Communications

α-Oxo Ketene Dithioacetal Chemistry. 3. A Regio- and Stereospecific Lithium Aluminum Hydride Reduction Resulting in the Formation of Stereochemically Defined β-Alkyl γ-Bis(methylthio) Alcohols

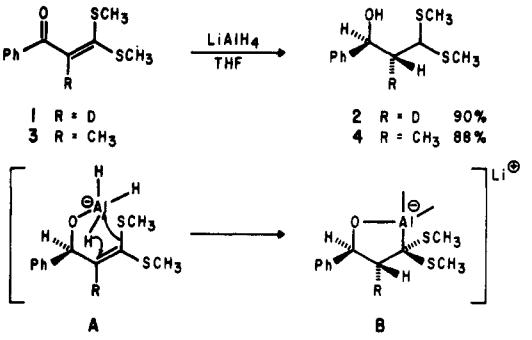
Summary: α-Oxo ketene dithioacetals are regio- and stereospecifically reduced via a novel reduction process to yield diastereomerically pure threo β-alkyl γ-bis(methylthio) alcohols in high yield.

Sir: Threo and erythro β-alkyl alcohols are characteristic structural elements found in many natural products.[1] In recent years, there has been considerable interest in the synthesis of macrolide and polyether antibiotics,[2] as well as pheromones[3] which contain these stereochemically defined functionalities. As a result of this interest a rapid growth in stereoselective and stereospecific methods for the construction of these units has appeared.[4,5]

We have recently described the regio- and stereospecific reduction of the C-2 deuterio α-oxo ketene dithioacetal **1**.[6,7] The intramolecularity of that reduction resulted in a totally stereospecific process (Scheme I) which afforded the threo β-deuterio alcohol **2** exclusively and in high yield.[8]

We have now investigated the generality of this reduction and find that a variety of α-oxo ketene dithioacetals can be converted to diastereomerically pure threo β-alkyl γ-bis(methylthio) alcohols in high yield.[9,10]

Scheme I



Reduction of α-oxo ketene dithioacetals lacking a C-2 substituent (i.e., **1**, **5**, **7**, and **13**) with lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF) proceeds smoothly over several hours at room temperature. In these cases isolation of the intermediate allylic alcohol, corresponding to intermediate A, is generally not possible since hydroalumination of the intermediate allylic olefin under these conditions is fast.[11] In contrast, reduction of systems containing a C-2 substituent (i.e., **3**, **9**, **11**, and **15**) requires elevated temperatures (refluxing THF) to effect complete reduction (A → B) and thereby offers the opportunity to stop the reduction at the allylic alcohol stage.

For example, reduction of **17**[12] with $LiAlH_4$ (1.0 equiv/THF) at room temperature afforded the allylic alcohol **18** in 95% yield whereas reduction of **17** below room temperature (1 h) and then at elevated temperature (3 h/refluxing THF) gave the diastereomerically pure and fully reduced threo alcohol **19**[9] in 98% yield.

As illustrated in Table I, the yields realized in these reductions are very high, and in general little more than flash chromatography (silica gel, 10–20% EtOAc/Skelly B) is required for purification. Due to the acid-sensitive nature of these compounds, the reductions are best quenched with saturated NH_4Cl.

(1) For an excellent review discussing the application of stereocontrol to natural product synthesis, see; Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(2) For a recent review on the total synthesis of ionophores, see: Wierenga, W. W. In "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 263. Also see: Heathcock, C. H. *Science (Washington, D.C.)* **1981**, *214*, 395. Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.

(3) For a recent review on this subject, see: Mori, K. In "The Total Synthesis of Natural Products"; Apsimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 1.

(4) For recent reviews of stereoselective aldol condensations, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, 13. Evans, D. A. *Aldrichim. Acta* **1982**, *2*, 23. (b) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203.

