of an organocerium reagent to α-sulfonamido ketone 8.

The next stage of the synthesis involved introduction of the carboxyl carbon (C-1) of the enol lactone function of 2. Alcohol 9 was first oxidized to ketone 10 (90%) (Scheme II). Not surprisingly, acylation of the tertiary hydroxyl group of 10 with a variety of phosgene-based reagents proved exceedingly difficult. However, it was eventually found that upon treatment of 10 with methyl chloroformate in triethylamine in the presence of 4-pyrrolidinopyridine, cyclic carbamate 11 was produced (80%). This compound is probably formed via initial acylation of the sulfonamide nitrogen, followed by intramolecular closure onto the hydroxyl group.

Exposure of 11 to methanolic sodium methoxide yielded the desired enol lactone 13 (70%). It would appear from inspection of models that direct C-acylation of an enolate derived from 11 is not possible. We believe that cyclic carbamate 11 is first opened by methoxide to carbonate 12. Moreover, the alkoxide base generates an equilibrating enolate mixture, of which only the regioisomer shown in 12 can undergo intramolecular acylation.

The SES protecting group of 13 was removed with fluoride[11] and acidification upon workup hydrolyzed the acetonide moiety (45–50%). The resulting racemic amino diol 14 was acylated with *N*-Cbz-L-alanine and the diastereomers were separated by preparative TLC on silica gel (30% isolated yield of each isomer). Hydrogenolysis of the Cbz group (80%) afforded (–)-bactobolin (2), which was identical with an authentic sample.[17,18] We have thus completed a totally stereoselective synthesis of bactobolin in sixteen steps from readily available α-keto lactone 3.

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(17) We are grateful to Dr. T. Munakata, Yoshitomi Pharmaceutical Industries, Ltd., for a generous sample of natural bactobolin.

(18) All compounds were characterized spectrally and by elemental analysis and/or high-resolution mass spectrometry.

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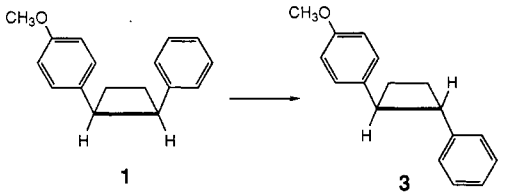
Dioxygen-Promoted Cation Radical Reactions in Brønsted Acids

Summary: Contrary to previous reports, the trifluoroacetic acid promoted cis → trans isomerizations of 1-*p*-anisyl-2-phenylcyclobutane and 1,2-di-*p*-anisylcyclopropane are *not* proton catalyzed; results are presented suggesting that cation radical reactions can be initiated in Brønsted acids when dioxygen is present.

Sir: The difficulties in distinguishing cation radical catalysis from Brønsted acid catalysis *under aminium ion initiation* have been the subject of recent discussion in the literature.[1] For example, Gassman and Singleton have suggested that several aminium ion initiated Diels–Alder reactions are, in fact, catalyzed by adventitious acid which is produced in the reaction mixture.[1a,b] We demonstrate here the inverse of this experiment, namely, that cation radical reactions can apparently be initiated in Brønsted acids *when dioxygen is present.*

The trifluoroacetic acid promoted stereomutations of *cis*-1-*p*-anisyl-2-phenylcyclobutane (1) and *cis*-1,2-di-*p*-anisylcyclopropane (2) have both been claimed to be proton-catalyzed reactions.[2] We were naturally concerned with these reports because of our work[3] on the cis → trans isomerization of 1-*p*-anisyl-2-vinylcyclopropane catalyzed by one-electron oxidants, including the aminium ion salt p-$BrPh_3N^{\bullet+}$ SbF_6^-. We excluded an acid-catalyzed mechanism for this reaction by showing that the addition of 2,6-di-*tert*-butylpyridine did *not* prevent the isomerization. Our work, coupled with the long-known propensity for cation radical formation in Brønsted acids,[4] prompted us to reinvestigate the reaction mechanisms for the trifluoroacetic acid promoted isomerizations of 1 and 2. Especially relevant was the report by Shine and Piette that dioxygen was necessary for the one-electron oxidation of thianthrene in trifluoroacetic acid.[5,7] A similar observation has been made for one-electron oxidations in trifluoromethanesulfonic acid.[6,7] Thus our initial goal was to determine if the presence of dioxygen affected the isomerizations of 1 and 2.

