The Reaction of Ethylmagnesium Bromide with Acetophenones and Trifluoroacetophenones

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It has been repeatedly[2] observed that carbonyl compounds carrying fluorinated alkyl groups undergo considerable reduction in reactions with Grignard reagents containing β-hydrogen atoms. The mechanism for both addition and reduction was reasoned[3] to resemble that proposed by Whitmore[4] for the Grignard reaction of nonfluorinated carbonyl compounds: 2,2,2-trifluoracetophenone underwent asymmetric reduction with an optically active organometallic; therefore, coordinative complexing took place in the transition state between the carbonyl compound and the organometallic. The earlier observation[2c] that fluorinated carbonyl compounds did not form measurable complexes with magnesium bromide etherate, and hence with the more weakly Lewis acidic Grignard reagents, was rationalized[3] by assuming a very low complex concentration but fast transfer of the organic radical in case of addition, or of hydrogen in case of reduction.

Both electronic and steric effects exerted by the carbonyl substituents may be held responsible when reduction occurs. An indication thereof was obtained on comparison of the calculated effective diameters of the substituents on selected aldehydes with the reduction to addition ratios obtained after reaction with ethylmagnesium halide.[4]

This note deals with the reaction between ethylmagnesium bromide and selected phenyl ketones carrying trifluoromethyl adjacent to the carbonyl group or on the aromatic ring. The information concerning the behavior of fluorinated aryl ketones toward the organometallic is scant. Moreover, the placing of the trifluoromethyl substituent on the *m* and *p* position of the ring was reasoned to shed some light on the relative importance of electronic and steric effects in this type of reaction. Electron withdrawal by fluorine is known to be transmitted to some extent by vinylogy, both in aliphatic[5] and in aromatic[6] systems. Hence, if electron withdrawal indeed governs the reduction to addition ratio to a major extent, it should be demonstrated by the occurrence of some reduction of the trifluoromethylphenyl ketones.

The ketones I and VIII were prepared and subjected to reaction with excess ethylmagnesium bromide in the cold. The products were analyzed by vapor phase chromatography (see Table I). For the purpose of v.p.c. analysis, all possible tertiary (addition) and secondary (reduction) alcohols were synthesized independently by standard procedures. Yields and physical properties of products are listed in Table II.

Table I

Reaction of Fluorinated Phenyl Ketones with Ethylmagnesium Bromide

	Ketones	Yield, %	Products, %	
			Addition	Reduction
I	$C_6H_5COCH_3$[a]	93	100	0
II	*m*-$CH_3C_6H_4COCH_3$	90	100	0
III	*p*-$CH_3C_6H_4COCH_3$	95	100	0
IV	$C_6H_5COCF_3$	97[b]	19	81
V	*m*-$CH_3C_6H_4COCF_3$	96[c]	11	89
VI	*p*-$CH_3C_6H_4COCF_3$	94[d]	13	87
VII	*m*-$CF_3C_6H_4COCH_3$	90	100	0
VIII	*p*-$CF_3C_6H_4COCH_3$	94	100	0

[a] A. N. Nesmeyanov and V. A. Sazonova, *Bull. Acad. sci. USSR, class sci. chim.*, 499 (1941) [*Chem. Abstr.*, **37**, 2723 (1943)] report obtaining the addition product. [b] Mixture b.p. 110–112° (54 mm.), $n^{20}{}_D$ 1.4585. [c] Mixture b.p. 96.5–98° (15 mm.), $n^{20}{}_D$ 1.4644. [d] Mixture b.p. 102–103° (5 mm.), $n^{20}{}_D$ 1.4650.

The ketones I, II, and III were investigated for comparison with their fluorinated analogs; the absence of reduction was not surprising.

