Table I. Bromination of Aromatic Compounds with $DBUHBr_3$

no.	substrate	product	method	time, h	molar ratio, 1/subs.	yield,[a] %	mp, °C or bp, °C/Torr found	mp, °C or bp, °C/Torr lit.[15]
1	benzene	bromobenzene	D	0.5	1:2	70	153–155/760	152/760
2	mesitylene	2-bromomesitylene	B	1	1:1	76	103–106/16	105–107/16
3	acetanilide	4-bromoacetanilide	A	0.5	1:1	80	167–168	168
4	aniline	2,4,6-tribromoaniline	A	0.25	3:1	86	119–120	122
5	phenol	2,4,6-tribromophenol	A	0.25	3:1	89	92–94	95
6	nitrobenzene	1-bromo-3-nitrobenzene	D	12	1.1:1	62	53–55	56
7	naphthalene	1-bromonaphthalene	C	2	1.2:1	65	132–135/12	132–135/12
8	anthracene	9-bromoanthracene	C	0.25	1:1	70	96–98	100
		9,10-dibromoanthracene	C	0.5	2:1	95	223–225	226
9	phenanthrene	9-bromophenanthrene	C	3	1.2:1	60	62–64	65–66
10	biphenylene	2-bromobiphenylene	B	2	1:1	75	63–65	64–65[10]
11	thiophene	2-bromothiophene	A	0.25	1:2	68	152–154/760	155–156/760
		2,5-dibromothiophene	C	0.5	2:1	75	209–211/760	210/760

[a] Isolated pure product.

afforded 1: 92%; glittering-orange flakes; mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 8.35 (br s, 1 H, NH), 3.60 (m, 6 H), 2.88 (m, 2 H), 2.17 (m, 2 H), 1.80 (m, 6 H); IR (KBr) ν 3350 (m, NH), 3250 (m, br) 2925 (m, CH), 1640 (s, N=C) cm^{-1}. Anal. Calcd for $C_9H_{17}Br_3N_2$: C, 27.51; H, 4.36; N, 7.16; Br, 61.07. Found: C, 27.60; H, 4.32; N, 7.13; Br, 60.85.

HBr acetic acid solution may be replaced by 45% hydrobromic acid (180 mL) to give $DBUHBr_3$ in 85% yield.

General Procedure for Bromination of Aromatics with 1. Method A. The appropriate proportion of the molar ratio of 1 was added to a vigorously stirred solution of the aromatic substrate (10 mmol) in 50% aqueous DMF (25 mL) over a period of 10 min. The mixture was stirred at room temperature for the specified reaction time and then diluted with water (100 mL). After complete precipitation of the product, it was filtered in vacuo and washed with water. For liquid products, the aqueous solution was extracted with ether, separated, washed with water, dried, and evaporated under reduced pressure.

Method B. $DBUHBr_3$ (4 g, 10 mmol) was added to a solution of the aromatic substrate (10 mmol) and $HgCl_2$ (10 mmol) in DMF (25 mL). The mixture was stirred vigorously at room temperature for the specified reaction time. Diluted HCl (100 mL) was added, and it was stirred continuously until precipitation was completed. The product was then filtered in vacuo and washed with water. Liquid products were extracted with ether, separated, and washed with water and aqueous $NaHCO_3$. They were then dried and evaporated under reduced pressure.

Method C. The appropriate proportion of the molar ratio of 1 was added to a gently refluxing solution of the aromatic substrate (10 mL) in acetic acid over a period of 10 min. The mixture was stirred at reflux for the specified reaction time until no more HBr was evolved. The cold reaction mixture was diluted with water and extracted with ether. The organic layer was separated, washed with water and aqueous $NaHCO_3$, dried, and evaporated under reduced pressure. Anthracene products were isolated by filtration of the cold reaction mixture.

