[CONTRIBUTION FROM THE STANFORD UNIVERSITY DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING]

Asymmetric Reductions. IV. The Action of the Grignard Reagent from (+)-2-Methylbutyl Chloride on 2,2,2-Trifluoroacetophenone

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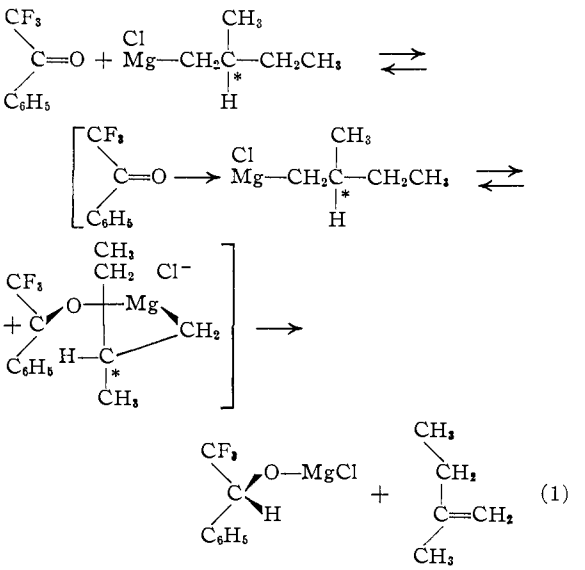
2,2,2-Trifluoroacetophenone has been treated with the optically active Grignard reagent from (+)-2-methylbutyl chloride. The only product isolated was the corresponding reduction product, 2,2,2-trifluoro-1-phenylethanol (81–91% yield). This product showed a high optical rotation (α_D +7.22 to +7.85 neat). This result makes it appear highly probable that the same mechanism prevails for the Grignard reduction reaction of either fluorinated or non-fluorinated carbonyl compounds.

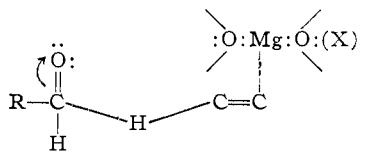
We have studied the extent of asymmetric reduction of various ketones by the optically active Grignard reagent from (+)-2-methylbutyl chloride.[2-6] By extending these studies to certain fluorinated carbonyl compounds, it should be possible to obtain information concerning the relative importance of the steric factors *versus* the electronic effects in determining the course of this asymmetric Grignard reduction reaction. Since the action of optically active Grignard reagents on the alkyl phenyl ketone series[5,7,8] has been studied more extensively than any other, we chose trifluoromethyl phenyl ketone, 2,2,2-trifluoroacetophenone, for the initial investigation. The high inductive effect of the fluorine atom and the tendency for fluorinated compounds to give high yields of reduction products in the Grignard reaction are well known and have been the subject of several investigations.[9-11]

The mechanism of the Grignard reduction reaction has been reviewed recently.[12] The preponderance of evidence, including the recent deuterium studies by Dunn and Warkentin,[13] supports the mechanism first proposed by Whitmore[14] involving the initial formation of a complex between the carbonyl compound and the Grignard reagent followed by a shift of the hydrogen with its pair of electrons from the β-carbon atom, this transfer of a "hydride ion" being accomplished by means of a six-membered ring transition state. This is illustrated in the following equation with the optically active (+)-2-methylbutylmagnesium chloride and 2,2,2-trifluoroacetophenone.



(1)

The recent study by McBee, Pierce and Meyer,[11] which showed that fluorinated compounds do not measurably complex with magnesium bromide, and presumably therefore do not complex with Grignard reagents to any appreciable extent, would appear to cast doubt on the above mechanism as applied to fluorinated carbonyl compounds. These authors state: "the cyclic mechanism of Whitmore does not apply to the reducing reactions of Grignard reagents on perfluoro compounds, therefore, unless there are very small amounts of unstable complexes formed which were not detected by the experimental conditions used." An alternate mechanism was offered for consideration involving the intermolecular transfer of the hydrogen with its electron pair from the Grignard reagent (or from the $RMgX_2^-$ ion) to the carbonyl carbon atom.



It was also stated that, "It is conceivable that the magnesium halide portion of the Grignard reagent could approach the carbonyl oxygen during this process and then the formation of the alkoxide salt would be a further aid to reaction. This, however, would impose a rigid orientation on the transition state of the reaction."