(5) For a review on diastereogenic additions of crotylmetal compounds to aldehydes, see: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. Mukaiyama, T. In "Asymmetric Reactions and Processes in Chemistry"; Eliel, E. L.; Otsuka, S., Eds.; American Chemical Society: Washington, DC, 1982, ACS Symp. Ser. No. 185, Chapter 2. For recent examples using chiral allylboranes, see: Brown, H. C.; Jadhav, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. For recent examples using optically active allylstannanes, see: Hayashi, T.; Konishi, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 281. Also see: Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1326. For recent examples using allylstannanes, see: Yamamato, Y.; Maeda, N.; Maruyama, K. *Ibid.* **1983**, 774. Pratt, A. J.; Thomas, E. J. *Ibid.* **1982**, 1115.

(6) Gammill, R. B.; Gold, P. M.; Mizsak, S. A. *J. Am. Chem. Soc.* **1980**, *102*, 3095.

(7) For reductions of allylic dithioacetal systems, see ref 6 and Redlich, H.; Schneider, B.; Francke, W. *Tetrahedron Lett.* **1980**, *21*, 3009.

(8) For examples of stereoselective hydride reductions leading to β-alkyl alcohol systems, see: Nakata, T.; Oishi, T. *Tetrahedron Lett.* **1980**, *21*, 1641 and references therein.

(9) The diastereomeric purities of these reduction products were established by either ^1H NMR (90 or 200 MHz), ^{13}C NMR, or HPLC analysis and in the case of **4**, comparison with an authentic mixture of both diastereomers. Satisfactory ^1H NMR, ^{13}C NMR, IR, mass spectra, combustion analysis and/or exact mass measurements were obtained on all new compounds. Representative data are given below. **4**: mp 68.2–70.5 °C; IR (mull) 2963, 2957, 2922, 2905, 2854, 1456, 1373, 1178, 1032, 1021, 762 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.4 (s, 5 H, Ar), 4.78 (d, 1 H, J = 9 Hz, methine at sulfur), 4.18 (d, 1 H, J = 3 Hz, methine at oxygen), 2.28 (s, 3 H, SCH_3), 2.18 (s, 3 H, SCH_3), 2.15–2.20 (m, 1 H, methine at methyl), 0.86 (d, 3 H, J = 9 Hz); ^{13}C NMR ($CDCl_3$, ppm) 143.21, 128.47, 127.85, 127.66, 126.82, 76.62, 58.32, 45.63, 15.42, 12.38. **12** (oil); IR (mull) 2958, 2916, 1436, 1422, 1086, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.17 (d, 1 H, J = 3 Hz, methine at sulfur), 3.75 (m, 1 H, methine at oxygen), 2.25 (s, 3 H, SCH_3), 2.22 (s, 3 H, SCH_3), 1.10–2.20 (m, 9 H); ^{13}C NMR ($CDCl_3$, ppm) 71.69, 58.14, 50.64, 35.87, 26.38, 26.74, 25.85, 25.70, 24.85, 15.87, 15.48. **16**: IR (mull) 2973, 2917, 1504, 1455, 1436, 1423, 1378, 1150, 1010, 912, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 7.39 (m, 1 H, furan), 6.30 (m, 2 H, furan), 4.80 (dd, 1 H, J = 5 and 10 Hz, methine at oxygen), 4.07 (d, 1 H, J = 4 Hz, methine at sulfur), 2.23 (s, 3 H, SCH_3), 2.28 (s, 4 H, SCH_3 and methine at methyl), 0.89 (d, 3 H, J = 9 Hz). **23** (oil); IR (mull) 2921, 1670, 1436, 1420, 1375, 1102, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 5.26 (q, 1 H, J = 7 Hz), 5.11 (t, 1 H, J = 6 Hz, vinyl hydrogen), 3.22 (d, 2 H, J = 6 Hz), 2.30 (s, 6 H, SCH_3), 1.72 (s, 6 H, vinyl methyls), 1.31 (d, 3 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, ppm) 152.02, 132.37, 122.94, 69.87, 30.65, 25.75, 22.34, 18.06, 17.27, 16.77. **24** (oil); IR (mull) 2969, 2916, 2887, 2857, 1436, 1426, 1376, 1123, 1111, 1052, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) 5.12 (t, 1 H, J = 6 Hz), 3.99 (q, 3 H, J = 7 Hz), 3.86 (d, 1 H, J = 4 Hz, methine at sulfur), 2.65 (s, 1 H, OH), 2.22 (s, 3 H, SCH_3), 2.18 (s, 3 H, SCH_3), 1.70–2.40 (m, 3 H, aliphatic), 1.65 (s, 3 H, CH_3), 1.62 (s, 3H, CH_3), 1.20 (d, 3 H, J = 6 Hz).