We first verified that 1[8] is indeed isomerized to 3 in distilled trifluoroacetic acid when no special precautions are made to exclude dioxygen. Our isomerization half-life in trifluoroacetic acid-*d* (3.25 h at 25 °C) was noticeably different, however, from that reported earlier (5.25 h at 25 °C).[2a] This discrepancy was easily rationalized by the



following series of experiments. *When degassed*[9] CF_3CO_2D *was vacuum transferred into an NMR tube containing 1 and sealed, the isomerization was dramatically slower.* For example, after 12 days no trans isomer was detected by ^1H NMR.[10] Only after much longer reaction times was a small amount of isomerization observed (5.2% after 32 days). The deuteriation of the *p*-anisyl ring,[2a] however, was not affected by degassing. The rate of deuterium incorporation into the *p*-anisyl ring of trans cyclobutane

(1) (a) Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 6085. (b) Gassman, P. G.; Singleton, D. A. *J.* Am. *Chem. Soc.* **1984**, *106*, 7993. (c) Reynolds, D. W.; Lorenz, K. T.; Chiou, H.-S.; Bellville, D. J.; Pabon, R. A.; Bauld, N. L. *J. Am. Chem. Soc.* **1987**, *109*, 4960.

(2) (a) Flippin, L. A.; Dombroski, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 4661. (b) Flippin. L. A. Ph.D. Thesis, University of Colorado, Boulder, 1980.

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(6) Yang, G. C.; Pohland, A. E. *J. Phys. Chem.* **1972**, *76*, 1504.

(7) For discussions on the mechanism of electron transfer, see: (a) Ij Aalbersberg, W.; Hoijtink, G. J.; Mackor, E. L.; Weijland, W. P. *J. Chem. Soc.* **1959**, 3049. (b) Ij Aalbersberg, W.; Gaaf, J.; Mackor, E. L. *J. Chem. Soc.* **1961**, 905. (c) Akaba, R.; Sakuragi, H.; Tokumaru, K. *Tetrahedron Lett.* **1984**, 665.

(8) 1 was prepared as follows. Condensation (Lawson, J. E.; Dennis, R. D.; Majewski, R. F.; Gallo, D. G. *J. Med. Chem.* **1974**, *17*, 383) of *p*-methoxyphenacyl bromide with ethyl benzoylacetate provided 1-*p*-anisoyl-2-benzoylethane. This substance was reductively coupled (Baumstark, A. L.; Bechara, E. J. H.; Semigran, M. J. *Tetrahedron Lett.* **1976**, 3265) to give 1-*p*-anisyl-2-phenylcyclobutene which was, in turn, hydrogenated (Dodson, R. M.; Zielske, A. G. *J. Org. Chem.* **1967**, *32*, 28.) to give 1.

(9) The degassing procedure consisted of four to six successive freeze–pump (2×10^{-6} Torr)–thaw cycles.

(10) Our ^1H NMR detection limits are ca. 2%.

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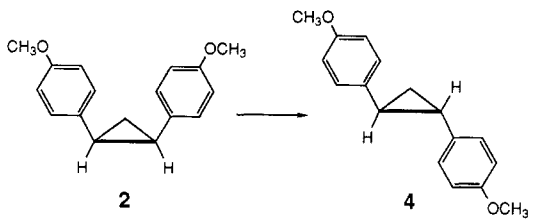
3 was followed by ^1H NMR spectroscopy and found to be identical for degassed and oxygenated samples ($t_{1/2} \approx 11$ h at 20 °C).[11] Thus ring deuteriation is presumably a simple proton-catalyzed reaction.

Clearly, however, trifluoroacetic acid is not an effective catalyst for the cis → trans isomerization. On the other hand, when a degassed sample of 1 which showed no isomerization after 6 days was opened and exposed to a dioxygen atmosphere, the ^1H NMR spectrum recorded after 15 min showed that the cis isomer was completely consumed. The predominant product was the trans isomer (40%). The sensitivity of the isomerization rate to dioxygen readily explains the small difference in the half-lives above. It also excludes a simple[12] acid-catalyzed mechanism for the isomerization. The dioxygen dependence instead recommends a cation radical mechanism.