The amount of reduction product obtained from IV (81%) was high when compared with that from trifluoroacetone (14%)[2c] and was not easily explained by a much larger steric requirement of the phenyl group when compared with the methyl group. Moreover, although the noticeable increase in reduction undergone by V, when compared with IV, may be attributed to steric hindrance exerted by the *m*-methyl substituent, a similar rationalization seems difficult in the case of VI, with methyl in the *p*-position. This suggested that the addition to reduction ratio was subject to an electronic effect exerted by the methyl substituent and transmitted through the ring.

The isolation of only addition products between ethylmagnesium bromide and VII or VIII demonstrated the inability of trifluoromethyl to effect reduction by conjugative electron withdrawal. Hence, if electron withdrawal by fluorine affects the course of the Grignard reaction with carbonyl compounds, then it must be so only when the fluorinated substituent is placed adjacent to the carbonyl group.

Experimental[7]

Starting Materials.—Trifluoroacetic acid, *m*- and *p*-trifluoromethylbenzoic acid, acetophenone, and *p*-methylacetophenone, commercial materials, were distilled or recrystallized before use; *m*- and *p*-trifluoromethylbenzoyl chloride were prepared according to Corse, *et al.*,[8] and Burger and Hornbaker,[9] respectively. 2,2,2-Trifluoroacetophenone, the new compound *m*-methyl-2,2,2-trifluoroacetophenone, and *p*-methyl-2,2,2-trifluoroacetophenone were prepared by treating the appropriate Grignard reagents with trifluoroacetic acid according to Levine and Dishard.[10] *m*-Methylacetophenone, *m*-trifluoromethylacetophenone, and *p*-

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[1] Based in part on the thesis submitted by S. Resconich to the Graduate School of Purdue University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] (a) K. N. Campbell, J. D. Knobloch, and B. K. Campbell, *J. Am. Chem. Soc.*, **72**, 4380 (1950); (b) E. T. McBee, O. R. Pierce, and J. F. Higgins, *ibid.*, **74**, 1736 (1952); (c) E. T. McBee, O. R. Pierce, and D. D. Meyers, *ibid.*, **77**, 83 (1955); (d) R. N. Haszeldine, *J. Chem. Soc.*, 1748 (1953).

[3] H. S. Mosher, S. E. Stevenot, and D. O. Kimble, *J. Am. Chem. Soc.*, **78**, 4374 (1956).

[4] (a) F. C. Whitmore and R. S. George, 103rd National Meeting of the American Chemical Society, Atlantic City, N. J., April, 1941, as quoted by H. S. Mosher and E. Combe, *J. Am. Chem. Soc.*, **72**, 3994 (1950); (b) C. G. Swain and H. B. Boyles, *ibid.*, **73**, 870 (1951).

[5] A. L. Henne and C. J. Fox, *ibid.*, **73**, 2323 (1951).

[6] J. D. Roberts, R. L. Webb, and E. A. McElhill, *ibid.*, **72**, 408 (1950).

[7] All temperatures are uncorrected. Analyses were performed by Dr. C. S. Yeh, Purdue University. The infrared spectra were determined by Miss M. Haley and Mrs. W. Dilling, Purdue University, for pure liquids as capillary films on a Perkin-Elmer Model 21 spectrophotometer.

[8] J. W. Corse, R. G. Jones, Q. F. Sopers, C. W. Whitehead, and O. K. Behrens, *J. Am. Chem Soc.*, **70**, 2837 (1948).

[9] A. Burger and E. D. Hornbaker, *J. Org. Chem.*, **18**, 194 (1953).

