methoxy phthalide isoquinoline (−)-cordrastine II[2] (**3c**). In contrast, boron tribromide under similar reaction conditions was not selective and cleaved **3a** to give mainly the corresponding tetraphenol.[2] This may be related to the stronger nucleophilic character of the bromide ion.

The above transformations demonstrate that boron trichloride can be used to selectively cleave a methylenedioxy group in methoxy-substituted aromatic compounds.

Experimental Section[8]

4,5-Dimethylcatechol (1b).—To 378 mg (2.5 mmol) of 4,5-methylenedioxy-*o*-xylene[4] (**1a**) dissolved in 70 ml of methylene chloride was added at room temperature 5 ml of a methylene chloride solution containing 585 mg (5 mmol) of boron trichloride. The solution was stored at ambient temperature for 3 hr; 5 ml of methanol was added and evaporated. The residue was crystallized from a mixture of benzene and petroleum ether to give 300 mg (80%) of **1b**, mp 89–91°, identical in mixture melting point and tlc with authentic 4,5-dimethylcatechol.[5] Under these reaction conditions 4,5-dimethoxy-*o*-xylene[5] (**1c**) was recovered unchanged.

6,7-Dimethoxy-1-(3,4-dihydroxybenzyl)isoquinoline Hydrochloride (2b HCl).—To a solution of 323 mg (1 mmol) of 6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline[6] (**2a**) in 15 ml of methylene chloride at 4° was added 7.1 ml of a methylene chloride solution containing 234 mg (2 mmol) of boron trichloride. The solution was stored at 4° for 5 hr; 5 ml of methanol was added and evaporated. The residue was dissolved in 30 ml of water and rendered neutral with saturated sodium bicarbonate; the resulting precipitate was collected and dissolved in ethanolic hydrogen chloride. The solution was evaporated and the residue crystallized from ethanol to give 275 mg (78%) of **2b** HCl, mp 232–233°, identical in mixture melting point, tlc, and nmr with authentic **2b** HCl.[7] Under these reaction conditions, papaverine (**2c**) was recovered unchanged.

(+)-1(*R*)-[6,7-Dimethoxy-3(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3b).—To a solution of 6 g (14.3 mmol) of (−)-β-hydrastine hydrochloride (**3a** HCl) in 350 ml of methylene chloride at room temperature was added a solution of 3.34 g (28.6 mmol) of boron trichloride in 50 ml of methylene chloride. The resulting turbid mixture was stirred at room temperature for 6 hr; 50 ml of methanol was added over 10 min and then evaporated. The residue was dissolved in 150 ml of 1 *N* hydrochloric acid, washed with chloroform, heated for 20 min at 95°, cooled, and then neutralized with saturated sodium bicarbonate. The resulting precipitate was collected, washed with water, dried, and crystallized from chloroform to give 4.3 g (81%) of **3b**: mp 199–200°; nmr δ 2.45 (s, 3, NCH_3), 1.90–3.20 (m, 4, CH_2CH_2), 3.83, 3.86 (2 s, 6, 2 OCH_3), 3.94 (d, 1, J = 4 Hz, CHN), 5.54 (d, 1, J = 4 Hz, CHO), 6.35, 7.23 (2 d, 2, J_{ortho} = 8 Hz, aromatic), 6.35, 6.45 (2 s, 2, aromatic); uv max 218 nm (ε 29,000) (infl), 235 (12,500) (infl), 293 (6400), 313 (4500); $[\alpha]^{25}D$ +218° (*c* 1, 1 *N* HCl); ORD (*c* 0.371, MeOH) $[\phi]_{600}$ +10°, $[\phi]_{589}$ +12°, $[\phi]_{331}$ −4250° (tr), $[\phi]_{315}$ 0, $[\phi]_{295}$ +6000° (tr), $[\phi]_{232}$ +40,000° (pk), $[\phi]_{227}$ 0, $[\phi]_{209}$ −232,000° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{360}$ 0, $[\theta]_{315}$ −8400, $[\theta]_{294}$ −5100, $[\theta]_{278}$ −6000, $[\theta]_{255}$ 0, $[\theta]_{220}$ +106,000, $[\theta]_{210}$ 0, $[\theta]_{204}$ −145,000.

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.43; H, 5.64; N, 3.77.

