Ferric Chloride in Acetic Anhydride. A Mild and Versatile Reagent for the Cleavage of Ethers

Bruce Ganem* and Vernon R. Small, Jr.‡

Department of Chemistry, Cornell University, Ithaca, New York 14850

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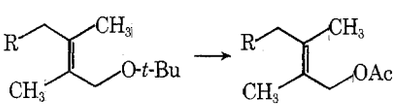
The reaction of anhydrous ferric chloride in acetic anhydride with a variety of ethers has been examined in order to elucidate the mechanism and scope of this ether-to-acetate transformation. Ethers **1**, **2**, and **8** are transformed to the corresponding acetates **3**, **4**, and **9** without cis–trans olefin isomerization. Cleavage of optically active ethers **5** and **6** affords substantially racemized 2-octyl acetate. *tert*-Butyldimethylsilyl ether **7** is rapidly cleaved with nearly complete retention of configuration. In light of the data presented, a mechanism involving O-acylation followed by SN1 or SN2 attack by acetate is discussed.

In 1914, Knoevenagel observed the formation of ethyl acetate in the reaction of diethyl ether with ferric chloride in acetic anhydride.[1] Since that time, this unusual reagent for the fragmentation of ethers has largely been ignored by the synthetic chemist although other combinations of Lewis acids with carboxylic acid chlorides and anhydrides are known to convert ethers to esters.[2,3] Unfortunately the problem with aliphatic ethers as useful OH protecting groups has always been the dearth of gentle yet effective techniques for releasing the parent alcohol. Recently our own research demanded such a method, consequently we undertook to explore the advantages of ferric chloride–acetic anhydride for this purpose. The current renewed interest in the importance of alcohol protecting groups[4] prompts us to report our remarkable findings with this complex.

We had occasion to prepare the trans-allylic ethers **1** and **2**[5] and hoped to remove the *tert*-butyl protecting group without effecting double bond isomerization. When either **1** or **2** was exposed to a trace of ferric chloride in acetic anhydride as solvent ($FeCl_3$–Ac_2O), these ethers were smoothly converted to the corresponding trans acetates **3** and **4** along with an equivalent amount of *tert*-butyl acetate.[6,7] No trace of the cis isomer could be detected.[8] In contrast,



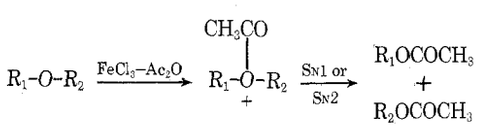
1, R = Cl **3**, R = Cl
2, R = OAc **4**, R = OAc

treatment of the ether **2** with dilute stannic chloride in acetic anhydride at 0° led to significant cis–trans isomerization during formation of diacetate **4**. These and other results are summarized in Table I.

Using this method, simple substances such as di-*n*-butyl or diisopropyl ether were readily transformed into 2 equiv of the corresponding acetate. Exposure of some benzylic ethers to this reagent revealed an interesting phenomenon. Whereas benzyl 2-octyl ether was converted after 17 hr at 80° to equal amounts of benzyl and 2-octyl acetates, benzyl butyl ether afforded by the same procedure butyl acetate but no benzyl acetate. Experiments firmly established that benzyl acetate alone in $FeCl_3$–Ac_2O was rapidly transformed at 80° to a mixture of acetylated products complexed to the Lewis acid and therefore insoluble in hexane. However, when benzyl acetate was exposed to $FeCl_3$–Ac_2O in the presence of an equimolar quantity of either *n*-butyl acetate or 2-octyl acetate, the Friedel–Crafts acetylation was dramatically retarded. Almost all of the benzyl acetate (along with *n*-butyl or 2-octyl acetate) was recovered after 17 hr at 80°. This remarkable effect, although unclear, may be due to selective complexation by the ester carbonyl moiety as a strong Lewis base.

In any event, the preceding experiments clearly distinguish two competing reactions of benzylic ethers in $FeCl_3$–Ac_2O. Evidently benzyl 2-octyl ether was converted to a mixture of acetates faster than it underwent acetylation, but benzyl butyl ether was first acetylated, then cleaved to provide *n*-butyl acetate as the only hexane-soluble product. As expected, diphenyl ether and equilenin were also acetylated but not cleaved at the ether linkage.