Additional support for a cation radical isomerization mechanism was provided by the reaction of 1 with *p*-$BrPh_3N^{\bullet+}$ SbF_6^- (**5**). Treatment of 1 with 30 mol % **5** and 300 mol % tris(*p*-bromophenyl)amine (**6**)[13] in methylene chloride at 0 °C for 25 min (under N_2) provided a 5:95 mixture of 1/3 in 95% yield. Addition of 2,6-di-*tert*-butylpyridine (**7**) under these conditions resulted in a lower cis → trans conversion. In a representative experiment with 1, 30 mol % **5**, 300 mol % **6**, and 33 mol % **7**, the 1:3 ratio was 60:40 (90% yield). A control experiment showed that 20 mol % 2,6-di-*tert*-butypyridinium hexafluoroantimonate in methylene chloride (22 °C, 2 h) did not cause isomerization of 1. We will return below to discuss the results in the presence of **7**.

As yet, the detailed stereomutation mechanism of the presumed cyclobutane cation radical intermediate remains unclear.[14] It may involve a one-bond cleavage[3] or a two-bond cleavage mechanism.[15,16] Work is in progress to distinguish these possibilities.

Next we describe our results with a much more "acid"-sensitive compound, **2**.[17] When **2** was dissolved in oxygenated CF_3CO_2D at room temperature a deep purple color immediately developed. An ^1H NMR spectrum recorded after 15 min showed that the cis isomer was consumed. The major product was the trans isomer **4** (50%). When degassed CF_3CO_2D was added to **2** the purple color was



similarly observed, although it was less intense. ^1H NMR analysis after 15 min revealed that the cis isomer was again consumed; the sole product was **4**. Thus, within the time scale limits of the NMR analysis, simple freeze–pump–thaw degassing[9] of CF_3CO_2D does not detectably slow the isomerization rate of **2**. It is important to emphasize, however, that the apparent failure to suppress the isomerization of **2** by degassing does not necessarily support an acid catalyzed mechanism, as we demonstrate below.

The lower oxidation potential[18] of **2** (E_p = 0.98 V) vs 1 (E_p = 1.37 V) suggested to us that the former might simply be more sensitive to the trace amounts of dioxygen which necessarily remain after degassing. To further reduce the concentration of dioxygen, the degassed CF_3CO_2D was first pretreated by stirring with ferrocene (E_p = 0.34 V). It was then vacuum transferred onto a mixture of ferrocene and **2** (1:100 molar ratio). Under these conditions the solution was almost colorless (light tan) and the isomerization rate was dramatically suppressed. For example, after 6 days only 4.3% of **2** had isomerized to **4**. The addition of ferrocene did not affect the deuteriation of the aromatic rings. The deuteriation of **4**[11] in CF_3CO_2D at 22 °C occurred only at the carbon atoms ortho to the methoxy group, and the incorporation rates in the presence and absence of ferrocene were the same ($t_{1/2} \approx 34$ h at 20 °C).

More direct evidence for a dioxygen dependence was obtained when a *catalytic* amount of trifluoroacetic acid was used. For example, addition of 20 mol % trifluoroacetic acid, which had been previously distilled under nitrogen and subsequently oxygenated, to a nitrogen-purged solution of **2** in methylene chloride provided 64% isomerization after 105 min at room temperature. In an otherwise identical experient using trifluoroacetic acid which was *not* oxygenated, only 9% isomerization was observed.[19] These results are *not* consistent with a proton-catalyzed isomerization mechanism. As with 1, they suggest a cation radical route.

The isomerization of **2** to **4** could also be effected with *p*-$BrPh_3N^{\bullet+}$ SbF_6^- (**5**). In methylene chloride at room temperature (under N_2), treatment of **2** with 8.7 mol % **5** for 100 min provided **4** in 95% yield. Reaction of **2** with 9.5 mol % **5** in the presence of 10.4 mol% 2,6-di-*tert*-butylpyridine (**7**) resulted in a much lower cis → trans conversion (4.4%).[20]

It seems clear that the lower cis → trans conversions for the aminium ion catalyzed isomerizations of **2** and of 1 (vide supra) with added **7** can*not* be attributed to the suppression of proton catalyzed reactions. The results instead suggest that **7** inhibits isomerization by some other mechanism, perhaps by deprotonation of intermediate cation radicals. Whatever the exact mechanism, the usefulness of **7** as a mechanistic probe for proton catalysis in

(11) The competitive deuterium incorporation rates of 1 in degassed and undegassed CF_3CO_2D and of **2** in CF_3CO_2D with and without ferrocene could not be performed because of concomitant cis → trans isomerization under the latter conditions in both cases.