Method D. A mixture of the aromatic substrate (10 mmol), Ag_2SO_4 (4.70 g, 15 mmol), and concd H_2SO_4 (25 mL) was stirred vigorously at room temperature. $DBUHBr_3$ (4.4 g, 11 mmol) was added, over 30 min, and stirred continuously for the specified reaction time. The reaction mixture was then poured onto crushed ice (150 g), and the resulting AgBr was collected on a Buchner funnel. The filtrate and the precipitate were extracted with ether, and the combined extracts were washed several times with water to remove any remaining acid and evaporated under reduced pressure.

2,4,4,6-Tetrabromocyclohexa-2,5-dienone. The selective brominating agent was prepared from 2,4,6-tribromophenol according to Calo's method:[14] 78%; mp 122–124 °C. (lit.[15] mp 125 °C).

3-Bromoindole. The title compound was prepared as described in ref 12: 72%; mp 65–66 °C dec (lit.[12] mp 65–66 °C).

2,4,5-Tribromoimidazole. A mixture of imidazole (0.68 g, 10 mmol), $DBUHBr_3$ (4 g, 10 mmol), and $CaCO_3$ (2 g, 20 mmol) in CH_2Cl_2 (25 mL) and CH_3OH (10 mL) was stirred at room temperature for a period of 12 h, during which the orange color of the mixture disappeared. The solid $CaCO_3$ was filtered off, the filtrate was concentrated, and the residue was diluted with water. The aqueous mixture was extracted with ether, separated, dried, and evaporated under reduced pressure to give the title compound: 60% (based on $DBUHBr_3$) as white crystals; mp 220–222 °C (lit.[13] 221–222 °C).

Recovery of $DBUHBr_3$ from the Reaction Medium. The aqueous mother liquor, resulting after isolation of the product, was treated successively with 45% aqueous hydrobromic acid (1.7 equiv to $DBUHBr_3$, used in bromination process) and $NaBrO_3$ (0.34 equiv). The mixture was stirred until complete precipitation of 1, which was filtered and recrystallized from acetic acid: yield 60–68%.

Registry No. 1, 138666-59-8; DBU, 6674-22-2; $HgCl_2$, 7487-94-7; Ag_2SO_4, 10294-26-5; 2,4,5-tribromoimidazole, 2034-22-2; imidazole, 288-32-4; benzene, 71-43-2; mesitylene, 108-67-8; acetanilide, 103-84-4; aniline, 62-53-3; phenol, 108-95-2; nitrobenzene, 98-95-3; naphthalene, 91-20-3; anthracene, 120-12-7; phenanthrene, 85-01-8; biphenylene, 259-79-0; thiophene, 110-02-1; bromobenzene, 108-86-1; 2-bromomesitylene, 576-83-0; 4-bromoacetanilide, 103-88-8; 2,4,6-tribromoaniline, 147-82-0; 2,4,6-tribromophenol, 118-79-6; 1-bromo-3-nitrobenzene, 585-79-5; 1-bromonaphthalene, 90-11-9; 9-bromoanthracene, 1564-64-3; 9,10-dibromoanthracene, 523-27-3; 9-bromophenanthrene, 573-17-1; 2-bromobiphenylene, 17573-59-0; 2-bromothiophene, 1003-09-4; 2,5-dibromothiophene, 3141-27-3.

Supplementary Material Available: Table I containing bromination data for 12–24 with $DBUHBr_3$ and Table II containing ^1H NMR shifts of 1–27 (6 pages). Ordering information is given on any current masthead page.

(14) Calo, V.; Ciminale, F.; Lopez, L.; Todesco, P. E. *J. Chem. Soc. C* **1971**, 3652.
(15) *Dictionary of Organic Compounds*; Chapman & Hall: New York, 1982.

The Critical Role of β-CF_3 in the Regioselective Dehydrochlorination of 2-Chloro-4,4,4-trifluoro-2-methylbutane with Hindered Amines and Metal Oxides

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The use of steric effects to control the regiochemistry of 1,2-elimination reactions has been a recognized strategy since the mid-50's.[1,2] Since then, the understanding of

(1) Brown, H. C.; Moritani I. *J. Am. Chem. Soc.* **1953**, *75*, 4112.
(2) Brown, H. C.; Wheeler, O. H. *J. Am. Chem. Soc.* **1956**, *78*, 2199.