The mechanism as well as the stereochemistry of this ether-to-acetate transformation was of interest. When optically active methyl 2-octyl ether (**5**) was heated with $FeCl_3$–Ac_2O, 2-octyl acetate appeared which was largely (96%) racemized and of inverted configuration. However, cleavage of (+)-benzyl *d*-2-octyl ether (**6**) afforded (+)-*d*-2-octyl acetate which had undergone 85% racemization.[9] While cholesteryl methyl ether was smoothly transformed to cholesteryl acetate in high yield, cholestanyl methyl ether (**12**) was converted to a mixture of 3α- and 3β-cholestanyl acetates as well as to Δ^2-cholestene.[3a,10] These data support a dual mechanism involving O-acylation of the ether followed by dissociation of the more stable carbonium ion or by nucleophilic displacement at the oxonium ion by acetate.

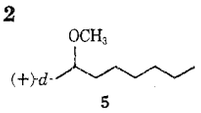
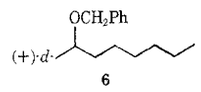
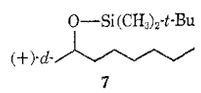
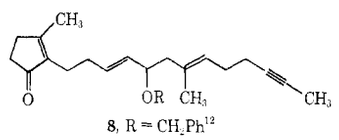


The present fragmentation is not limited to classic alkyl ethers alone. Since its inception as an oxygen protecting group,[11] the *tert*-butyldimethylsilyl moiety has been widely employed as an alcohol blocking agent which is easily removed by treatment with tetra-*n*-butylammonium fluoride.[4a] We have observed that these silyl ethers are rapidly cleaved (15 min, 0°) using $FeCl_3$–Ac_2O. For example, (+)-*tert*-butyldimethylsilyl *d*-2-octyl ether (**7**) afforded *d*-2-octyl acetate in 92% yield with 88% retention of configuration. This technique complements the direct deprotection by fluoride and further illustrates the unexplored potential of $FeCl_3$–Ac_2O for selective ether cleavage.

We have also demonstrated the exceptional mildness of this reagent by converting ether **8**[12] into its acetate **9** in quite acceptable yield without olefin isomerization. As is evident from its highly functionalized structure, this sub-

‡ Department of Chemistry, Stanford University, Stanford, Calif. 94305.

Table I

Ether	Time, hr	Temp, °C	$FeCl_3$, equiv	Product[a] (% yield)[b]
n-Butyl ether (142-96-1)	16	80	0.2	*n*-Butyl acetate (45)
Isopropyl ether (108-20-3)	24	80	0.15	Isopropyl acetate (83)
$PhCH_2O$ *n*-Bu (588-67-0)	17	80	0.32	*n*-Butyl acetate (88)
1	0.25	0	0.1	**3** (83)
2	0.66	38	0.1	**4** (76)
 **5**	24	80	0.22	2-Octyl acetate (64)
 **6**	22	80	0.34	Benzyl acetate (45) 2-Octyl acetate (45)
 **7**	0.25	0	0.15	2-Octyl acetate (92)
 8, R = CH_2Ph[12]	5	50	0.55	**9** (**8**, R = Ac) (44)[c]
3β-Cholesteryl methyl ether (**10**)	1	25	0.16	3β-Cholesteryl acetate (**11**) (87)
3β-Cholestanyl methyl ether (**12**)	17	25	0.15	3β-(Cholestanyl acetate (31) 3α-Cholestanyl acetate (14) Δ^2-Cholestene (10)

[a] These products were identified by their nmr and ir spectra and by comparison with authentic samples. [b] Yields are based on distilled or chromatographed products. [c] This yield has not been maximized.

stance is completely incompatible with the two most common methods for removing benzylic ethers: metal–ammonia reduction or catalytic hydrogenation. Such specificity along with its simplicity and versatility should make the ferric chloride–acetic anhydride reagent a worthwhile alternative to current techniques for dealing with ethers as protecting groups in synthesis.[16]

Experimental Section

Melting points were determined using a Kofler hot-stage microscope. Nmr spectra of deuteriochloroform or deuteriobenzene solutions were recorded on a Varian A-60 or T-60 spectrometer with tetramethylsilane as an internal standard. Ir spectra were determined as neat films or in solution on a Perkin-Elmer 137 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Gas–liquid chromatographic analyses were carried out on a Hewlett-Packard HP-402 or 5750B gas chromatograph using the following columns: (a) 3% XE-60 (6 ft) on 80–100 gas chromatograph Q; (b) 3% SE-30 (5 ft) on Chromosorb W 60–80; (c) 3% OV-17 (6 ft).

Materials. Commercially available di-*n*-butyl and diisopropyl ether (Matheson Coleman and Bell) were distilled from sodium. Benzyl butyl ether (MCB) was washed with $FeSO_4$ and then distilled from sodium. Cholestanyl methyl ether,[3a] cholesteryl methyl ether,[3a] methyl *d*-2-octyl ether,[13] and benzyl *d*-2-octyl ether[14] were prepared as described in the literature. Acetic anhydride (ACS reagent grade, J. T. Baker) was distilled. Anhydrous ferric chloride (MCB) was used directly.