(10) That these alcohols are indeed threo has been established by single-crystal X-ray analysis and will be reported in a subsequent publication.

(11) Careful reduction of the *tert*-butyl system **7** at 0 °C does allow one to isolate the corresponding allylic alcohol. Attempts to isolate the allylic alcohol generated in the reduction of **3** (aryl system) is problematic due to the inherent lack of stability of the doubly activated (allylic and benzylic) alcohol.

(12) Dieter, R. K.; Jenkitkasewong, Y. *Tetrahedron Lett.* **1982**, *23*, 3747.

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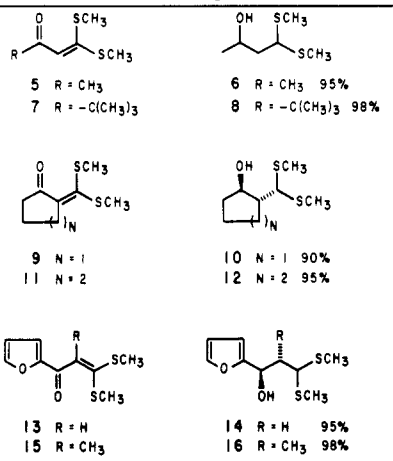
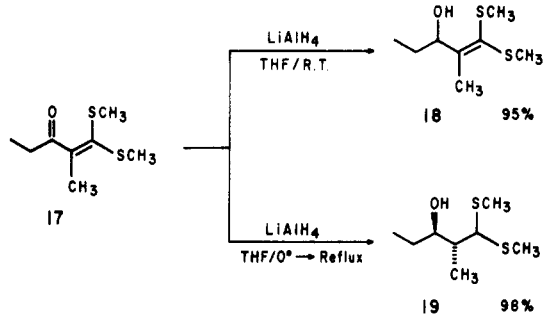
Table I. Reduction of α-Oxo Ketene Dithioacetals with $LiAlH_4$

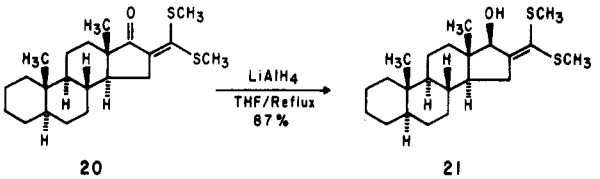


From a mechanistic point of view, specifically regarding the transition state of the hydroalumination step, it is



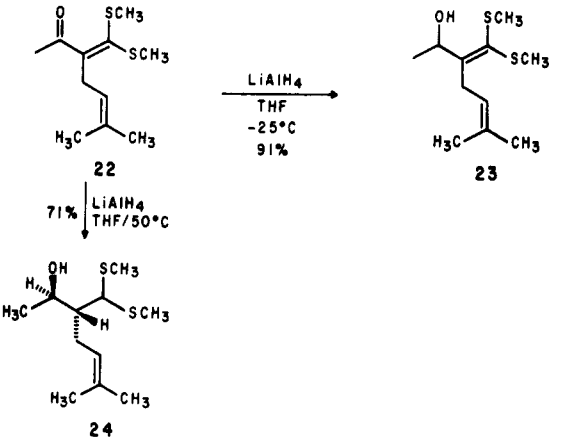
interesting to note that reduction of systems bearing a C-2 substituent, while requiring heat for the hydroalumination step, proceed with the same efficiency and stereospecificity as those lacking such substitution. It is also worth noting that α-oxo ketene dithioacetals **13** and **15**, in which the aryl group has been replaced by a synthetically manipulative aromatic heterocycle, undergo smooth reduction to alcohols **14** (95%) and **16** (97%), respectively.[13] Such α-hydroxy furans have been used effectively as an entry to a variety of modified unsaturated sugars.[14]