0022-3263/92/1957-2741$03.00/0

Table I. Distribution of Alkenes from the Dehydrochlorination of 2-Chloro-4,4,4-trifluoro-2-methylbutane (1) with Hindered Bases

base	T (°C)	convn (%)	t (h)	product mol % 2	3	4	2/3	matl bal (%)
2,6-diMe-Pyr[a]	250	100	1.5	53	22	24	2.4	104
	200	96	12	46	31	23	1.5	98
	175	84	48	39	45	16	0.86	97
	150	21	48	28	63	8.8	0.44	97
2-*t*-BuPyr	250	98	1.5	75	19	6.4	4.0	92
3,4-diMePyr	250	100	2.2	28	58	13	0.48	100
MgO	250	99	4.0	99.8	0.19	0	5.2×10^2	85
	150	57	11	85	15	0	5.7	108
CaO	250	91	4.0	87	13	0	6.7	111
	150	37	11	84	16	0	5.3	103
$KOC(C_2H_5)_3$	30	64	1.5	0.32	100	0	3.2×10^{-3}	90

[a] Pyr = pyridine.

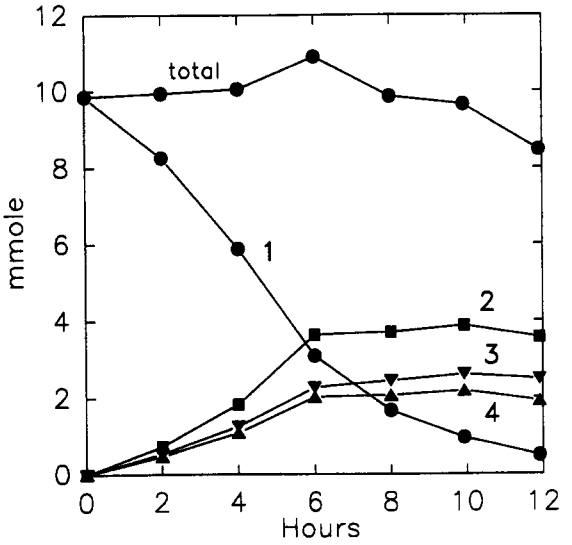
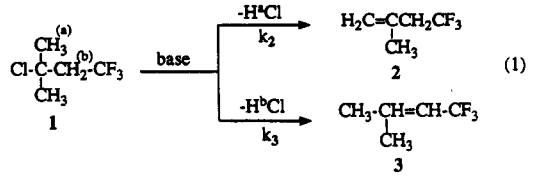


Figure 1. Dehydrochlorination of 2-chloro-4,4,4-trifluoro-2-methylbutane with 2,6-dimethylpyridine at 200 °C.

such effects has significantly improved, especially in alkoxide-promoted eliminations.[3] It seems clear that a hindered base must participate in the rate-controlling step in order to express a high level of steric control. This limits the occurrence of such control to the range of second-order elimination reactions. With E1 reactions, the cation undergoes conformational equilibration before losing a proton, and the more stable alkene is the dominant product.[4]

This report describes an example of regioselective dehydrochlorination of a *tertiary* chloride, 2-chloro-4,4,4-trifluoro-2-methylbutane (1), to give 4,4,4-trifluoro-2-methyl-1-butene (2) with hindered amines and alkaline-earth oxides (eq 1). The critical dependence of this selectivity on the presence of CF_3 in the β position is also described.



Despite the availability of relatively acidic β-protons (H^b) in 1, dehydrochlorination with 2-alkyl- and 2,6-dialkyl-substituted pyridines gives mainly the alkene 2 over 3 at ≥200 °C (Table I). A single byproduct is also formed that is assigned the structure 1,1,1-trifluoro-3-methylbutane (4) based largely on its ^{13}C- and ^1H-NMR spectra. The source of hydrogen in the formation of 4 appears to be the substituted pyridines. This conclusion is based on the wide variation in the amount of 4 produced depending on the amine used and the fact that the three products are made in parallel reactions, their ratios remaining essentially constant with conversion (Figure 1).

