5.27 (br s, 0.6 H, α-anomeric proton; β-anomeric proton apparently masked by HOD); ^{13}C NMR (D_2O) δ (α-anomer) 29.6, 64.7, 65.3, 68.6, 69.4, 95.2; (β-anomer) 29.0, 64.4, 69.3, 70.4, 73.2, 94.5.[6,7]

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.43; H, 7.67.

The *p*-nitrobenzenesulfonylhydrazone of **7**[1] had mp 107-110 °C dec (lit.[1] mp 113-120 °C dec).

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Registry No. **3**, 63167-70-4; **4**, 73635-97-9; **5**, 73635-98-0; **6**, 73635-99-1; **7**, 18439-27-5; **7** *p*-nitrobenzenesulfonylhydrazone, 73636-00-7; *N,N'*-thiocarbonyldiimidazole, 6160-65-2.

(6) It is interesting to note that the equilibrium ratio of α- and β-anomers of **7** in aqueous solution (determined by NMR measurements) is 62:38, quite similar to the 67:33 ratio observed for D-mannose.[7]

(7) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).

Reaction of Triflic Anhydride with Grignard Reagents. Oxidizing Properties of Triflic Anhydride

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As a leaving group, the trifluoromethanesulfinate ($CF_3SO_2^-$) group should possess greater lability than nonfluorinated analogues such as methanesulfinate ($CH_3SO_2^-$). This is borne out by studies of Hendrickson and coworkers[2] which show facile loss of the trifluoromethanesulfinate group in 1,2- and 1,3-eliminations as well as reductive eliminations. Additionally, our studies with α-keto triflates[3,4] have shown that base-promoted 1,2-elimination of trifluoromethanesulfinic acid (a formal oxidation process) can occur in preference to α-elimination of trifluoromethanesulfonic acid. We were therefore interested in developing methods to complement those of Hendrickson[2,5] for the preparation of trifluoromethyl sulfones (triflones) and to exploit the apparent excellent leaving-group properties of the trifluoromethanesulfinate moiety.

Hendrickson[5] has discussed some of the problems associated with the reaction of organolithium reagents with electrophilic triflating agents such as triflic anhydride. Subsequent reactions of the organolithium reagent with the "triflone" product are, in some cases, detrimental to the production of high yields. In attempting to circumvent some of these problems, we turned to Grignard reagents which we felt would be less basic, kinetically, and less nucleophilic than the corresponding organolithium reagents. Surprisingly, the reaction of phenylmagnesium bromide with triflic anhydride (-78 to 0 °C) gave only about 7% phenyl trifluoromethyl sulfone. The major product (75%) was bromobenzene (eq 1). A similar reaction occurs with phenylmagnesium iodide, giving iodobenzene (69%). A formal oxidation of Grignard reagent by triflic anhydride had occurred. This reaction appears to be quite general.

$$\underset{1}{PhMgBr} + \underset{2}{(CF_3SO_2)_2O} \rightarrow \underset{3}{PhBr} \quad (1)$$

Table I. Reaction of Grignard Reagents with Triflic Anhydride

reacn no.	RMgX	% RX	% RSO_2CF_3
1	C_6H_5MgBr	75	7
2	C_6H_5MgI	69	*a*
3	*p*-$CH_3C_6H_4MgBr$	72	5
4	*p*-$CH_3OC_6H_4MgBr$[b]	75	14
5	*p*-$CH_3OC_6H_4MgBr$[c]	57	21
6	*p*-ClC_6H_4MgBr	81	*a*
7	*m*-$CF_3C_6H_4MgBr$	78	trace[d]
8	1-naphthyl-MgBr	75	*a*
9	$C_6H_5C{\equiv}CMgBr$	63	5
10	*n*-$C_8H_{17}MgBr$	69	24
11	cyclohexyl-MgBr	78	trace[d]
12	*n*-$C_8H_{17}MgCl$	5	87
13	*n*-C_4H_9MgCl	*e*	86
14	$C_6H_5CH_2MgCl$	13	87
15	$CH_2{=}CHCH_2MgCl$	*e*	54
16	cyclohexyl-MgCl	14	16

[a] None detected. [b] Grignard reagent forms a two-phase system. This reaction was carried out by using the lower phase which was 1.69 M in Grignard reagent. [c] This reaction was carried out by using the upper phase which was 0.35 M in Grignard reagent. [d] Detected by GC-MS (<2%). [e] Not analyzed for RX.