Interestingly, reduction of the 5α-androstan-17-one ketene dithioacetal **20** yielded only the carbonyl reduction



product **21** (87%). There was no evidence of olefinic hydroalumination even after extended reaction times at elevated temperatures. Apparently the C-18 angular methyl prevents the aluminum hydride moiety from assuming the

Scheme II



orientation necessary for the hydroalumination step.[15]

To further explore the synthetic aspects of this chemistry, and specifically the hydroalumination step, we investigated the reduction of α-oxo ketene dithioacetal **22**. While we did not anticipate a problem in the initial reduction step, we were curious to see if the presence of an additional olefinic site in the molecule would in any way interfere with the hydroalumination process.[16] Reduction of **22** with $LiAlH_4$ under the usual conditions (1.0 equiv of $LiAlH_4$/THF/room temperature and then reflux) gave a complex mixture of products, many of which appeared to result from over reduction (desulfuration) of the desired β-alkyl γ-bis(methylthio) alcohol (Scheme II). At lower reaction temperatures (−25 °C/30 min), we found that the intermediate allylic alcohol **23**[9] could easily be isolated in 91% yield. This result established without doubt that the hydroalumination step in this case was in fact not as straightforward as in the previous examples studied. By carefully monitoring the reaction (temperature and time), we found that reduction of **22** could smoothly be achieved by heating the reaction at 50 °C for 3 h. In this manner, **24**[9] could be isolated in 71% yield after silica gel chromatography (25% EtOAc/Skelly B).

α-Oxo ketene dithioacetals undergo a novel two-step reduction with $LiAlH_4$.[17] The first reduction proceeds at room temperature (or below) and occurs at the carbonyl carbon. That reduction is followed by the stereospecific hydroalumination of the resulting allylic olefin. The result is the formation of stereochemically defined β-alkyl γ-

(13) For the microbiological reduction of similar furan systems, see: Akita, H.; Furuichi, A.; Koshiji, H.; Horikoshi, K.; Oishi, T. *Tetrahedron Lett.* **1982**, *23*, 4051. For microbiological reduction of β-keto esters to give diastereomerically pure β-alkyl alcohols, see: Hoffmann, R. W.; Helbig, W.; Ladner, W. *Tetrahedron Lett.* **1982**, *23*, 3479.

(14) Ziegler, F. E.; Thottathil, J. K. *Tetrahedron Lett.* **1981**, *22*, 4883. Weeks, P. D.; Brennan, T. M.; Brannegan, D. P.; Kuhla, D. E.; Elliott, M. L.; Watson, H. A.; Wlodecki, B.; Breitenbach, R. *J. Org. Chem.* **1980**, *45*, 1109. Piancatelli, G.; Scettri. A.; D'Auria, M. *Tetrahedron Lett.* **1977**, 2199. Lefebvre, Y. *Ibid.* **1972**, 133. Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973.

(15) For another example of a reaction that fails to undergo the second hydride deliverly, see ref 6.

(16) Reduction of systems such as **22** also offer the potential for the generation of erythro β-alkyl alcohols. The scope of this strategy is presently under investigation in our laboratory.