(−)-1(*R*)-[6,7-Dimethoxy-3(*S*)-phthalidyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(−)-Cordrastine II HBr] (3c HBr).—A mixture of 1 g (2.67 mmol) of **3b** in 20 ml of methanol was treated with an excess of diazomethane in ether; volatiles were removed at 40° in a stream of nitrogen; the residue was suspended in water, extracted with ethyl acetate and evaporated. The residue was dissolved in ethanolic hydrogen bromide, evaporated, and crystallized from ethanol to give 1.1 g (86%) of **3c** HBr, mp 212–213°, $[\alpha]^{25}D$ + 188° (*c* 1, MeOH), identical in mixture melting point, nmr, and optical rotation with (−)-cordrastine II hydrobromide previously described.[2]

Registry No.—**3b**, 35337-18-9; **3c** HBr, 34417-89-5; boron trichloride, 10294-34-5.

Acknowledgement.—We wish to thank the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, and Dr. V. Toome for the uv, ORD and CD spectra. We are grateful to Mr. J. Van Burik for his skillful technical assistance.

(8) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Nmr spectra were obtained in DMSO-d_6 on a Varian Ha-100 instrument. Uv spectra were measured in ethanol with a Cary recording spectrophotometer Model 14M and optical rotations with a Perkin–Elmer instrument. Rotatory dispersion curves were determined at 23° with a Durrum–Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Reported yields are of isolated products homogeneous to tlc.

Studies on the Reaction of Phenylmagnesium Bromide with Acetonitrile[1]

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Received February 15, 1972

Phenylmagnesium bromide is reported to react with acetonitrile to give poor yields of acetophenone except in cases where an excess of the latter reagent is employed.[3,4] It has been proposed that the acetonitrile molecule undergoes tautomerization and, in this form, can be thought of as a "pseudo-acid" which, when treated with the Grignard reagent, gives rise to considerable amounts of benzene.[5]

$$C_6H_5MgBr + CH_3C{\equiv}N \longrightarrow C_6H_6 + BrMgCH_2CN \rightleftharpoons CH_2{=}C{=}NMgBr$$

The idea of hydrogen abstraction by the Grignard reagent is supported by the fact that benzonitrile, which has no active hydrogen atom, generally gives good yields of ketone with the Grignard reagent. Propionitrile, which has a less labile hydrogen than acetonitrile, is reported to give a good yield of ketone.[6] Pivalonitrile and trifluoroacetonitrile also give excellent yields of *tert*-butyl phenyl ketone and α,α,α-trifluoroacetophenone, as are shown in Table I.

We became interested in a more detailed study of the reaction of acetonitrile with the Grignard reagent since the low yield of acetophenone suggests that a much greater "active" hydrogen effect is present than when propionitrile is used.

The first attempts were directed toward establishing the true source of benzene produced in the reaction of acetonitrile and phenylmagnesium bromide. The technique of isotopic labeling was used for this purpose. Trideuterioacetonitrile was substituted for acetonitrile, and mass spectrographic analysis of the benzene produced in the reaction with phenylmagnesium bromide

(1) This work was partially supported by a grant from the Committee on Institutional Studies and Research, Murray State University, Murray, Kentucky.

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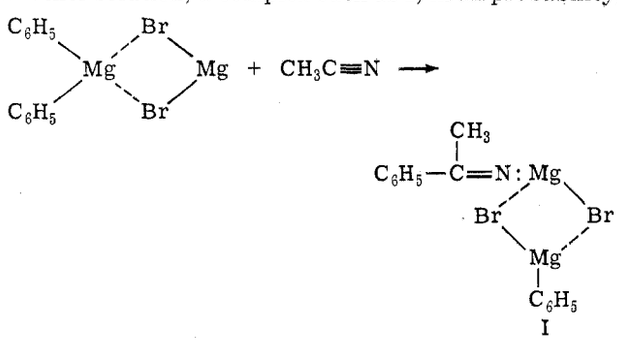
TABLE I
KETONES PREPARED FROM REACTION OF GRIGNARD REAGENT WITH NITRILES

Nitrile	Grignard reagent	Ketone	% yield[a]	Reported yield[b]
Acetonitrile	Phenylmagnesium bromide	Acetophenone	42 (68)[c]	37–45 (70)[d]
Acetonitrile	3,5-Dibromophenylmagnesium bromide	3,5-Dibromoacetophenone	1 (52)[e]	
Acetonitrile	*n*-Pentylmagnesium bromide	2-Heptanone	44[c]	14
Acetonitrile	Benzylmagnesium chloride	Methylbenzyl ketone	34[c]	16
Acetonitrile	*n*-Octylmagnesium bromide	2-Decanone	49[c]	
Propionitrile	Phenylmagnesium bromide	Propiophenone	94	80–91
Pivalonitrile	Phenylmagnesium bromide	Pivalophenone	90	72
Trifluoroacetonitrile	Phenylmagnesium bromide	α,α,α-Trifluoroacetophenone	82	
Trideuterioacetonitrile	Phenylmagnesium bromide	α,α,α-Trideuterioacetophenone	65	