General Procedure for the Cleavage of Simple Dialkyl Ethers. Conversion of Di-*n*-butyl Ether to Butyl Acetate. To a solution of di-*n*-butyl ether (4.64 g, 35.5 mmol) and acetic anhydride (15 ml) in a flask equipped with condenser and drying tube was added anhydrous ferric chloride (1.0 g, 6.2 mmol). A mild exothermic reaction ensued. The dark reaction mixture was heated on a steam bath (internal temperature 80°) for 16 hr, then fractionally distilled to afford *n*-butyl acetate (32 mmol, 46%) along with small amounts of acetic acid and acetic anhydride. These impurities could be removed by washing the distillate with sodium bicarbonate solution.

Cleavage of Benzyl *n*-Butyl Ether. A solution of benzyl *n*-butyl ether (3.0 g, 18.3 mmol) in acetic anhydride (7 ml) was treated with ferric chloride (1 g, 6.2 mmol) and then heated at 80° (steam bath) for 17 hr. After cooling, the dark reaction product was partitioned between hexane and water. Three hexane extracts were combined, filtered, washed twice with water and three times with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. Distillation afforded 1.85 g (88%) of butyl acetate, bp 126–27°, having nmr and ir spectra identical with an authentic sample.

Synthesis of 1-Acetoxy-4-chloro-*trans*-2,3-dimethyl-2-butene (3) from 1. To a solution of 1[5] (49 mg, 0.26 mmol) in acetic anhydride (2 ml) at 0° under N_2 was added ferric chloride (4 mg, 0.02 mmol). The mixture was stirred 15 min at 0° then worked up by extraction with three portions of hexane. The combined extracts were washed with water and sodium bicarbonate solution, dried ($MgSO_4$), and concentrated. Kugelrohr distillation of the crude product (70°, 100 mm) afforded 39 mg (83%) of **3**: nmr (benzene-d_6) δ 4.44 (s, 2 H), 3.70 (s, 2 H), 2.58–2.68 (broad s, 9 H); ir 5.77 μ; glc (XE-60, 65°) one peak, retention time 8.0 min.

A portion of this material was stirred with 2 equiv of sodium acetate (anhydrous) in hexamethylphosphoric triamide (HMPA) at room temperature for 12 hr. This reaction afforded a sample of diacetate **4** containing only the trans isomer: nmr (benzene-d_6) δ 4.50 (s, 4 H), 1.68 (s, 12 H); (in $CDCl_3$) δ 4.65 (s, 4 H), 2.07 (s, 6 H), 1.80 (s, 6 H), ir (film) 5.78 μ; glc (OV-17, 90°) one peak, retention time 12.2 min. None of the corresponding cis isomer could be detected either by nmr (methylene absorption at δ 4.74) or by glc (OV-17, 90°, retention time 10.8 min).

Synthesis of 4-Acetoxy-*trans*-2,3-dimethyl-2-butenyl *tert*-Butyl Ether (2) from 1. A mixture of 1[5] (79 mg, 0.4 mmol) and anhydrous sodium acetate (77 mg, 0.94 mmol) in dry HMPA was stirred at room temperature under N^2 for 12 hr. After partitioning between hexane and water, the hexane fraction was dried ($MgSO_4$) and concentrated. The residue was purified by Kugelrohr distillation (70° (100 mm)) to afford 85 mg (95%) of **2** as an oil; nmr ($CDCl_3$) δ 4.62 (s, 2 H), 3.84 (s, 2 H), 2.04 (s, 3 H), 1.80 (s, 6 H), 1.22 (s, 9 H); ir (film) 5.77 μ.

Synthesis of 1,4-Diacetoxy-*trans*-2,3-dimethyl-2-butene (4) from 2. A solution of **2** (45 mg, 0.20 mmol) in acetic anhydride (0.5 ml) was treated with 4 mg (0.02 mmol) of ferric chloride. This mixture was stirred under N_2 at 38° for 35 min. Work-up by hexane extraction as described above afforded an orange oil. Kugelrohr

distillation (80° (100 mm)) yielded 30 mg (76%) of **4** as a colorless oil. Its spectral data were identical with that given above. Again, no cis isomer could be detected by nmr or glc as described above.