(17) A representative reduction follows. Lithium aluminum hydride (0.68 g, 17.5 mmol) was suspended in THF (75 mL) and cooled to 0 °C. α-Oxo ketene dithioacetal **17** (3.33 g, 17.5 mmol), in THF (15 mL), was added dropwise to the above suspension and stirred continuously for 1 h. The reaction was then refluxed for 3 h. The reaction was cooled to 0 °C and carefully quenched with saturated ammonium chloride (25 mL), extracted with ether, and dried with Na_2SO_4, and the solvent was removed in vacuo to yield 4.18 g of the crude alcohol. Flash chromatography over silica gel (100 g, 10% ethyl acetate/Skellysolve B) afforded 3.32 g of **19** (98% yield) as a colorless oil. Silica gel TLC: R_f 0.25 in 10% ethyl acetate/Skellysolve B; IR (film) 3428, 2969, 2935, 2917, 2877, 1458, 1437, 1423, 1379, 1069, 973 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.05 (d, 1 H, J = 4.3 Hz, -C*H*(SCH_3), 3.58–3.70 (br m, 1 H, HOC*H*- with D_2O, dt, J = 8.0 and 3.2 Hz), 2.20 (s, 3 H, SCH_3), 2.17 (s, 3 H, SCH_3), 1.95–2.05 (m, 1 H, C*H*CH_3), 1.30–1.75 (m, 2 H, CH_3CH_2CH), 1.00 (d, 3 H, CH_3CH, J = 7.2 Hz), 0.98 (t, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, ppm) 74.45, 67.89, 58.78, 44.12, 27.22, 15.13, 12.47, 9.84; mass spectrum calcd for $C_8H_{18}OS_2$ 194.0796, found 194.0799; ions at m/e (relative intensity) 194 (35), 147 (50), 107 (37), 89 (100), 88 (31), 73 (25), 61 (29), 59 (33), 45 (25), 41 (39). Anal. Calcd for $C_8H_{18}OS_2$: C, 49.44; H, 9.33; S, 33.00. Found: C, 49.71; H, 9.17; S, 32.73.

bis(methylthio) alcohols in extremely high yield. Reduction of systems bearing a C-2 substituent other than methyl, i.e., **22**, are also reduced stereospecifically; however, the yield is somewhat lower. This study clearly demonstrates that α-oxo ketene dithioacetals, which are readily available from ketones, carbon disulfide, and an alkylating agent, provide a new and interesting entry to acyclic stereocontrol.

Further studies exploiting the synthetic potential of α-oxo ketene dithioacetals and in particular taking advantage of the stereochemically defined nature of the organometallic intermediate B will be reported in due course.

Registry No. **1**, 32268-43-2; **2**, 74291-93-3; **3**, 61541-58-0; **4**, 91002-91-4; **5**, 17649-86-4; **6**, 91002-92-5; **7**, 51507-09-6; **8**, 91002-93-6; **9**, 17649-89-7; **10**, 91002-94-7; **11**, 17649-90-0; **12**, 91002-95-8; **13**, 78078-05-4; **14**, 91002-96-9; **15**, 91002-97-0; **16**, 91002-98-1; **17**, 51507-08-5; **18**, 84307-86-8; **19**, 91002-99-2; **20**, 91003-00-8; **21**, 91003-01-9; **22**, 91003-02-0; **23**, 91003-03-1; **24**, 91032-20-1; $LiAlH_4$, 16853-85-3.

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Ferrous Ion Catalysis of Reactions of Nucleophiles with Aryl Halides[1]

Summary: Reactions of ketone enolate ions and of diethyl phosphite ion with bromo- and iodobenzene in ammonia or dimethyl sulfoxide solution occur in preparatively useful amounts under catalysis by iron(II) salts, apparently via the $S_{RN}1$ mechanism.

Sir: In the recent decade it has been demonstrated in several instances that plain aryl halides, without electron-attracting activating substituents, often react very satisfactorily with nucleophiles providing that reaction is appropriately provoked. Of major interest among such processes are reactions that occur by the radical chain $S_{RN}1$ mechanism.[2] The propagation cycle for this mechanism is shown in Scheme I.

Scheme I

$$ArX\cdot^- \rightarrow Ar\cdot + X^- \quad (M1)$$

$$Ar\cdot + Y^- \rightarrow ArY^-\cdot \quad (M2)$$

$$ArY^-\cdot + ArX \rightarrow ArY + ArX^-\cdot \quad (M3)$$

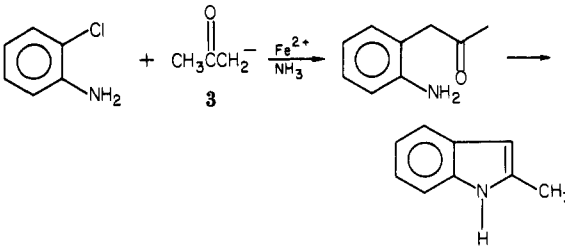
Although this mechanism occasionally is spontaneously initiated, it generally does not occur unless "switched on" through action by the chemist. Photostimulation is often effective, as is initiation by supplying electrons either as solvated electrons[2] or from a cathode.[3] Each of these methods of provocation suffers disadvantages in certain circumstances.

