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An Investigation of Abnormal Products in the Reaction of Benzyl and 2-Thenyl Grignard Reagents with ^{14}C -Carbon Dioxide (I)

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An investigation of the abnormal products formed in the carbonation of benzyl and 2-thenyl Grignard reagents has been carried out. Using the reverse isotope dilution technique, it has been shown that neither *ortho*- nor *para*-toluic acids are formed in measurable amounts during the reaction of benzylmagnesium bromide with carbon dioxide. 2-Thenylmagnesium chloride reacts to produce acids, about 64% of which is the normal product, 2-thienylacetic acid, 30% the *ortho*-abnormal product, 2-methyl-3-thenoic acid, and probably a small amount (1.0 - 1.5%) is the *para*-abnormal product, 5-methyl-2-thenoic acid.

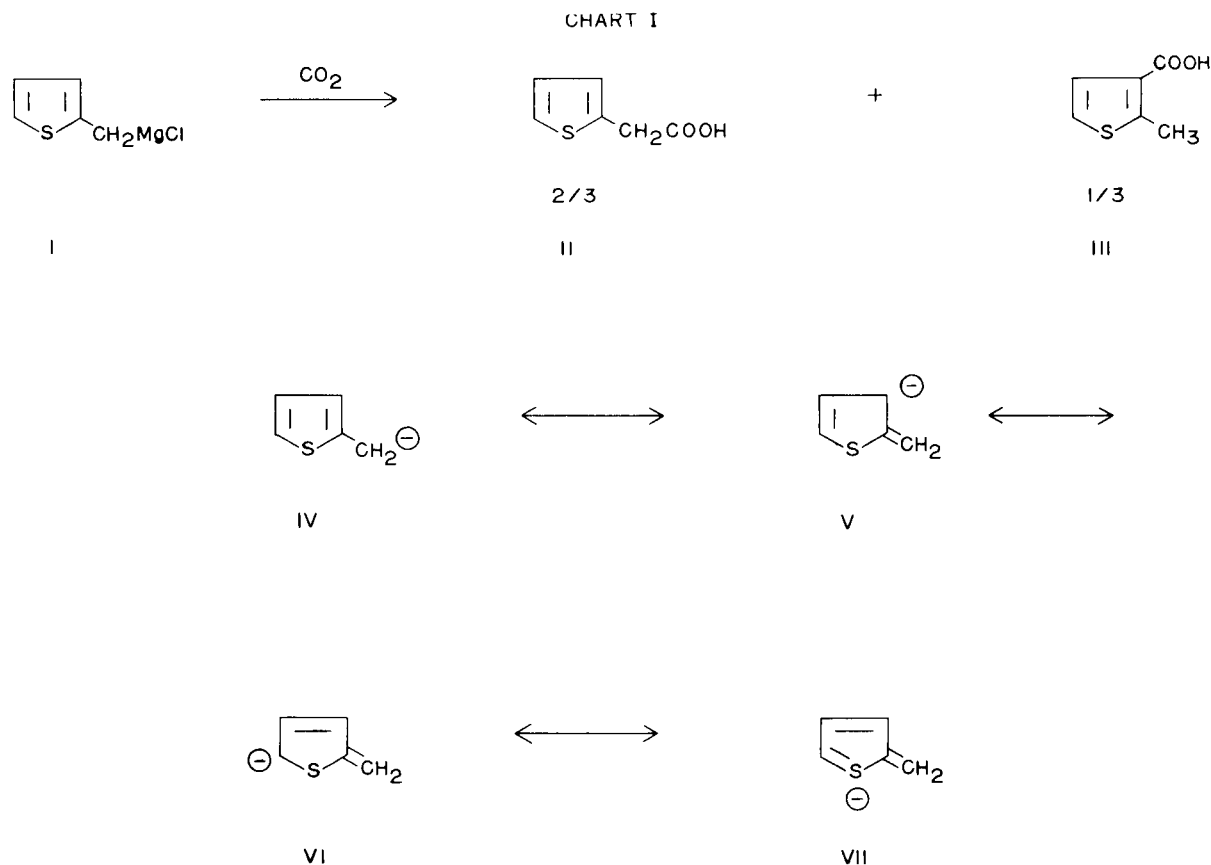
The formation of abnormal products in the reaction of benzyl-type Grignard reagents has frequently been observed. For example, the reaction of benzylmagnesium chloride with formaldehyde leads to *o*-methylbenzyl alcohol as the principal product, rather than β -phenylethanol (3). The abnormal product is usually *ortho*-substituted, although in at least two instances (4, 5) *para* products have been obtained in small yields with reagents other than carbon dioxide. Austin and Johnson (4) studied the reaction of benzylmagnesium chloride with a variety of reagents, and found that abnormal products were formed with formaldehyde, ethylene oxide, and ethyl chloro-carbonate, but not with carbon dioxide, simple ketones, or esters (other than formic esters). Gilman and Kirby (6) noted that no abnormal products were obtained from the reaction of carbon dioxide with α - and β -naphthylmethylmagnesium chloride, an observation which has been confirmed by Lawesson (7). On the other hand, Moser and Sause (8) obtained "abnormal" *ortho* product on carbonation of *m*-methylbenzylmagnesium bromide.