Table I gives yields of aryl bromides produced by reaction of the corresponding arylmagnesium bromides with triflic anhydride. The yields are all good. The presence of electron-donating or electron-withdrawing substituents on the aromatic ring does not appear to drastically alter the course of the reaction. One does begin to see larger amounts (up to 21%) of the sulfone in the case of *p*-methoxyphenylmagnesium bromide. The acetylenic Grignard reagent phenylethynylmagnesium bromide gives the same type of reaction as do the aliphatic reagents *n*-octylmagnesium bromide and cyclohexylmagnesium bromide.

It is quite apparent from Table I that the reaction of aryl- and alkylmagnesium bromides is not the method of choice for the production of trifluoromethyl sulfones. However, the reaction is of interest from a mechanistic standpoint. A mechanism is suggested in eq 2-5. It is

$$2RMgBr \rightleftharpoons MgBr_2 + R_2Mg \quad (2)$$

$$MgBr_2 + (CF_3SO_2)_2O \rightarrow CF_3SO_2Br + CF_3SO_3^- \quad (3)$$

$$CF_3SO_2Br + Br^- \rightarrow Br_2 + CF_3SO_2^- \quad (4)$$

$$R_2Mg + 2Br_2 \rightarrow 2RBr + MgBr_2 \quad (5)$$

proposed that the magnesium bromide, formed from the Grignard reagent via the Schlenk equilibrium,[6] initiates the oxidation-reduction process. Nucleophilic attack of bromide on triflic anhydride could produce trifluoromethanesulfonyl bromide and triflate ion according to eq 3. Further reaction of trifluoromethanesulfonyl bromide with bromide ion could give bromine and trifluoromethanesulfinate ion, the reduced product.[7] It is suggested that the aryl (alkyl) bromides arise from reaction

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(7) This mechanism for the formation of bromine has analogy. Potassium trifluoromethanesulfinate can be prepared by the reaction of CF_3SO_2Cl with potassium iodide in acetone. Elemental iodine is also formed. See ref 2, footnote 4.

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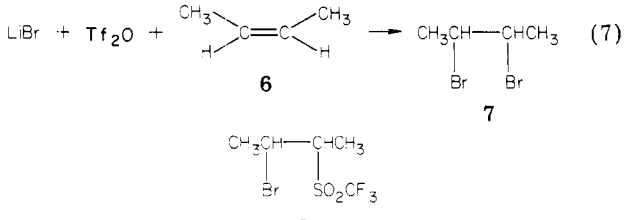
of elemental bromine with the organometallic reagent (either diaryl- or arylmagnesium bromide.)

The mechanism given above is suggested for the following reasons. Solutions of magnesium bromide in ether, prepared by reaction of ethylene dibromide with magnesium in ether, react with triflic anhydride at −78 °C to form a yellow orange solution which is an active brominating agent. Addition of the silyl enol ether derivative of acetophenone (**4**) to triflic anhydride–magnesium bromide

$$MgBr_2 + \underset{\mathbf{2}}{Tf_2O} + \underset{\mathbf{4}}{Me_3SiOC(Ph)=CH_2} \rightarrow \underset{\mathbf{5}}{PhC(O)CH_2Br} \quad (6)$$

mixtures at −78 °C gave phenacyl bromide (**5**) in 89 and 93% yields.[8] The silyl enol ether derivative of cyclohexanone, likewise, gave a 65% yield of α-bromocyclohexanone. The reaction of triflic anhydride with lithium bromide at −78 °C follows a similar course. The silyl enol ether **4** reacts with this mixture to also give a 93% yield of phenacyl bromide (**5**).