[10] R. Levine and K. T. Dishard, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

TABLE II

YIELDS AND PHYSICAL PROPERTIES OF PRODUCTS

Compound	Yield, %	B.p. (mm.), °C.	n^{20}D	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
$C_6H_5COCF_3$[a]	50	151–152	1.4583				
m-$CH_3C_6H_4COCH_3$[b]	42	100–101 (15)	1.5296				
m-$CH_3C_6H_4COCF_3$	51	79 (24)	1.4576	57.45	57.75	3.72	3.89
p-$CH_3C_6H_4COCF_3$[c]	28	57 (5)	1.4661				
m-$CF_3C_6H_4COCH_3$[d]	66	85 (10)	1.4621				
p-$CF_3C_6H_4COCH_3$[e]	52	79–80 (8)	1.4604	57.45	57.17	3.72	3.78
m-$CH_3C_6H_4CHOHCH_3$[f]	79	104–105 (12)	1.5235				
p-$CH_3C_6H_4CHOHCH_3$[g]	84	108 (14)	1.5212				
$C_6H_5CHOHCF_3$[h,i]	93	87–88 (16)	1.4610	48.65	48.38	2.43	2.59
m-$CH_3C_6H_4CHOHCF_3$[j]	53	98 (14)	1.4641	56.84	56.81	4.74	4.81
p-$CH_3C_6H_4CHOHCF_3$[k]	84	102 (15)	1.4629	56.84	56.91	4.74	4.74
m-$CF_3C_6H_4CHOHCH_3$[l]	89	105–107 (19)	1.4585				
p-$CF_3C_6H_4CHOHCH_3$	80	106–107 (18)	1.4585	56.84	56.73	4.74	4.92
m-$CH_3C_6H_4C(CH_3)OHC_2H_5$	79	103–104 (8)	1.5189	80.48	80.80	9.76	9.87
p-$CH_3C_6H_4(CH_3)OHC_2H_5$[m]	82	109–110 (10)	1.5179				
$C_6H_5C(CF_3)OHC_2H_5$	70	91–92 (15)	1.4671	58.82	59.02	5.39	5.15
m-$CH_3C_6H_4C(CF_3)OHC_2H_5$	80	101 (13)	1.4710	60.55	60.80	5.96	6.20
p-$CH_3C_6H_4(CF_3)OHC_2H_5$	73	105–106 (15)	1.4714	60.55	60.55	5.96	6.11
m-$CF_3C_6H_4C(CH_3)OHC_2H_5$[n]	96	107 (16)	1.4629	60.55	60.29	5.96	5.95
p-$CF_3C_6H_4C(CH_3)OHC_2H_5$[o]	90	113–114 (18)	1.4632				

[a] Levine and Dishart[10] report b.p. 150–152°. [b] K. Y. Auwers, *Ann.*, **408,** 243 (1951), reports b.p. 109° (12 mm.), n^{20}D 1.5306. [c] J. H. Simmons, W. T. Black, R. F. Clark [*J. Am. Chem. Soc.*, **75,** 5621 (1953)] report b.p. 179.2°, n^{25}D 1.4664. [d] W. J. Humphlett, M. J. Weiss, and C. R. Hauser [*ibid.*, **70,** 4020 (1948)] report b.p. 198–200°. [e] W. T. Caldwell and G. C. Schweiker [*ibid.*, **75,** 5884 (1953)] report b.p. 81–84° (9 mm.). [f] K. v. Auwers and H. Kolligs [*Ber.*, **55,** 40 (1922)] report b.p. 108–109° (12 mm.), n^{15}D 1.5226. [g] A. Klages and R. Keil [*ibid.*, **36,** 1635 (1903)] report b.p. 120° (19 mm.). [h] E. T. McBee, O. R. Pierce, and J. F. Higgins [*J. Am. Chem. Soc.*, **74,** 1736 (1952)] report b.p. 64–65 (5 mm.), n^{20}D 1.4610. [i] Calcd. for 3,5-dinitrobenzoate, m.p. 119–120°: C, 48.65; H, 2.43; N, 7.57. Found: C, 48.38; H, 2.59; N, 7.78. [j] Calcd.: F, 30.00. Found: F, 29.72. [k] Calcd.: F, 30.00. Found. F, 29.89. [l] C. S. Marvel, C. G. Overberger, R. E. Allen, and J. F. Saunders [*J. Am. Chem. Soc.*, **68,** 736 (1946)] report b.p. 100–102° (17 mm.), n^{20}D 1.4585. [m] H. Rupe and J. Burgin [*Ber.*, **44,** 1219 (1911)] report b.p. 108.5–109° (10 mm.). [n] Calcd.: F, 26.15. Found: F, 26.40. [o] Calcd. for 3,5-dinitrobenzoate, m.p. 92–93°: C, 52.43; H, 3.64. Found: C, 52.44, H, 3.45.