Abnormal products have frequently been observed in the reaction of carbon dioxide with certain hetero-methyl Grignard reagents. Campaigne and Le Suer (9) attributed the formation of 3-methyl-2-thenoic acid in the reaction of carbon dioxide with 3-thenylmagnesium bromide to the availability of the highly reactive 2-position *ortho* to the methylmagnesium group. Sherman and Amstutz (10) found that carbonation of 3-furylmethylmagnesium chloride produced a mixture of acids consisting of 90% 3-methyl-2-furoic acid and 10% 3-furylacetic acid. Abnormal *ortho* products have been found (11, 12) in the carbonation of 2-thenylmagnesium chloride, 2-benzothienylmethylmagnesium chloride and 3-benzothienylmethylmagnesium chloride. Gaertner (11) isolated 15% of 2-methyl-3-thenoic acid and 29% of 2-thienylacetic acid from the crude acids obtained on carbonation of 2-thenylmagnesium chloride. He concluded that these were the only acid products, and that they were formed in a ratio of two parts of 2-thienyl

acetic acid to one part of 2-methyl-3-thenoic acid. Quantitative estimates of abnormal and normal products were based on fractional crystallization of pure isomers from crude products (11), a method which could introduce some errors due to solubility differences. Also, small amounts of other products might be lost. The isotope dilution technique is particularly well suited to analyses of this type, since accurate quantitative determinations of pure substances in crude mixtures can be made. We have therefore reinvestigated the reaction of benzylmagnesium halide with carbon dioxide, using carbon-14 as a tracer, to determine if any *ortho*- or *para*-carbonation takes place. Carbonation studies on 2-thenyl system, to verify the accuracy of the previous analysis (11) have also been performed.

RESULTS AND DISCUSSION

By use of a modified cyclic reactor (13), benzylmagnesium bromide was prepared in 99% yield, and the solution was standardized. This solution was carbonated with ^{14}C -carbon dioxide, and the crude acids were isolated. An aliquot was purified. Radioactivity assay of the purified phenylacetic- ^{14}C acid provided a base level of radioactivity for the dilution experiments. To aliquots were then added known weights of non-radioactive *o*-toluic and *p*-toluic acids, and these were then reisolated. The molar radioactivities of these samples indicated that less than 0.01% of *ortho*- or *para*-toluic acids were present. 2-Thenyl chloride was prepared by chloromethylation of thiophene, and then converted to 2-thenylmagnesium chloride in the cyclic reactor. It was necessary to use care in this preparation, since it was found that the Grignard reagent was somewhat unstable. The preparation was carried out at high dilution under an atmosphere of helium. This Grignard reagent in solution was carbonated with excess carbon- ^{14}C dioxide, and from an aliquot of product 2-thienylacetic- ^{14}C acid was isolated and then assayed for radioactivity (30.1 mc./mole).



Aliquot samples of the crude acid mixture were diluted with pure samples of 2-thienylacetic acid, 2-methyl-3-thenoic acid and 5-methyl-2-thenoic acid. These acids were recrystallized, assayed, and the yield of each isomeric acid was calculated. The results of two experiments are presented in Table I.

