing accidental equivalence.

(16) Calculated by both molecular mechanics and the AM1 semiempirical method, the latter procedure giving a 7.56 kcal/mol energy difference.

(17) No high-level computations have been reported concerning this rotation process, but the experimental barrier would appear to be less than 5 kcal/mol. It is quite possible that the triplet energy surface might drop below that of the singlet at the 90° twist state. The photochemical behavior of **1b** would also be of interest.