(12) A referee suggested an alternative possibility, namely, that dioxygen may somehow assist in a proton-catalyzed isomerization reaction. In addition to lacking any precedent, this hypothesis would necessitate two distinct types of proton-catalyzed mechanisms: one that requires dioxygen (isomerization) and one that does not (ring deuteriation). Furthermore, it is not obvious how such a mechanism would accommodate the ferrocene results with **2**. Finally, the aminium ion catalyzed isomerizations of 1 and **2** cannot involve a dioxygen-assisted proton-catalyzed mechanism because these reactions are performed under N_2.

(13) The omission of **6** resulted in lower cis → trans conversions, typically 10–20%. The origin of this effect is as yet unclear. One possibility is that addition of **6** results in a lower steady-state concentration of $1^{\bullet+}$, which, in turn, might permit unimolecular isomerization of $1^{\bullet+}$ to compete more effectively with its dimerization.

(14) Cyclobutane cation radicals have been proposed intermediates in the cis → trans isomerization of 1,2-diphenoxycyclobutane under photooxidation conditions. (a) Evans, T. R.; Wake, R. W.; Jaenicke, O. In *The Exciplex*; Gordon, M., Ware, W. R., Ed.; Academic: New York, 1975; p 345. (b) Mattes, S. L.; Luss, H. R.; Farid, S. *J. Phys. Chem.* **1983**, *87*, 4779.

(15) Bauld, N. L.; Pabon, R. *J. Am. Chem. Soc.* **1983**, *105*, 633.

(16) If the reaction proceeded via the two-bond cleavage mechanism, one might expect styrene and *p*-methoxystyrene to be formed as well as their *cis*- and/or *trans*-1,2-diarylcyclobutane homodimers. GC analysis showed that none of these six potential products were formed during the cis → trans isomerization.

(17) Prepared by the reaction of *p*-methoxybenzaldehyde with *p*-methoxystyrene under Clemmensen reduction conditions, cf.: Burdon, J.; Price, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 893.

(18) The oxidation potentials (E_p vs SCE) were obtained by cyclic voltammetry (150 mV/s) at a platinum electrode in acetonitrile with ca. 0.1 M tetrabutylammonium hexafluorophosphate as the supporting electrolyte and were irreversible for 1 and **2**.

(19) We assume the residual 9% isomerization was caused by adventitious dioxygen.

(20) A control experiment showed that 23 mol % 2,6-di-*tert*-butylpyridinium hexafluoroantimonate in methylene chloride (22 °C, 2 h) did not cause isomerization of **2**.

aminium ion catalyzed reactions is clearly limited.

In conclusion, our results illustrate that cation radical mechanisms for isomerizations in Brønsted acids + dioxygen have not been rigorously excluded. Although the mechanism of the electron-transfer step is not fully understood, it likely involves a substrate–dioxygen charge-transfer complex.[7] Finally, we should warn that an analogous mechanistic dilemma may arise for Lewis acid promoted reactions. Many Lewis acids are known to promote one-electron oxidation (e.g. $SbCl_5$, $AlCl_3$, and BF_3).[4] It will be interesting to see how general the Brønsted acid and Lewis acid promoted electron-transfer reactions are.

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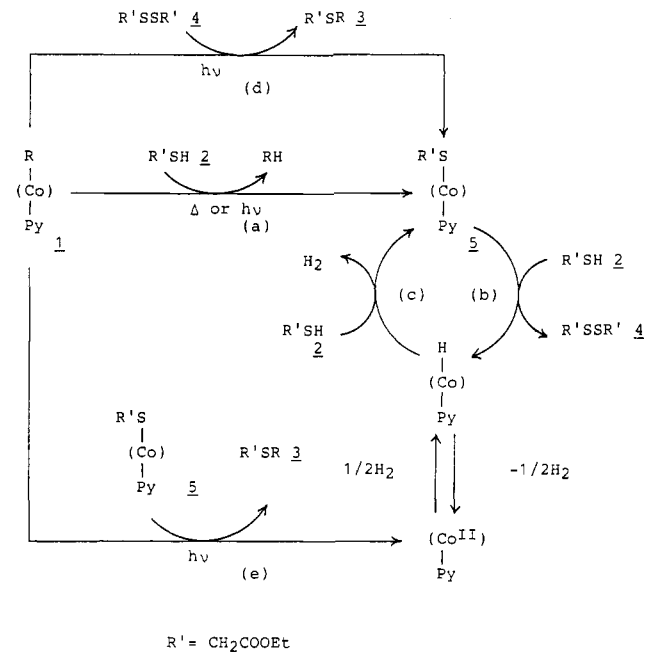
Homolytic Alkyl Group Transfer Reaction of Photoactivated Alkylcobaloximes into Thiols