TABLE I

Percent of Isomeric Acids in Carbonation of
2-Thienylmagnesium Chloride

	Experiment	
	I (d)	II (d)
2-thienylacetic acid	65.9 (a)	68.6 (b)
2-methyl-3-thenoic acid	32.3 (a)	30.1 (b)
5-methyl-2-thenoic acid	1.8 (c)	1.3 (c)

(a) Radioactivity assayed after three recrystallizations. (b) Assayed after six recrystallizations. (c) Corrected for "carry-over" of radioactive 2-methyl-3-thenoic acid. (d) Adjusted to 100%. The combined yields were 93.6% (I) and 94.6% (II). The remaining substance was a radioactive resin.

In view of the small amount of 5-methyl-2-thenoic acid obtained, and the importance of this finding, *i.e.*, a "*para* product" in reaction with carbon dioxide, it was necessary to determine whether the

radioactivity ascribed to this compound was really due to the formation of 5-methyl-2-thenoic acid in the reaction, or to radioactive contamination with some other product. Therefore, a sample of radioactive 2-methyl-3-thenoic acid was mixed with pure 5-methyl-2-thenoic acid, and the latter acid was reisolated by the procedure employed in the dilution experiment. The results indicate that, even though a small amount of 2-methyl-3-thenoic acid is carried along in the recrystallization of 5-methyl-2-thenoic acid, this amount is much less than the quantity of 5-methyl-2-thenoic acid actually found. It is thus probable that from 1.0 to 1.5% of *para* product was produced during the carbonation of 2-thienylmagnesium chloride.

These experiments confirm the work of Gaertner (11), showing that his predicted ratio of two parts of normal product to one part of "abnormal" product on carbonation of 2-thienyl Grignard was remarkably accurate. Gaertner (11) observed no carbonation in the 5-position, and interpreted his results as confirming the Johnson (14) cyclic mechanism. Since evidence for carbonation in the 5-position of 2-thienylmagnesium chloride has now been presented, to the extent that such carbonation occurs, a second mechanism must be considered.

The suggestion by Campaigne and Le Suer (9) that "abnormal" carbonation will occur more extensively in a position which preferentially undergoes electrophilic attack, implicit in the work of Moser and Sause (8), was confirmed by the observations of

Gaertner (12) in the benzothiophene series, where "abnormal" carbonation in the 3-position exceeded that in the 2-position. Similar observations have been made in the 3-thenyl series (13), where "abnormal" carbonation is the favored reaction over "normal" product by a factor of 3 to 2. These observations indicate that when a position *ortho* or *para* to the methylene group in an arylmethyl Grignard reagent has an enhanced reactivity to electrophilic attack, attack of a carbonyl reagent will occur to a greater extent at that position.

The cyclic mechanism satisfactorily accounts for the predominance of *ortho* products in most examples. The concept of a resonating carbanion (IV, V, VI, VII) seems a reasonable explanation for the small amount of *para* product occasionally encountered. For example, in the 2-thenyl series, the much greater contribution of VI over V (due to resonance VI \leftrightarrow VII) (15) can account for some reaction at this position, even though the cyclic mechanism strongly favors reactions with V (16).

EXPERIMENTAL (17)

Benzylmagnesium Bromide.

A standard solution of benzylmagnesium bromide was prepared by allowing 26.3 g. of benzyl bromide (0.154 mole) in 100 ml. of dry ether to drop slowly through the magnesium-packed column of the modified cyclic reactor (13) for six hr., while 200 ml. of dry ether in the boiling flask was refluxed through the column at about 15 ml./hr. In this way 325 ml. of water-white 0.47 molar solution (99% by titration) of benzylmagnesium bromide was obtained. This solution was stored in a glass-stoppered flask for later use. It was shown to be perfectly stable on storage, since 71 days later a sample proved to be 0.48 molar on titration (the slight increase due to small loss of solvent by evaporation).

Carbonation of Benzylmagnesium Bromide.

Using a vacuum-line technique, 1.2 g. of $\text{Ba}^{14}\text{CO}_3$ (equivalent to 264 mg. $^{14}\text{CO}_2$) was decomposed with perchloric acid, and frozen down in a flask containing 10 ml. of frozen 0.47 M benzyl Grignard solution. The mixture was then melted and stirred for ten minutes. After decomposing with 10% phosphoric acid, the mixture was extracted exhaustively with ether, and the ether solution then extracted in turn with 5% sodium carbonate solution. Neutralizing the basic extract produced 285 mg. (45%) of crude acids. The base-extracted ether solution contained 185 mg. of neutral radioactive oil which gave a positive test for ketones. A standard solution of the crude acids was prepared by dissolving the total yield in *n*-heptane in a 25 ml. volumetric flask.