trifluoromethylacetophenone were prepared by reaction of the appropriate acid chlorides with ethoxymagnesiomalonic ester according to Bowman.[11] Though known, with the one exception, most ketones were prepared by different procedures from those reported; their physical properties are included in Table II.

General Procedure for Reaction of Phenyl Ketone with Ethylmagnesium Bromide.—The Grignard reagent was prepared in the usual fashion from ethyl bromide (21.8 g., 0.2 mole) and sublimed magnesium turnings (6.8 g., 0.2 g.-atom) in 100 ml. of anhydrous ether. The solution was filtered under a nitrogen pressure into a dry reaction flask. The ketone (0.1 mole) was dissolved in 20 ml. of ether and added dropwise over a 1-hr. period at 0°. The solution was stirred for 6 hr. while warming to room temperature. Hydrolysis was effected with 100 ml. of saturated ammonium chloride. The organic layer was separated, dried over anhydrous sodium sulfate, and the ether distilled. The residue was subjected to v.p.c. analysis and vacuum distilled to give the products. The v.p.c. analysis was carried out on a Perkin-Elmer Model 154-B fractometer in conjunction with a Leeds and Northrup Speedomaz type G recorder. Helium was used as the carrier gas maintained at 18 lb./in.^{2} at a flow rate of 42 ml. per min. at a temperature of 179°, using a Carbowax 1500 column. Components were identified by comparison with the retention times of authentic samples. Areas under the peaks were measured with a polar planimeter.

General Procedure for Independent Preparation of the Secondary Alcohols.—The ketone (0.116 mole) was added dropwise to a solution of lithium aluminum hydride (1.52 g., 0.04 mole) in 100 ml. of anhydrous ether. The solution was stirred and the addition regulated to produce gentle reflux. Ten minutes after the addition was completed, water was added slowly and the reaction mixture poured onto 100 g. of ice in 400 ml. of 10% sulfuric acid. The organic layer was separated and the aqueous layer extracted with six 20-ml. portions of ether, whereupon the combined ether solution was dried over anhydrous potassium carbonate and distilled to give the products.

General Procedure for Independent Preparation of the Tertiary Alcohols.—A solution of the aryl Grignard was prepared from the aryl halide (0.2 mole) and sublimed magnesium turnings (0.2 g.-atom) in 150 ml. of anhydrous ether. The remaining procedure was identical with that described previously for the general Grignard reaction, using 2-butanone or 1,1,1-trifluoro-2-butanone (0.1 mole), depending on the alcohol desired. The products were distilled.

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The Preparation of 6-Trifluoromethylisatin

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The 4-, 5-, and 7-trifluoromethylisatins have been prepared[1] by the cyclization in acid of α,α,α-trifluoro-2-oximinoacetotoluidides (Sandmeyer isatin synthesis[2,3]). The 6-trifluoromethylisatin (I), a valuable intermediate for the preparation of 7-trifluoromethylquinoline derivatives, has not been described to date. The Sandmeyer method yields none of the 6-isomer,[1,4,5] and other acid-catalyzed intramolecular cyclizations of N-

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[2] T. Sandmeyer, *Helv. Chim. Acta*, **2,** 234 (1919).

[3] Reviewed briefly by P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 207–210.

[4] B. R. Baker, R. E. Schaub, J. P. Joseph, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, **17,** 164 (1952).

[5] P. W. Sadler, *ibid.*, **21,** 169 (1956).