One test of the mechanism of the Grignard reducing reaction when applied to fluorinated carbonyl compounds would be to obtain a measure of the rigid orientation of the transition state by deter-

(1) Taken in part from the thesis of Joseph Stevenot presented to Stanford University in partial fulfillment for the M.S. degree, 1955.

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(3) H. S. Mosher and E. La Combe, *ibid.*, **72**, 4991 (1950).

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(12) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall Inc., New York, N. Y., 1954, p. 154–158.

(13) G. E. Dunn and J. Warkentin, *Canadian J. Chem.*, **34**, 75 (1956).

(14) F. C. Whitmore, paper presented before the Atlantic City Meeting of the ACS, April, 1943.

mining the stereospecificity of the reduction reaction when the optically active Grignard reagent from (+)-2-methylbutyl chloride was used. Equation 1 illustrates the reaction in question.

2,2,2-Trifluoroacetophenone has now been treated with this optically active Grignard reagent. The only product isolated was 2,2,2-trifluoro-1-phenylethanol, the reduction product. In each of four runs the product showed high optical activity ($\alpha^{25}D$ about +7.5° neat). The stereospecificity of this reaction strongly suggests that there is no difference in kind between the mechanism of the Grignard reduction reaction of fluorinated and non-fluorinated carbonyl compounds. In light of these results and the excellent evidence that magnesium bromide does not complex measurably[11] with fluorinated carbonyl compounds, it appears that a small amount of an unstable complex, formed between the fluorinated carbonyl compound and the Grignard reagent, can react *via* the cyclic mechanism rapidly to give the observed reaction products. As noted by McBee, Pierce and Meyer, it would not be necessary that a measurable amount of complex be present at any one time. This view has also been expressed recently by Dunn and Warkentin.[13] Also as noted by the former authors, the high inductive effect of the fluorine atoms would increase the positive character of the carbonyl carbon atom, thereby facilitating the transfer of the "hydride ion." The suggestion of an *intermolecular* transfer of hydrogen in such a manner that there is an orientation of the magnesium toward the carbonyl oxygen becomes indistinguishable from the formation of an unstable complex.

It is quite possible that an *intermolecular* reaction could still be stereospecific. One is inclined to attribute a greater steric requirement to the *intramolecular* (or intracomplex) reaction than to its intermolecular counterpart. In addition, the effect of temperature on the proportion of isomers in the intermolecular reaction should be much greater than in the intramolecular case. The rather slight effect of a 100° temperature difference on the extent of asymmetric reduction of methyl *t*-butyl ketone by the Grignard reagent from (+)-2-methylbutyl chloride[2] can be taken as evidence in favor of the intercomplex mechanism. A completely satisfactory answer to this question probably can be obtained only by extensive kinetic studies. Until such studies have been made, the existing evidence seems best interpreted in terms of the intercomplex transfer of the β-hydrogen through a six-membered transition state.

The extensive amount of reduction observed with perfluorinated carbonyl compounds has generally been attributed to some unique inductive effect of the fluorine atoms on the carbonyl carbon. The argument has been that since a fluorine atom is only a little larger than a hydrogen atom, a trifluoromethyl group is about the same size as a methyl group. Therefore the high yield of reduction products cannot be attributed to steric factors as has commonly been done for the non-fluorinated carbonyl compounds.[10] Although the fluorine atom is only slightly larger than the hydrogen atom, the steric effect of the trifluoromethyl group can hardly be neglected. It is seen from the calculated effective diameters[15] of the various groups in the following table that the trifluoromethyl group is significantly larger than the methyl group and not far from half way between the size of the methyl and *t*-butyl groups. This table also gives the yields of addition *versus* reduction by the action of ethylmagnesium bromide on a series of comparable aldehydes.

TABLE I

ADDITION *Versus* REDUCTION BY ETHYLMAGNESIUM BROMIDE ON RCHO

R 15	$-CH_3$	$-CF_3$[a]	$-CCl_3$[b]	$-C(CH_3)_3$[c]
Effective diameter of R, Å.	4.0	5.1	6.3	6.2
% Addition	100	60	10–15	68
% Reduction	0	20	50–60	14

[a] Reference 10. [b] Reference 12, p. 245. [c] See Experimental.