What is the nature of the electrophilic brominating agent? In principle trifluoromethanesulfonyl bromide could function as such a reagent. The bromine in this sulfonyl bromide should be quite electrophilic due to the potent electron-withdrawing CF_3SO_2 group. However, it is felt that elemental bromine (produced as in eq 4) is the true brominating agent due to the color developed at −78 °C when magnesium bromide or lithium bromide reacts with triflic anhydride. Additionally, the addition of *cis*-2-butene to a lithium bromide–triflic anhydride mixture at −78 °C or addition of lithium bromide to a mixture of excess triflic anhydride and *cis*-2-butene in ether gave only *dl*-2,3-dibromobutane (**7**) and none of the bromo sulfone



(7)

8. This argues in favor of bromine and against trifluoromethanesulfonyl bromide as the active brominating agent.

The reaction of *n*-octylmagnesium chloride with triflic anhydride follows a different course than that of the bromide. *n*-Octyl trifluoromethyl sulfone is formed in 87% yield. *n*-Butylmagnesium chloride and benzylmagnesium chloride also give good yields of the corresponding sulfones. Allylmagnesium chloride affords the allylic triflone in 54% yield. This route appears to be a good one for the formation of primary alkyl triflones. This is understandable in terms of the mechanism for halide formation given in eq 2–5. Reactions 3 and 4 are expected to proceed more slowly with chloride and hence the sulfone-producing reaction predominates. It was therefore hoped that the reaction of triflic anhydride with alkylmagnesium chlorides would be synthetically useful as a general method for triflone formation. This hope has not been realized. The secondary Grignard reagent cyclohexylmagnesium chloride gave a significant amount (14%) of cyclohexyl chloride on reaction with triflic anhydride and only a 16% yield of the secondary triflone based on triflic anhydride. This method was not further pursued as a source of more complex triflones.

(8) Solutions of magnesium bromide in ether, formed by reaction of ethylene dibromide with magnesium in ether, form a two-phase system. The upper phase was 0.16 M while the lower phase was 2.49 M. Yields given represent those obtained by using the upper and lower phases respectively.

Experimental Section

Reaction of Grignard Reagents with Triflic Anhydride. General Procedure. The Grignard reagents in Table I were prepared by standard procedures. Concentrations were generally approximately 1 M as determined by quenching an aliquot in water and titration. Reaction of *p*-methoxybromobenzene gave a two-phase system as did 1-bromonaphthalene. Concentrations of each phase were determined by the standard titrimetric procedure. Reaction 8 was carried out by using the bottom phase of the 1-naphthylmagnesium bromide solution which was 1.49 M. Phenylethynylmagnesium bromide (reaction 9) was prepared by refluxing ethylmagnesium bromide with 1.1 equiv of phenylacetylene. A solution of approximately 0.80 g of triflic anhydride in 4 mL of ether was cooled to −78 °C and 1.15 equiv of the appropriate Grignard reagent was added dropwise via syringe. The mixture was allowed to slowly warm to room temperature. Ammonium bromide solution was then added and the ether phase was separated. Samples of the halide products were isolated by preparative gas chromatography after determination of yields by gas chromatography with internal standards. The yields of halides given in Table I are GC yields except for reactions 1 and 9, which represent isolated yields. The yields of sulfones in reactions 12–15 represent isolated yields after distillation and crystallization in the case of benzyl trifluoromethyl sulfone (mp 99–100 °C) (reaction 14). The yields of sulfones in reactions 4, 5, and 10 represent GC yields while the yield in reaction 16 was determined by NMR. The yields of sulfones in reactions 1, 3, and 9 are estimated yields from GC without correction for detector response. The following preparation of *n*-butyl trifluoromethyl sulfone represents a typical procedure.

Reaction of *n*-Butylmagnesium Chloride with Triflic Anhydride. A solution of 0.79 g of triflic anhydride in 4 mL of ether was cooled to −78 °C and 3.15 mL of a 1.03 M solution of *n*-butylmagnesium chloride in ether was added dropwise by syringe. After the solution was slowly warmed to room temperature, ammonium bromide solution was added. After the ether phase was dried over Na_2SO_4, the solvent was removed by distillation through a Vigreux column. Distillation through a short-path condenser gave 0.46 g (86%) of *n*-butyl trifluoromethyl sulfone, bp 75 °C (20 mm).