We now report that iron(II) salts effectively catalyze what appear to be aromatic $S_{RN}1$ reactions. Thus bromobenzene (29 g) and excess pinacolone enolate ion (**1**) in ammonia solution react during 75 min in the dark to form 1-phenyl-3,3-dimethyl-2-butanone (**2**) in 58% yield (eq 1)

$$PhBr + \underset{\mathbf{1}}{Me_3CC(O)CH_2^-} \xrightarrow[NH_3]{Fe^{2+}} \underset{\mathbf{2}}{PhCH_2C(O)CMe_3} + Br^- \quad (1)$$

in the presence of $FeSO_4$ (15 mol % with respect to PhBr) but fail to react if the iron salt is absent. Iodobenzene gives a higher yield, 87% (isolated and weighed). Acetone enolate ion (**3**) reacts similarly forming phenylacetone (**6**). Details appear in Table I.

It is noteworthy that this principle of catalysis is also effective in the reaction[4] of *o*-chloroaniline with **3** to form 2-methylindole in 51% yield (eq 2).



(2)

Another nucleophile well-behaved in aromatic $S_{RN}1$ reactions is diethyl phosphite ion (**4**);[2] see eq 3. It reacts

$$PhI + \underset{\mathbf{4}}{(EtO)_2PO^-} \xrightarrow[NH_3]{Fe^{2+}} \underset{\mathbf{5}}{PhP(O)(OEt)_2} + I^- \quad (3)$$

with iodobenzene in the dark under iron(II) catalysis to form 98% of diethyl phenylphosphonate (**5**) in 20 min time and even 48% of **5** in 1 min. As when reaction is photostimulated,[5] PhBr reacts less satisfactorily with **4**.

Reaction of PhI with a mixture of **1** and **4** was faster when provoked by $FeSO_4$ (Table I, run 9) than by Pyrex-filtered irradiation in our Rayonet photochemical reactor. However, the relative reactivity of the two nucleophiles (**4** being 1.4 times as reactive as **1**) was the same as under photostimulation.[6] This observation strongly suggests that the same intermediate reacts with the nucleophiles in both systems, and supports assignment of the $S_{RN}1$ mechanism to these reactions.

The efficacy of various iron species as catalysts was explored. In reaction with a mixture of **1** and **4**, hydrated ferrous sulfate was much less effective than the thoroughly dried salt.[7] Iron(III) salts showed little catalytic activity, nor did iron(II) chelated with acetylacetone. Also ineffective was whatever low-valent iron species is formed by reduction of $Fe(NO_3)_3$ with potassium in ammonia (run 14). Also rather ineffective, in lieu of iron(II) salts, were CuCl (run 11) and $SnCl_2$ (run 18). As solvent, dimethyl sulfoxide served reasonably well with catalyst $FeCl_2$ (runs 16 and 17).

Attempts to observe iron(II) catalysis of reactions of PhI with the conjugate bases of phenol and diethyl malonate were unsuccessful. These nucleophiles are generally unreactive in aromatic $S_{RN}1$ systems.[2]

Because of mentioned analogies with recognized $S_{RN}1$ processes, we think that these iron(II)-catalyzed reactions

(1) We gratefully acknowledge support of this research by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation.
(2) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413.
(3) Saveant, J. M. *Acc. Chem. Res.* **1980**, *13*, 323.
(4) Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1546.
(5) Bunnett, J. F.; Traber, R. P. *J. Org. Chem.* **1978**, *43*, 1867.
(6) Galli, C.; Bunnett, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 7140.
(7) Salts were dried 6 h under vacuum over P_2O_5 in a drying pistol heated by refluxing toluene.

0022-3263/84/1949-3041$01.50/0