Regioselectivity in this reaction must originate from steric control because the unhindered isomeric base 3,4-dimethylpyridine gives the opposite orientation. When performed with MgO, elimination to the alkene 2 is essentially regiospecific at 250 °C, and none of the hydrogenolysis product 4 forms. Moreover, selectivity remains high even at 150 °C. The crystalline oxide surface must, therefore, be a highly hindered environment with respect to elimination in this system. MgO also differs from the substituted pyridines in that the ratio of 2 to 3 systematically increases with conversion (Figure 2). This is likely caused by the changing oxide surface as Cl and OH sites develop. Changing stereoselectivity with conversion has also been reported for the dehydrohalogenation of 2,3-dihalobutanes with metal oxide surfaces, including MgO.[5]

In sharp contrast to the fluorinated chloride 1, the unfluorinated analogue, 2-chloro-2-methylbutane (5), gives mainly the corresponding 2-alkene, 2-methyl-2-butene (6), over 2-methyl-1-butene (7) under all conditions examined. Moreover, the ratio of 6 to 7 is nearly invariant with either the type of base used or temperature (Table II).

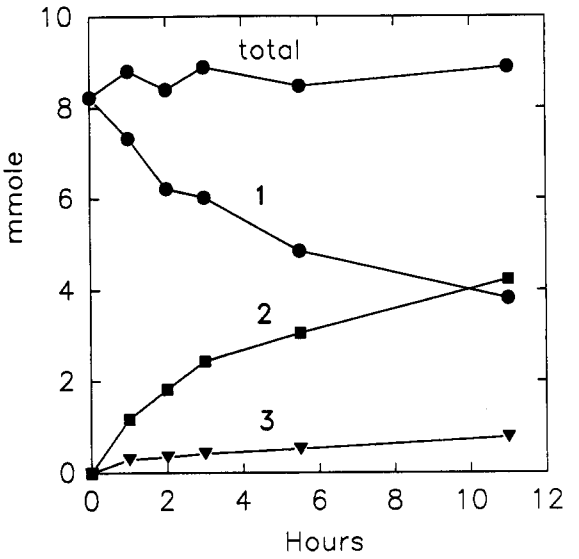


Figure 2. Dehydrochlorination of 2-chloro-4,4,4-trifluoro-2-methylbutane with MgO in nonane at 150 °C.

Table II. Distribution of Alkenes from the Dehydrochlorination of 2-Chloro-2-methylbutane (5) with Hindered Bases

base	T (°C)	convn (%)	t (h)	product mol % 6	7	6/7	matl bal (%)
2,6-diMePyr[a]	250	99	1.5	34	66	0.53	106
	180	99	1.5	38	62	0.60	105
	130	34	8.8	38	62	0.61	106
3,4-diMePyr	180	97	1.6	37	63	0.59	125
MgO	150	99	1.0	30	70	0.43	118

[a] Pyr = pyridine.

(3) Bartsch, R. A.; Závada, J. *Chem. Rev.* **1980**, *80*, 454 and references cited.

(4) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley: New York, 1985; p 881, 889.

(5) Misono, M.; Yoneda, Y. *J. Catal.* **1974**, *33*, 474.