Reaction of 1-Phenyl-1-(trimethylsiloxy)ethylene with Magnesium Bromide–Triflic Anhydride. A solution of magnesium bromide in ether was prepared by reacting 37.6 g of ethylene dibromide with 5.8 g of magnesium in 180 mL of ether. A two-phase mixture resulted. Evaporation of the ether from a 2-mL aliquot of the upper phase and titration with $AgNO_3$ indicate this phase is 0.16 M in $MgBr_2$. By a similar procedure, the bottom phase was determined to be 2.49 M in $MgBr_2$. A solution of 0.80 g of triflic anhydride in 2 mL of ether was cooled to −78 °C and 20 mL of the upper $MgBr_2$ phase was added dropwise via syringe. A 0.50-g sample of 1-phenyl-1-(trimethylsiloxy)ethylene (**4**)[9] was added and the mixture was slowly warmed to room temperature. Water was added and stirring was continued for 5 min. The product, α-bromoacetophenone (**5**), was identified by GC–MS comparison with an authentic sample. The yield was 0.46 g (89%) as determined by GC using *n*-dodecane as an internal standard. In a second run, using the lower magnesium bromide–ether phase, an analogous procedure gave a 93% yield of α-bromoacetophenone.

Reaction of 1-(Trimethylsiloxy)cyclohexene with Magnesium Bromide–Triflic Anhydride. The procedure was analogous to that described above. Addition of 0.50 g of 1-(trimethylsiloxy)cyclohexene[9] to a mixture of 0.87 g of triflic anhydride and 20 mL of 0.16 M $MgBr_2$ at −78 °C gave, after distillation, 0.34 g (65%) of α-bromocyclohexanone, which was identified by NMR spectral comparison with an authentic sample.

Reaction of 1-Phenyl-1-(trimethylsiloxy)ethylene with Lithium Bromide–Triflic Anhydride. A 1.167 M solution of

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LiBr in ether was prepared by reaction of ethylene dibromide with lithium in ether. Addition of 0.44 g of 4 to a mixture of 0.76 g of triflic anhydride and 5.0 mL of LiBr solution at −78 °C gave 0.43 g (95%) of α-bromoacetophenone as determined by GC vs. *n*-dodecane as an internal standard. In a second run, the yield was 92%.

Reaction of *cis*-2-Butene with Lithium Bromide–Triflic Anhydride. A solution of 0.78 g of triflic anhydride in 3 mL of ether was cooled to −78 °C and 4 mL of 1.167 M LiBr in ether was added. *cis*-2-Butene (0.5 g) was bubbled into the mixture, which was then slowly warmed to room temperature. A standard aqueous workup and distillation gave 0.36 g of *dl*-2,3-dibromobutane which was identified by NMR spectral comparison with an anthentic sample.

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Registry No. Bromophenylmagnesium, 100-58-3; iodophenylmagnesium, 16002-63-4; bromo-*p*-tolylmagnesium, 4294-57-9; bromo(*p*-methoxyphenyl)magnesium, 13139-86-1; bromo(*p*-chlorophenyl)magnesium, 873-77-8; bromo(α,α,α-trifluoro-*m*-tolyl)magnesium, 402-26-6; bromo-1-naphthylmagnesium, 703-55-9; bromo(phenylethynyl)magnesium, 6738-06-3; bromooctylmagnesium, 17049-49-9; bromocyclohexylmagnesium, 931-50-0; chlorooctylmagnesium, 38841-98-4; butylchloromagnesium, 693-04-9; benzylchloromagnesium, 6921-34-2; allylchloromagnesium, 2622-05-1; chlorocyclohexylmagnesium, 931-51-1; bromobenzene, 108-86-1; iodobenzene, 591-50-4; *p*-bromotoluene, 106-38-7; *p*-bromoanisole, 104-92-7; 1-bromo-4-chlorobenzene, 106-39-8; *m*-bromo-α,α,α-trifluorotoluene, 401-78-5; 1-bromonaphthalene, 90-11-9; (bromoethynyl)benzene, 932-87-6; 1-bromooctane, 111-83-1; bromocyclohexane, 108-85-0; 1-chlorooctane, 111-85-3; α-chlorotoluene, 100-44-7; chlorocyclohexane, 542-18-7; phenyl trifluoromethyl sulfone, 426-58-4; *p*-tolyl trifluoromethyl sulfone, 383-10-8; *p*-[(trifluoromethyl)sulfonyl]anisole, 15183-74-1; phenylethynyl trifluoromethyl sulfone, 52843-77-3; 1-octyl trifluoromethyl sulfone, 73587-47-0; 1-butyl trifluoromethyl sulfone, 52208-94-3; benzyl trifluoromethyl sulfone, 4855-02-1; allyl trifluoromethyl sulfone, 73587-48-1; cyclohexyl trifluoromethyl sulfone, 73587-49-2; triflic anhydride, 358-23-6.