These experiments from various sources were not carried out under comparable conditions. On the basis of calculated radical diameters, the amount of reduction of the *t*-butyl member of this series should be nearer to that of the trichloromethyl analog. On the other hand, these results are also clearly inconsistent with any prediction based solely on the high inductive effect of fluorine since replacement by chlorine, with its lower inductive effect, results in higher per cent. reduction. More data of a strictly comparable nature are needed. At present neither steric effects nor inductive effects alone can be used to explain the results satisfactorily.

The original purpose of this study was to compare the per cent. asymmetric reduction of 2,2,2-trifluoroacetophenone with other alkyl phenyl ketones[5] in order to arrive at a better understanding of the steric and electronic effects operating in the asymmetric reduction reaction. This comparison required that the rotation and relative configuration of the pure optical isomer of 2,2,2-trifluoro-1-phenylethanol be known. So far, attempts at the resolution of this secondary alcohol have been completely unsuccessful. Upon treatment of the acid phthalate of 2,2,2-trifluoro-1-phenylethanol with brucine, splitting of the ester resulted with the formation of brucine phthalate and the original carbinol. To obviate the treatment with a base such as brucine, attempts were made to prepare the *d*-tartranilate[16] and the 1-methoxyacetate.[17] The former could not be made and the latter would not crystallize. Accordingly this broader aspect of the problem must await a complete resolution of the 2,2,2-trifluoro-1-phenylethanol.

Experimental

2,2,2-Trifluoroacetophenone was prepared initially by the Friedel–Crafts reaction of trifluoroacetyl chloride on ben-

(15) These are calculated as the maximum diameter of the rotating group using the tetrahedral angle and the following values. Van der Waal radii: H, 1.01; F, 1.35; Cl, 1.55 Å. Bond distances: C–H, 1.10; C–F, 1.36; C–Cl, 1.76; C–C, 1.54 Å. See G. Briegleb, *Fortsch. Chem. Forsch.*, 1, 642 (1950).

(16) F. Barrow and R. G. Atkinson, *J. Chem. Soc.*, 639 (1937).

(17) A. W. Ingersoll, in "Organic Reactions," John Wiley and Sons, N. Y., Vol. II, p. 381, 1944.

TABLE II

Run		Ketone, moles	Yield, %	α_D (neat)	$n^{20}D$	B.p., °C.	Press., mm.
1	Normal addn.	0.056	96	+7.59 (23°)	1.4568	52	2
2	Normal addn.	.095	..	+7.68 (26°)	1.4575	128	760
3	Normal addn.	.17	86	+7.85 (27.8°)	1.4575	125–127	760
4	Reverse addn.	.06	81	+7.22 (26°)	1.4568	74–78	10

zene[18,19] but the yields were erratic, the best being 31%. The action of phenyl Grignard on trifluoroacetonitrile[20] gave the desired ketone in good yield and was a much more satisfactory method.

The Grignard Reaction.—(+)-2-Methylbutyl chloride, 10.5 g. (0.10 mole), $n^{20}D$ 1.14130, $\alpha^{24}D$ +1.44, was converted to the Grignard reagent with 2.4 g. of magnesium in 110 ml. of anhydrous ether under a nitrogen atmosphere in a rigorously dried apparatus in the usual manner. The reaction mixture was allowed to settle and transferred under a nitrogen atmosphere with filtration through a glass wool plug to a second reaction flask. 2,2,2-Trifluoroacetophenone, 10.1 g. (0.056 mole), b.p. 152°, $n^{20}D$ 1.4580, mixed with 35 ml. of ether, was added with stirring over a two-hour period to the Grignard solution. After stirring 20 hours, the mixture was hydrolyzed by an ice-cold ammonium chloride solution. The ether layer and ether extracts were dried over anhydrous magnesium sulfate, the ether removed through a short column, and the residue distilled *in vacuo* to give 9.81 g. (0.055 mole), 96% yield, b.p. 52° (2 mm.), $n^{20}D$ 1.4568, $\alpha^{23}D$ +7.59 (neat). The infrared spectrum showed no absorption at 5.84 μ characteristic of the carbonyl bond of the starting ketone. A sample of this product from a previous reaction, b.p. 128°, $n^{20}D$ 1.4595, $\alpha^{20}D$ +7.68, was submitted for analysis.

Anal. Calcd. for $C_8H_7F_3O$: C, 54.55; H, 4.00. Found: C, 54.47; H, 4.21.