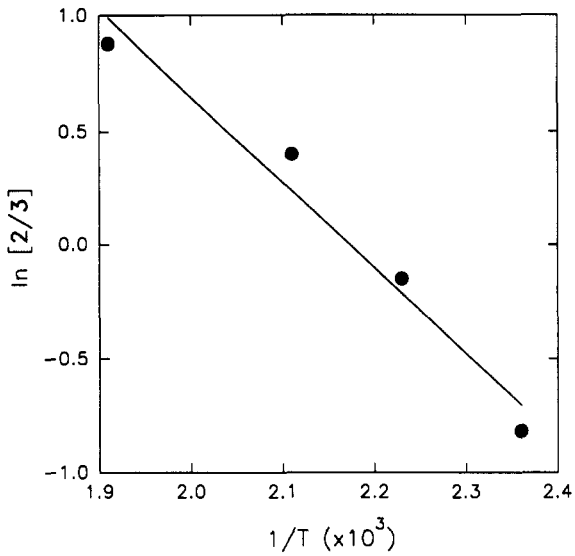


Figure 3. Dependence of ln [2/3] on $1/T$(K) for the dehydrochlorination of 1 in 2,6-dimethylpyridine.

Clearly, the elimination chemistry of 2-chloro-2-methylbutane is greatly influenced by fluorine substitution on the β-carbon. The insensitivity of 5 to steric features in the base and the dominance of the internal alkene 6 support an E1 reaction model or possibly an E2 transition state very close to that of E1.[6] However, the opposite behavior of the fluorinated analogue 1 is most consistent with a second-order elimination having strong involvement of base, possibly shifted toward E1cb by Cl and CF_3. According to this model, selective elimination to the 1-alkene occurs because CF_3 suppresses the cationic route. This effect is more important than the increased acidity of H^b that must result from its presence and which should enhance 2-alkene formation.

An isokinetic point exists within the temperature range examined in the dehydrochlorination of 1 with 2,6-dimethylpyridine. The rate of elimination to 2 overtakes that leading to 3 at between 175 °C and 200 °C due to changing contributions of the activation enthalpies and entropies with temperature. The ratio of fluoroalkenes is readily expressed in terms of activation parameters and temperature (eq 2), and Figure 3 displays the data plotted

$$\ln (k_2/k_3) = \ln (\mathrm{mol}_2/\mathrm{mol}_3) = \frac{\Delta H_3^{\ddagger} - \Delta H_2^{\ddagger}}{RT} + \frac{\Delta S_2^{\ddagger} - \Delta S_3^{\ddagger}}{R} \quad (2)$$

in this way. The highest temperature data point at 250 °C is the least accurate since some conversion occurs before the reaction temperature is reached. The lower temperature points are, therefore, more reliable. Nevertheless, it is clear that the slope is negative and intercept positive. Therefore, bond energies favor the formation of the 2-alkene, as expected. However, the transition state leading to the 1-alkene is more probable and dominates at high temperatures.

The above chemistry makes possible the synthesis of the previously unknown fluoroalkene 2, which we have examined as an intermediate in the synthesis of new polyethers.[7] However, the extent to which electron-withdrawing β substituents on *tertiary* chlorides can serve as a tool for the regioselective synthesis of 1-alkenes needs further study.

(6) Bunett, J. F.; Migdal, C. A. *J. Org. Chem.* **1989**, *54*, 3041.
(7) Nicholas, P. *J. Polym. Sci., Polym. Chem. Ed.*, In press; U.S. Patent 5 032 648.

Experimental Section

1,1,1,3-Tetrachloro-3-methylbutane. This material was prepared by a procedure similar to that described by Kharasch.[8] A 3-L autoclave was charged with 210.8 g (3.75 mol) of isobutylene, 1153.5 g (7.50 mol) of carbon tetrachloride, and 56.9 g of benzoyl peroxide. The mixture was shaken, heated to 100 °C, and held there for 4 h. The maximum pressure developed was approximately 90 psig. The dark reaction product was filtered and combined with the crude product from a second run. The combined products were distilled through a packed column, bp 61–2 °C/10 mm, 451.7 g. The combined yield, including that in the forerun, was 470.8 g (2.24 mol), 60%.