Synthesis of Cholesteryl Acetate from Cholesteryl Methyl Ether 10. Cholesteryl methyl ether[3a] (0.253g, 0.63 mmol) was dissolved in 1:1 acetic anhydride–ethyl acetate (4 ml) with gentle warming. After cooling to room temperature, ferric chloride (16 mg, 0.1 mmol) was added and the purple reaction mixture was stirred 1 hr at room temperature, then poured into water and extracted three times with hexane. The combined extracts were washed with water and $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated to a white solid. Column chromatography of this crude product on silica gel eluting with 1:4 ether–hexane afforded 0.217 g (87%) of cholesteryl acetate, mp 109–111° (after one recrystallization from methanol; reported[3a] mp 110–111°), which was identical by ir, nmr, and glc analysis (XE-60, 250°, retention time 5.4 min) with an authentic sample.

Cleavage of Cholestanyl Methyl Ether 12. A solution of **12**[3a] (0.329 g, 0.82 mmol) in ethyl acetate (2 ml) was diluted with acetic anhydride (2 ml). Ferric chloride (20 mg, 0.12 mmol) was added and the reaction mixuture was stirred at room temperature for 17 hr, then worked up by hexane extraction in the usual fashion. Glc analysis of the crude product (XE-60, 250°) indicated three major products. Column chromatography (silica gel, 2:98 ether–hexane) afforded 33 mg (10%) of Δ^2-cholestene. Further elution produced 0.150 g of 32:68 mixture of 3α- and 3β-cholestanyl acetates which represents yields of 14 and 31% for these respective acetates. Their identity was established by glc coinjection with authentic samples (retention times 4.5 and 5.0 min, respectively) as well as by nmr spectroscopy.

Cleavage of Methyl *d*-2-Octyl Ether 5. (+)-Methyl *d*-2-octyl ether (2.0 g, 13.9 mmol, $[\alpha]^{20}D$ +6.90°; prepared[13] using 95% (+)-*d*-2-octanol (Aldrich) $[\alpha]^{20}D$ 9.5°) was dissolved in acetic anhydride (5 ml). Ferric chloride (0.5 g, 3.1 mmol) was added and the reaction mixture was heated (steam bath) at 80° for 24 hr. The usual work-up (hexane extraction; water, $NaHCO_3$ washing) afforded 1.77 g of crude product after solvent removal. Kugelrohr distillation (90–100° (20 mm)) afforded 1.50 g (64%) of 2-octyl acetate identical by ir and nmr with an authentic sample and exhibiting one peak on glc analysis (XE-60, 69°, retention time 2.6 min); $[\alpha]^{20}D$ −0.27° which corresponds to 3.8% inversion of configuration.

The enantiomeric purity of a sample of (+)-*d*-2-octyl acetate (kindly provided by Professor J. P. Collman, Stanford University) was unchanged after heating in $FeCl_3$–Ac_2O for 24 hr at 80°.

Cleavage of Benzyl *d*-2-Octyl Ether 6. Ferric chloride (0.5 g, 3.1 mmol) was added to a solution of **6**[14] (2.0 g, 9.2 mmol, $[\alpha]^{20}D$ +25.57°, 94% enantiomeric purity) in acetic anhydride (5 ml) and the resulting solution was heated at 80° for 22 hr. Work-up by hexane extraction in the usual manner yielded 2.186 g of crude product. Kugelrohr distillation afforded 1.317 g (45%) of a 1:1 mixture of octyl and benzyl acetates by glc analysis (XE-60, 72°, retention times 2.2 and 7.1 min, respectively), having $[\alpha]^{20}D$ +1.01° (*c* 51, benzyl acetate). This represents 15.2% retention.

Synthesis of *tert*-Butyldimethylsilyl *d*-2-Octyl Ether 7. The procedure of Corey and Venkateswarlu was followed.[4a] A solution of (+)-*d*-2-octanol (3.0 g, 23 mmol, $[\alpha]^{20}D$ 9.25°, 93% optically pure) in dry *N*,*N*-dimethylformamide (20 ml) was stirred with imidazole (5.42 g, 80 mmol) and *tert*-butyldimethylsilyl chloride (4.5 g, 30 mmol, Willowbrook Labs) under N_2 at room temperature for 15 hr. The reaction mixture was then poured into water and extracted three times with hexane. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated. Distillation afforded 4.47 g (80%) of **7** as a colorless liquid: bp 117–118° (15 mm); $[\alpha]^{20}D$ 13.56° (93% enantiomeric purity); d^{20} 0.8099; nmr ($CDCl_3$) δ 3.70 (broad t, 1 H, J = 7 Hz), 1.11 (d, 3 H, J = 7 Hz), 0.85 (s, 9 H); ir (film) 3.40, 3.60, 6.80, 6.85, 7.28, 7.38, 7.97, 8.80, 8.91, 9.2–9.5, 9.92, 10.45, 10.62, 11.95, 12.90 μ. *Anal.* Calcd for $C_{14}H_{32}OSi$: C, 68.8; H, 13.1. Found: C, 68.7; H, 13.15.