Highly Stereoselective Hydrogenation of 3-Oxo-4-ene and -1,4-diene Steroids to 5β Compounds with Palladium Catalyst[1]

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The catalytic hydrogenation of 3-oxo-4-ene and -1,4-diene steroids is a convenient and widely employed route to 5β steroids.[2] Usually palladium catalysts are preferred for this purpose. The stereoselectivity to 5β, however, greatly depends on the reaction medium[2] and also on the functional groups in steroids.[2,3] The following media have been known to be effective for the favorable formation of 5β compounds: methanol or ethanol with potassium hydroxide,[2] pyridine,[4] and acetic acid with hydrobromic acid.[5] Among these media, pyridine appears to be the most useful in view of high stereoselectivity and lack of side reactions as well as its excellent property as a solvent for steroids.[6] With some steroids, however, stereoselectivity to 5β is not satisfactory even in pyridine. For example, in the hydrogenation of 11-oxoprogesterone in pyridine, Suvorov and Yaroslavtseva obtained the corresponding 5β ketone only in 17.4% yield, compared to 77.9% yield with progesterone.[4] Combe, Henbest, and Jackson also studied the effect of some nitrogen bases, but a solvent which is more stereoselective than pyridine has not been reported.[7]

In this study, various nitrogen bases have been surveyed in the hydrogenation of 3-oxo-4-ene and -1,4-diene steroids in order to find a more stereoselective solvent than pyridine and also to know the effects of the 1,2-unsaturation and the functional groups at C-11 and C-17 upon the stereochemistry of hydrogenation in basic media. Some 19-norsteroids have also been hydrogenated to see the effect of the angular methyl group at C-10. All hydrogenations were performed at room temperature and atmospheric pressure, using palladium black as the catalyst.

Table I shows the yields of saturated 5β ketones obtained with various nitrogen bases as solvents. It is seen that the most stereoselective is 4-methoxypyridine with which yields as high as 95–99.9% were obtained for most of the steroids hydrogenated. The effectiveness of 4-methoxypyridine is especially remarkable with the compounds **1e**, **1f**, and **2b**, where the yields of 5β ketones were rather low in the other solvents. The use of 4-methoxypyridine is also advantageous in that it is an excellent solvent for steroids and hydrogenation can be conducted in high concentration without loss in high stereoselectivity, as shown in preparative runs described in the Experimental Section.

4-Methoxypyridine (pK_a = 6.6) is a weaker base than 2,4,6-trimethylpyridine (pK_a = 7.4), 1-methylimidazole (pK_a = 7.06), and piperidine (pK_a = 11.1), although it is a stronger base than pyridine (pK_a = 5.2) and 4-methylpyridine (pK_a = 6.0). It is also noted that stereoselectivity is lower with triethylamine than with piperidine. These facts suggest that the nucleophilicity of nitrogen bases, rather than their pK_a's, is an important factor for the favorable formation of 5β compounds. The above results prompted us further to examine a substituted pyridine which is more basic than 4-methoxypyridine. Thus some steroids have been hydrogenated in the presence of 4-(dimethylamino)pyridine (pK_a = 9.7) which has been found to be a powerful catalyst for the acylation of hydroxyl groups.[8] The effect of 4-(dimethylamino)pyridine, however, is not so straightforward, as shown in Table II. Although stereoselectivity increased with **1e** and **1f** in pyridine and with **2b** in 4-methoxypyridine, it decreased in the cases of **1e** and **1f** in 4-methoxypyridine. Thus the effect of 4-(dimethylamino)pyridine is rather complex and further detailed studies are needed.

The effects of various substituents in steroids on the stereochemistry of hydrogenation in basic media appear

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(2) For reviews, see (a) H. J. E. Loewenthal, *Tetrahedron*, **6**, 269 (1959). (b) R. L. Augustine, "Organic Reactions in Steroid Chemistry," Vol. 1, J. Fried and J. A. Edwards, Eds., Van Nostrand Reinhold Company, New York, 1972, p 111. (c) R. L. Augustine, *Adv. Catal.*, **25**, 56 (1976).

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