2-Chloro-4,4,4-trifluoro-2-methylbutane (1). This procedure is similar to that reported by Tarrant, Attaway, and Lovelace.[9] A 3-L autoclave was charged with 776 g (3.68 mol) of 1,1,1,3-tetrachloro-3-methylbutane. A shut-off valve with a $^1/_4$ in. male Swagelok fitting was attached to the head of the autoclave together with a monel pressure gauge. The autoclave was cooled in an ice bath and a 20-mm vacuum applied. Liquid hydrogen fluoride was then charged through the shut-off valve from an inverted lecture bottle connected by a line of Teflon tubing. Flow was controlled with a stainless steel needle valve. The reactor was then heated to 60 °C with shaking and maintained at 60 °C for 2.5 h, during which time the pressure increased to 705 psig. The autoclave was then cooled in ice, vented, pressurized, and vented several times with nitrogen. It was opened and 120 mL of pyridine added. The contents were recovered and combined with an octane rinse. The crude product was distilled through a short column and the distillate collected up to a pot temperature of 142 °C. Distillation was stopped at this point due to the accumulation of a white solid in the condenser. A total of 333.4 g of clear, colorless liquid was collected. This was washed with water, dried, and redistilled through a spinning band column, bp 69 °C, 273.8 g (>99.7% pure by GC). Total yield of product, including forerun, was 295.9 g (1.85 mol), 50.1%.

Dehydrochlorination of 1 with Substituted Pyridines. A 20-mL, stainless steel pressure vessel was fitted with a thermowell, pressure relief valve, gauge, and a shut-off valve fitted with a rubber septum for the removal of liquid samples. The contents were stirred by a magnetic stirring disc. A solution was prepared comprising 10 mL of the amine, 1.50 g (9.38 mmol) of 1, and 200 μL of benzene (GC calibration standard). The actual weight of delivered benzene was determined following injection. This solution was then charged into the reactor. It was heated to the reaction temperature using a custom mantle and proportioning controller operating from the thermocouple inside the reactor. Periodically, the body of the reactor was rapidly quenched in ice and the reactor head heated with a hot air gun to vaporize any volatiles in the lines and condense them into the reaction mixture. Approximately 0.25-mL samples were removed for GC quantitation. The reactor was then reheated to the reaction temperature. GC was performed with a 60-m Vocol glass column (0.75 mm, Supelco) operating at 10 °C, followed by a temperature program to 170 °C at 30 °C/min. The structure assignment for 4 is based on the NMR spectra of a spinning band distillation fraction (bp 40 °C, 73% 2, 20% 4) recovered from a preparative-scale experiment. The ^{1}H-NMR spectrum included an unaccounted for resonance at δ 1.00 (d, J = 6 Hz) present in an amount corresponding to that of the unknown component as determined by GC. The ^{13}C NMR showed the corresponding CF_3 resonance slightly displaced from that of 2.

Dehydrochlorination of 1 with MgO and CaO. Analytical-scale experiments were performed as described for the substituted pyridines except 10 mL of nonane was used as the solvent with 24 mmol of either MgO or CaO powder. Preparative-scale experiments were performed in a 500-mL stirred, stainless steel pressure reactor, as described below.

4,4,4-Trifluoro-2-methyl-1-butene (2). The above pressure reactor was charged with 80 g (0.500 mol) of the chloride 1 in 230 mL of octane and 62.7 g (1.56 mol) of MgO powder. The contents

(8) Kharash, M. S.; Jensen, E. V.; Urry, W. H. *J. Am. Chem. Soc.* **1947**, *67*, 100.
(9) Tarrant, P.; Attaway, J.; Lovelace, A. M. *J. Am. Chem. Soc.* **1954**, *76*, 2342.