The activity of the sample was determined by isolating a sample of ^{14}C -phenylacetic acid. Concentration of 10 ml. of the standard heptane solution, and two recrystallizations from heptane gave 79 mg. of phenylacetic acid, m.p. 79-80°, radioactivity 21.33 ± 0.02 mc./mole (18).

Analysis of Benzyl Carbonation Product for Toluic Acids.

Six ml. of the standard heptane solution, containing 68.4 mg. of crude acid was evaporated to dryness in a centrifuge tube. To this was added 137.8 mg. of pure *o*-toluic acid, m.p. 105-106°, and the mixture recrystallized from 10 ml. of 10% acetic acid, and then four times from water. After drying *in vacuo* and sublimation, the recovered acid melted at 104-105°, and assayed at $1.7 \pm 0.3 \times 10^{-3}$ mc./mole. This is equivalent to approximately 0.01 mg. of radioactive *o*-toluic acid (0.014%) in the crude sample.

Another 6-ml. aliquot of the crude acid solution was diluted with 100.9 mg. of pure *p*-toluic acid (m.p. 183.0-184.0°) and recrystallized as above, m.p. 182.0-183.0°, radioactivity, $1.36 \pm 0.02 \times 10^{-3}$ mc./mole. This is equivalent to approximately 0.005 mg. of radioactive *p*-toluic acid (0.008%) produced in the carbonation of the benzyl Grignard.

Determination of Contamination of Recrystallized *o*-Toluic Acid with Radioactive Phenylacetic Acid.

A mixture of 19.5 mg. of $\text{C}_6\text{H}_5\text{CH}_2^{14}\text{CO}_2\text{H}$ (radioactivity, 21.3 mc./mole) and 128.5 mg. of *o*-toluic acid was homogenized by solution in 5% sodium hydroxide, reprecipitated with phosphoric acid, and recrystallized three times from water, m.p. 102-103°, assay, $3.4 \pm 0.2 \times 10^{-3}$ mc./mole. This is equivalent to 0.02 mg. of apparent radioactive *o*-toluic acid in the original sample.

2-Thenylmagnesium Chloride.

Ether was refluxed through the magnesium-packed column of the modified cyclic reactor at the rate of 20 ml./hr., and a slow stream of dry helium was introduced over the refluxing ether and allowed to escape through a bubble trap attached to the top of the reflux condenser. Then a solution of 9.3 g. (0.07 mole) of freshly prepared 2-thenyl chloride (19) in sufficient ether to make 100 ml. was added dropwise over a four and one-half hr. period. The final volume of colorless ether solution in the boiling flask was approximately 200 ml., which titrated at 0.324 M (93%). This solution deteriorated on standing, since after four days it was only 0.278 M, and after fifteen days the concentration of titratable Grignard was reduced to 0.202 M.

Carbonation of 2-Thenylmagnesium Chloride.

This carbonation was carried out in a vacuum line using the technique described for carbonation of the benzyl Grignard, except that the Grignard reagent was added to excess solid radioactive carbon dioxide in this case. After freezing 10.6 mmoles of $^{14}\text{CO}_2$, 25 ml. (8.1 mmoles) of standard Grignard was added. The crude acids obtained from this preparation weighed 831 mg. (72.3%). This material was dissolved in tetrahydrofuran and diluted to 25 ml. in a volumetric flask, giving a standard solution containing 33.25 mg./ml. Ten ml. of this solution was concentrated and taken up in hot 10% acetic acid, treated with activated charcoal to remove a trace of sticky yellow oil (radioactive!), the charcoal centrifuged and the clear supernatant transferred to a clean centrifuge tube and cooled to produce pale yellow needles. Two more recrystallizations from hot water, followed by drying and sublimation, produced soft white crystals of 2-methyl-3-thenoic acid melting at 112-114° (20), radioactivity = 30.11 ± 0.03 mc./mole.

Analysis of the Crude Carbonation Product for 2-Thienylacetic Acid.