Summary: Alkyl groups of alkylcobaloximes were transferred to alkylthiols by irradiation of alkylcobaloxime and thiol under anaerobic conditions; a radical route via homolytic substitution between alkylcobaloxime and disulfide, formed during the reaction, is proposed.

Sir: Currently, the reactivity of C–Co bond in alkylcobaloxime has received much attention as a stable organometallic reagent and also as a cobalamin (vitamin B_{12}) model.[1] We have investigated[2] the chemical reactivity of photoactivated alkylcobaloxime. The dealkylative substitution reaction of alkylcobaloxime has frequently been utilized in organic syntheses.[1c,3] Particularly, the reaction of organocobalt complexes with thiols has received much attention with respect to the function of methionine synthetase, a cobalamin (vitamin B_{12}) dependent enzyme.[4] It has not been shown, however, whether the methyltransfer reaction of the enzymic reaction proceeds in a radical or in an ionic manner. Schrauzer et al. have suggested[4a,b] the ionic mechanism in the methionine formation reaction with methylcobaloxime and homocysteine in alkaline media. The attempted[4a] homolytic alkyl-transfer reaction of alkylcobaloxime to alkylthiol has failed so far.

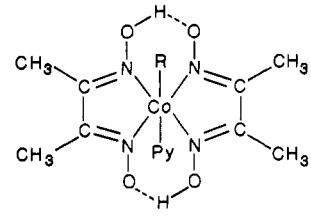
Scheme I



R'= CH_2COOEt

In this paper, we present the first successful example involving the homolytic alkyl-transfer reaction from alkylcobaloxime to some thiols induced by the cleavage of C–Co bond in alkylcobaloxime by irradiation with a visible light.

A mixture of alkylbis(dimethylglyoxymato)pyridinecobalt(III) (1)[5] (1.5 mmol), ethyl mercaptoacetate (2) (1 mmol), and 15 mL of CH_2Cl_2 in a Schlenk tube was deoxygenated and replaced with argon gas by the freeze–pump–thaw technique. The reaction vessel was irradiated



alkylbis(dimethylglyoxymato)pyridinecobalt(III)
R = methyl (**1a**), benzyl (**1b**); py = pyridine

with a tungsten lamp (400 W) for 24 h at 35 °C. The reaction proceeds according to eq 1, and the results are summarized in Table I. Product yield and conversion were determined by NMR.[6]

$$\underset{\mathbf{2}}{HSCH_2CO_2Et} \xrightarrow[h\nu]{RCo(DH)_2py\ (1)} \underset{\mathbf{3}}{RSCH_2CO_2Et} + \underset{\mathbf{4}}{(SCH_2CO_2Et)_2} \quad (1)$$

(1) (a) Schrauzer, G. N. *Acc. Chem. Res.* **1968**, *1*, 97. (b) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 238. (c) Johnson, M. D. *Acc. Chem. Res.* **1983**, *16*, 343.

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(5) Schrauzer, G. N. *Inorg. Synth.* **1968**, *11*, 61.

(6) Product yield was determined by the ^1H NMR peak area of organic products, which were separated from the reaction mixture by a silica gel column with a $CHCl_3$ solvent. Conversion was also determined by the ^1H NMR peak area of the reaction mixture: ^1H NMR ($CDCl_3$): δ 3.28 (d, 2 H, $HSCH_2CO_2Et$, **2**), 2.20 (s, 3 H, $CH_3SCH_2CO_2Et$, **3a**), 3.08 (s, 2 H, $PhCH_2SCH_2CO_2Et$, **3b**), 3.60 (s, 4 H, $(SCH_2CO_2Et)_2$, **4**), 2.30 (s, 12 H, CH_3 of **5**).

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