were stirred at 1000 rpm and heated at 180 °C for 10 h. The reactor was then cooled and the following product recovery apparatus was attached to the shut-off valve on the reactor head. A short length of heated, flexible stainless steel tubing was connected to a 24/40 joint attached to a 100 mL, 3-neck flask fitted with a condenser. The flask was cooled in an ice bath. The shut-off valve was opened and the stirred reactor heated as the crude 1-butene **2** was distilled into the flask. Heating was continued until the temperature of the reactor contents reached 120 °C. This synthesis was performed three times. The combined products comprised 143 g of clear, colorless liquid. This was distilled on a spinning band column, bp 37 °C, giving 81.2 g of **2** of purity >95%, including a 35.6-g fraction >99.6%. The combined yield of **2** from all fractions was 99.7 g (0.804 mol), 54%. The 1-butene **2** has a very high vapor pressure and is easily lost. Care must be taken to keep it cold and in a tight container. ^{1}H NMR ($CDCl_3$): δ 1.85 (s, 3), 2.80 (q, 2, J = 11 Hz), 5.01 (s, 1), 5.12 (s, 1). Mass spectrum (electron impact): m/e 124.

It is unclear why the analytical-scale experiment gives essentially a quantitative yield of the 1-butene **2** while the preparative-scale synthesis gives a 54% isolated yield. One important difference between the two is that the preparative runs are about three times more concentrated in MgO for the purpose of increasing reactor productivity. This much higher concentration of MgO causes the reaction medium to be much more viscous and difficult to stir. This could cause local overheating at the reactor walls and possibly inhibit the generation of fresh MgO surface during the reaction.

4,4,4-Trifluoro-2-methyl-2-butene (3). A 3-neck, 25-mL flask was fitted with a condenser, gas bubbler, septum, argon inlet, thermometer, and a magnetic stir bar. The flask was charged with 0.28 g (7.18 mmol) of potassium metal and 15 mL of 3-ethyl-3-pentanol under argon. The mixture was stirred at 30 °C until all of the potassium had been consumed, and 1.51 g (9.41 mmol) of **1** was injected. A rapid exotherm to 40 °C occurred as the solution became turbid with the precipitation of KCl. Stirring was continued for 1.5 h from the time **1** was added. Argon flow was stopped, and 200 μL of benzene was injected. Quantitative GC was performed as noted (Table I). The reaction product was recovered by distillation ^{1}H NMR ($CDCl_3$): δ 1.90 (br s, 6) and 5.45 (q, 1, J = 8 Hz). Mass spectrum (electron impact): m/e 124.

Dehydrochlorination of 2-Chloro-2-methylbutane (5). These experiments were performed as described for **1**. Authentic samples of **6** and **7** were used for characterization and calibration. The dehydrochlorination of **5** is much faster than **1**, and shorter reaction times are required.

Acknowledgment. I am pleased to acknowledge the skillful experimental assistance provided by Mr. Thomas Barker. My thanks also to Drs. Robert Kinsey, George Benedikt, and James Chen for NMR spectra and to Dr. Robert Lattimer for mass spectrometric analyses.

Registry No. **1**, 352-46-5; **2**, 138835-37-7; **3**, 352-42-1; **4**, 406-49-5; **5**, 594-36-5; **6**, 513-35-9; **7**, 563-46-2; MgO, 1309-48-4; CaO, 1305-78-8; $KOC(C_2H_5)_3$, 20484-37-1; 2,6-diMePyr, 108-48-5; 2-*t*-BuPyr, 5944-41-2; 3,4-diMePyr, 583-58-4.

Evidence for the Formation of Heterocyclic Arene Oxides and a γ-Keto Enal by Reaction of Menthofuran with Dimethyldioxirane