Cleavage of *tert*-Butyldimethylsilyl *d*-2-Octyl Ether (7). A solution of **7** (0.62 g, 2.5 mmol) in acetic anhydride (1.5 ml) was cooled to 0° under N_2. Ferric chloride (60 mg, 0.37 mmol) was added and 15 min later the reaction mixture was worked up by hexane extraction. Kugelrohr distillation of the crude product afforded 0.85 g (98%) of oil. Glc analysis showed this to be a 1:1 mixture of 2-octyl acetate and *tert*-butyldimethylsilyl acetate. Column chromatography (silica gel, benzene–hexane mixtures) afforded pure 2-octyl acetate (0.40 g, 92%, one peak on glc analysis); $[\alpha]^{20}D$ +5.78° (*c* 32.6, $CHCl_3$) which corresponds to 88% retention of configuration.

Cleavage of Benzyl Ether (8). Synthesis of 9. Ferric chloride (20 mg, 0.12 mmol) was added to a solution of **8**[12] (75 mg, 0.22 mmol) in acetic anhydride (1.0 ml) and the dark solution was stirred under N_2 at 55° for 5 hr. After cooling and partitioning between hexane and water, the combined organic extracts were washed with $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. Tlc (1:1 ethyl acetate–hexane) and glc (XE-60, 225°) analysis revealed the presence of only one other substance in addition to starting material. Column chromatography (silica gel, 1:3 ethyl acetate–hexane) separated 15 mg of **8** from 24 mg (44%) of the acetate **9**. Its identity with an authentic sample[15] of **9** was confirmed by their superimposable nmr and ir spectra, identical tlc behavior, and glc retention times (XE-60, 225°, 5.2 min): nmr ($CDCl_3$) δ 5.60–5.02 (complex m, 3 H), 2.02 (s, 3 H), 1.70 (broad s, 3 H), 1.61 (broad s, 3 H); ir 3.41, 5.76, 5.89, 6.09, 6.95, 7.22, 7.32, 8.10, 8.50, 9.31, 9.79, 10.41 μ.

Registry No.—**1,** 53060-22-3; **2,** 53060-23-4; **3,** 53060-20-1; **4,** 3780-51-6; **5,** 53142-02-2; **6,** 53060-24-5; **7,** 53060-25-6; **8** (R = CH_2Ph), 53060-26-7; **9,** 53060-21-2; **10,** 1174-92-1; **11,** 604-35-3; **12,** 53109-81-2; $FeCl_3$, 7705-08-0; acetic anhydride, 108-24-7.

References and Notes

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(5) These compounds originate from the addition of *tert*-butyl hypochlorite with 2,3-dimethyl-1,3-butadiene.[6] Details of their preparation and utility in stereospecific olefin synthesis will be reported elsewhere.
(6) W. Oroshnik and R. A. Mallory, *J. Amer. Chem. Soc.*, **72,** 4608 (1950).
(7) Prolonged reaction of the chloro ether **1** results in eventual displacement of the chloride by acetate.
(8) An authentic mixture of cis and trans **4** may be prepared from *cis,trans*-1,4-dibromo-2,3-dimethyl-2-butene [*cf.* O. J. Sweeting and J. R. Johnson, *J. Amer. Chem. Soc.*, **68,** 1057 (1946)] by reaction with sodium acetate (NaOAc) in hexamethylphosphoric triamide (HMPA). Besides being readily separable using gas–liquid chromatography, nmr spectroscopy in benzene-d_6 (see Experimental Section). The isomeric purity of **3** was determined by conversion to **4** with NaOAc–HMPA and subsequent analysis.
(9) Similar results have been noted in the reaction of *s*-butyl methyl ether with acids such as zinc chloride or stannic chloride: R. L. Burwell, Jr., L. M. Elkin and L. G. Maury, *J. Amer. Chem. Soc.*, **73,** 2428 (1951).
(10) In these two cases, ethyl acetate was also employed for added solubility of the starting ether in acetic anhydride.
(11) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, **90,** 4462 (1968).
(12) This compound has been synthesized stereospecifically by W. S. Johnson and S. Escher at Stanford University, and we thank them for a generous sample.
(13) J. Kenyon and R. A. McNicol, *J. Chem. Soc.*, **123,** 17 (1923).
(14) H. G. Rule and J. Bain, *J. Chem. Soc.*, 1894 (1930)
(15) Prepared by acetylation of the corresponding allylic alcohol.[12]

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