Samples of non-radioactive 2-thienylacetic acid and 2-methyl-3-thenoic acid were obtained by treating a large preparation of 2-thienylmagnesium chloride from the cyclic reactor with dry ice, and fractionally crystallizing the isomers as described by Gaertner (11). A 1-ml. aliquot of the solution of the crude, radioactive, carbonation product, whose preparation was described in the preceding section, and 299.5 mg. of pure 2-thienylacetic acid, m.p. 61-62°, was homogenized in ether solution and evaporated to dryness. The sample was then recrystallized three times from *n*-heptane, each time the supersaturated solution being triturated to prevent oiling. After the first crystallization, the stirring rod was not cleaned between crystallizations, and crystallization then occurred much more rapidly during trituration (seeding). This sample, m.p. 60-61° after sublimation, assayed at 1.928 ± 0.002 mc./mole. The calculation, $\frac{299.5 \times 1.93}{30.11 - 1.93} = 20.5$ mg., indicates 61.7% of radioactive 2-thienylacetic acid in the original sample.

Analysis of the Crude Carbonation Mixture for Methylthenoic Acids.

Two aliquots of 1 ml. each of the solution of crude carbonation products were evaporated to dryness in centrifuge tubes. To one was added 288.9 mg. of pure 2-methyl-3-thenoic acid, m.p. 116-117°, and to the second was added 153.0 mg. of pure 5-methyl-2-thenoic acid, m.p. 138.0-138.5° (21). Both samples were homogenized in base, reprecipitated with dilute sulfuric acid, centrifuged and recrystallized twice from 10 ml. of 10% acetic acid, once from water, filtered on sintered glass funnels and dried *in vacuo*. After sublimation, sample one melted at 112-114°, and assayed at 1.011 ± 0.001 mc./mole, which indicates the presence of 10.0 mg. of radioactive 2-methyl-3-thenoic acid (30.1%) in the original sample. Sample two melted at 133-134° after sublimation, and assayed at 0.242 ± 0.003 mc./mole, equivalent to 1.24 mg. (3.7%) of 5-methyl-2-thenoic acid in the original sample.

The Second Carbonation Experiment.

After four days, the 2-thenyl Grignard prepared above was retitrated as 0.278 M. A sample of 25 ml. was carbonated in the vacuum-line apparatus, as described for the benzyl Grignard, and worked up to yield 552 mg. (56%) of crude acids, which assayed at 25.86 ± 0.01 mc./mole, based on isolation of a sample of 2-methyl-3-thenoic acid. The initial crude sample was again contaminated with radioactive base-soluble resinous oil which was insoluble in water or hexane, but was soluble in ether or tetrahydrofuran. This is probably an open-chain polymeric acid formed by decomposition of the thiophene ring.

Three aliquots of 1 ml. each (22.1 mg. crude acids) were diluted with pure acids, and then recrystallized six times before assaying.

The results are as follows:

Sample one, 178.9 mg. of 2-methyl-3-thenoic acid added, assay 0.881 ± 0.002 mc./mole, equivalent to 6.3 mg. (28.5%) of radioactive 2-methyl-3-thenoic acid in the original sample.

Sample two, 156.7 mg. of 5-methyl-2-thenoic acid added, assay 0.0555 ± 0.0007 mc./mole, equivalent to 0.33 mg. (1.5%) of 5-methyl-2-thenoic acid in the original sample.

Sample three, 247.1 mg. of 2-thienylacetic acid added, assay 1.424 ± 0.006 mc./mole, equivalent to 14.33 mg. (64.9%) of 2-thienylacetic acid in the original sample.

Determination of Contamination of 5-Methyl-2-thenoic Acid by Radioactive 2-Methyl-3-thenoic Acid.

A mixture of 13.7 mg. of radioactive 2-methyl-3-thenoic acid (30.11 mc./mole, isolated in the first carbonation experiment) and 196.8 mg. of non-radioactive 5-methyl-2-thenoic acid was homogenized in base and recrystallized twice from 10% acetic acid, once from water, dried and sublimed. It melted at $132-133^\circ$ and assayed, 0.139 ± 0.003 mc./mole. This is equivalent to 0.91 mg. (6.7%) of the radioactivity carried over.

The sample was recrystallized twice more from 10% acetic acid and once again from water. After drying it melted at $135-136^\circ$, and assayed at 0.0237 ± 0.0032 mc./mole. This is equivalent to 0.153 mg. (1.1%) of the original radioactive 2-methyl-3-thenoic acid.

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