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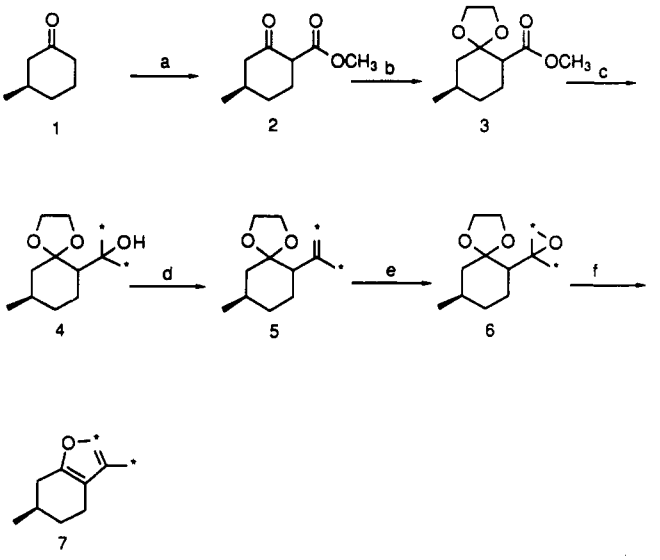
Epoxides have been proposed as reactive intermediates in the metabolism of furans,[1] but there is little evidence for the formation of such heterocyclic arene oxides. An epoxide of the *dihydro*furan, aflatoxin B_1, has been prepared and characterized,[2] and NMR data has been presented for a 4,5-epoxyfuran intermediate in the oxidation of a tetrasubstituted fungicidal furan, methfuroxam (2,4,5-trimethyl-*N*-phenyl-3-carboxamide), by *m*-chloroperoxybenzoic acid (*m*-CPBA).[3] In the case of less substituted furans, as well as methfuroxam, *m*-CPBA oxidation primarily yields ene diones and ene lactones.[3,4] More recently, an epoxide was characterized by NMR as a likely mutagenic product of the oxidation of 2,3-dimethylbenzo[*b*]furan by dimethyldioxirane.[5]

Scheme I[a]



[a] (a) NaH, THF, dimethyl carbonate; (b) ethylene glycol, *p*-TSOH, benzene; (c) $^{13}CH_3I$, Et_2O, Mg; (d) *p*-TSOH, benzene, Δ; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (f) 2 N HCl, pentane.

We now report that the oxidizing agent, dimethyldioxirane,[6] converts the terpenoid furan, menthofuran (4,5,6,7-tetrahydro-3,6-dimethylbenzofuran), to both a γ-keto enal and diastereomeric furan epoxides at low temperatures (−40 °C to −20 °C), which then form stable ene lactones at higher temperatures (0–20 °C). Menthofuran is of interest as a potentially toxic terpene in mint oils and as a proximate toxic mammalian metabolite of the monoterpene, (*R*)-(+)-pulegone.[7] The ultimate toxic species is unknown, although indirect evidence suggests that a γ-keto enal is formed that irreversibly binds to target tissue proteins.[8]

(1) For a review, see: Burka, L. T.; Boyd, M. R. *Bioactivation of Foreign Compounds*; Academic Press: New York, 1985; p 243.

(2) Baertschi, S. W.; Raney, K. D.; Stone, M. P.; Harris, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 7929.

(3) Ruzo, L. O.; Casida, J. E.; Holden, I. *J. Chem. Soc., Chem. Commun.* **1985**, 1643.

(4) Gingerich, S. B.; Jennings, P. W. *J. Org. Chem.* **1983**, *48*, 2606. Ravindranath, V.; Burka, L. T.; Boyd, M. R. *Science* **1984**, *224*, 884. Manfredi, K. P.; Jennings, P. W. *J. Org. Chem.* **1989**, *54*, 5186.

(5) Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha-Möller, C. R.; Wild, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 200. Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha-Möller, C. R.; Wild, D. *J. Am. Chem. Soc.* **1991**, *113*, 8005.

(6) For reviews, see: Adam, W.; Curci, R.; Edwards, S. D. *Acc. Chem. Res.* **1989**, *22*, 205. Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

(7) Gordon, W. P.; Huitric, A. C.; Seth, C. L.; McClanahan, R. H.; Nelson, S. D. *Drug Metab. Dispos.* **1987**, *15*, 589. McClanahan, R. H.; Huitric, A. C.; Pearson, P. G.; Desper, J. C.; Nelson, S. D. *J. Am. Chem. Soc.* **1988**, *110*, 1979. Moorthy, B.; Madyastha, P.; Madyastha, K. M. *Xenobiotica* **1989**, *19*, 217.

0022-3263/92/1957-2744$03.00/0