[a] Yield based on product isolated. Diethyl ether used as solvent except where noted. [b] M. S. Karasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, New York, N. Y., 1954, p 793. [c] Benzene used as solvent. [d] Higher yield of 70% obtained when Grignard reagent used in large excess. [e] Benzene used as solvent and trimethyl orthoacetate used instead of acetonitrile.

showed 46.8% monodeuteriobenzene. This indicated that 53.2% benzene was being derived from a source other than the "active" hydrogen atoms of acetonitrile. A significant isotope effect was observed because an increase in ketone yield from 42% to 65% was found.

If one assumes that the Grignard reagent is dimeric in ether solution, a complex such as I, in all probability,



would be formed. Hydrolysis of I should also be a source of benzene. In the first hydrolysis experiment, deuterium oxide was added to react with unreacted Grignard reagent in the complex, followed by addition of hydrochloric acid to complete the hydrolysis. Analysis of the benzene produced gave only 2.4% monodeuteriobenzene. This observation was attributed to the fact that I is ether insoluble and forms a "ball-shaped" conglomerate, allowing only the outer surface to come in contact with the D_2O.

In order that unreacted phenylmagnesium bromide in I be permitted to react completely with a labeled compound such as D_2O, complete hydrolysis would be essential. For this purpose, deuterium chloride in deuterium oxide was used as a means for hydrolysis of I. Mass spectrometric analysis of the benzene fraction gave 51.8% monodeuteriobenzene.

It is of interest to note that a change in solvent from ether to benzene gives an increase in yield from 42% to ~70% acetophenone.

Experimental Section[7]

General Procedure for Synthesis of Ketones.—The appropriate Grignard reagent was prepared from reaction of the halide (0.1 mol) with magnesium (0.1 g-atom) in anhydrous diethyl ether (100 ml). Precautions were taken to exclude moisture from the reaction flasks. In some cases, benzene was added dropwise to the freshly prepared Grignard reagent, and the ether removed by distillation prior to addition of the nitrile. The nitrile (0.1 mol) was added dropwise over a period of approximately 15 min. Most of the reactions are quite exothermic. After continuous stirring and refluxing for 2 hr, the mixture was hydrolyzed with hydrochloric acid and ice. Extraction with ether or benzene, followed by vacuum distillation, gave the ketone.

Labeling Experiments.—Substitution of trideuterioacetonitrile for acetonitrile yielded benzene (25 g, 32%) containing 46.8% monodeuteriobenzene. Mass spectrometric analysis of the resulting ketone showed no deuterium atoms in the $C_6H_5CO^+$ and $C_6H_5^+$ ions, but that the labeling is limited to the methyl group. Overall, 80.5% of the methyl hydrogens are deuterium atoms, which is very close to the theoretical, 83%.

Benzene (26 g, 33%) obtained as a product from reaction of acetonitrile and phenylmagnesium bromide followed by attempted hydrolysis with D_2O showed only 2.4% labeling. Benzene (25 g, 32%) obtained from the same reactants, but followed by hydrolysis with 20% DCl in D_2O, showed 51.8% labeling.

Registry No.—Phenylmagnesium bromide, 100-58-3; acetonitrile, 75-05-8; acetophenone, 98-86-2; 3,5-dibromoacetophenone, 14401-73-1; 2-heptanone, 110-43-0; methyl benzyl ketone, 103-79-7; 2-decanone, 693-54-9; propiophenone, 93-55-0; pivalophenone, 938-16-9; α,α,α-trifluoroacetophenone, 434-45-7; α,α,α-trideuterioacetophenone, 17537-31-4.

Acknowledgment.—The authors are grateful to Dr. Seymour Meyerson, Research and Development, American Oil Company, Whiting, Indiana, for assistance in the procurement and interpretation of mass spectral data on the labeled compounds.

(7) Isotopic compositions of the benzene and acetophenone samples obtained from the labeling reactions were measured at reduced ionizing voltage and 70 eV, respectively, on a Consolidated 21-102/103c mass spectrometer. All deuterium labeled compounds were obtained from Diaprep, Inc., Atlanta, Georgia, and had 99.5% minimum isotopic purities.

2*H*-1,2,3-Triazoles from the Ethyl Nitrocinnamates[1]

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Received April 18, 1972

The facile synthesis of 2*H*-1,2,3-triazoles by the addition of azide ion to activated acetylenes (eq 1) is not

(1) Abstracted from the Ph.D. thesis of Y. T., 1972.