The results from four such experiments are summarized in Table II.

***dl*-2,2,2-Trifluoro-1-phenylethanol.**—2,2,2-Trifluoroacetophenone, 70 g. (0.40 mole), was reduced in 100 ml. of ethanol in the presence of about 7 g. of W-2 Raney nickel catalyst with 3 atmospheres pressure of hydrogen. Hydrogen absorption was complete in 18 hours. Distillation gave 66.9 g. (94% yield), b.p. 52–54° (2 mm.), $n^{20}D$ 1.4570. The infrared spectrum showed no absorption at 5.84 μ characteristic of the starting ketone and was identical to that of the analyzed product prepared above.

Acid Phthalate of 2,2,2-Trifluoro-1-phenylethanol.—*dl*-2,2,2-Trifluoro-1-phenylethanol, 88 g. (0.50 mole), was added to a mixture of sublimed phthalic anhydride, 82 g. (0.55 mole) in 47.4 g. of anhydrous pyridine and the mixture heated on the steam-bath for six hours. Chloroform, 750 ml., was added and the solution cooled to 0° and extracted with two 200-ml. portions of ice-cold 10% hydrochloric acid. Crystals of the acid phthalate separated on standing; 65 g., m.p. 137–138°. The melting point was unchanged on recrystallization from chloroform. An additional 35 g. of product (64% yield) was obtained on working up the mother liquors.

Anal. Calcd. for $C_{16}H_{11}O_4F_3$: C, 59.26; H, 3.42. Found: C, 59.20; H, 3.72.

Hydrolysis of the uncrystallizable oil from the mother liquors yielded 7.4 g. (8.5%) of recovered 2,2,2-trifluoro-1-phenylethanol.

The acid phthalate of *dl*-2,2,2-trifluoro-1-phenylethanol, 5.0 g. (0.154 mole) and brucine alkaloid, 7.2 g. (0.154 mole as the tetrahydrate) were dissolved in warm acetone to give a clear solution which was immediately cooled. Crystals slowly deposited on standing at 0°. The rate of crystal formation was much faster at room temperature. After one week 8.58 g. (98% yield) of brucine phthalate, m.p. 215–216° (capillary), 198–199° (Kofler hot stage), $[\alpha]^{21}D$ +11.7 ± 0.2° ($CHCl_3$, *c* 10), +11.2 ± 0.2° ($CHCl_3$, *c* 5); +9.5 ± 0.5 ($CHCl_3$, *c* 2), was obtained. The melting point and rotation were identical to that from an authentic sample of brucine phthalate[21] prepared from brucine and phthalic acid, m.p. 215–216° (capillary), 198–199° (Kofler hot stage).

Anal. Calcd. for $C_{31}H_{32}N_2O_8$: C, 66.41; H, 5.75. Found: C, 66.33; H, 5.70.

From the mother liquors were recovered by vacuum distillation 1.60 g. (59% yield) of *dl*-2,2,2-trifluoro-1-phenylethanol, b.p. 54° (2 mm.), identified by infrared spectrum.

Several attempts to make the tartranilate[16] gave only the starting materials. The *l*-menthoxy acetate was prepared in the usual manner[17] but all attempts to obtain crystals were unsuccessful.

Reaction of Ethyl Grignard with Trimethylacetaldehyde.—Trimethylacetaldehyde, 15 g. (0.174 mole), was added with stirring and cooling to an ethyl Grignard solution, 85 ml., 2.18 *N* (0.18 mole). After stirring for six hours the mixture was hydrolyzed and the ether removed under a column. Liquid–gas partition chromatographic analysis of this residue, 18.4 g., gave the following composition: ethyl-*t*-butylcarbinol, 13.9 g., 68.5% yield; neopentyl alcohol, 2.2 g., 14.4% yield; trimethylacetaldehyde, 1.2 g., 8.0% recovery; ethanol, 0.4 g., 4.8% yield based on the ethyl Grignard taken; ether 0.6 g.

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(20) E. T. McBee, O. R. Pierce and O. D. Meyer, *ibid.*, **77**, 917 (1955).

(21) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 60 (1911), reported brucine phthalate m.p. 216°, $[\alpha]D$ +13.5° (*c* 5, CHCl). Because of the discrepancy in rotation (and in melting point when taken on the Kofler hot stage) our authentic sample was analyzed.