THE REACTION OF THE METHYLBENZYLMAGNESIUM HALIDES WITH CARBON DIOXIDE

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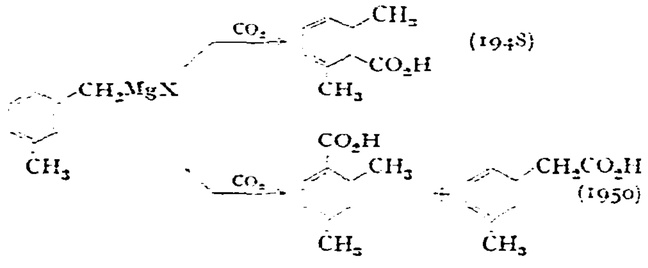
Several authors have reported that carbonation of benzylmagnesium chloride produces only the normal product, phenylacetic acid[1-3] in yields varying from 40-60%. Literature reports concerning the carbonation of the methylbenzylmagnesium halides, however, have been conflicting.

Mousseron and Du first reported[4] that carbonation of *o*-methylbenzylmagnesium bromide gave only *o*-tolylacetic acid[*]. They also reported[4] that carbonation of *p*-methylbenzylmagnesium bromide gave predominantly the normal product, *p*-tolylacetic acid along with 10% of an abnormal product, 2,5-dimethylbenzoic acid. The most intriguing aspect of this work[4] was the report that carbonation of *m*-methylbenzylmagnesium bromide produced *only* the abnormal product, 2,6-dimethylbenzoic acid. No yields were reported for any of these reactions and the products were apparently characterized only by their melting points.

In 1950 it was reported[5] that the structural assignment of Mousseron and Du[4] for the abnormal carbonation product of *m*-methylbenzylmagnesium bromide was in error, and, that the abnormal product actually obtained from this reaction was rather 2,4-dimethylbenzoic acid in addition to an undisclosed amount of the expected normal product, namely *m*-tolylacetic acid.



From the available data, it thus appeared that, only when a methyl group was situated *ortho*, could normal carbonation products be expected as the sole product from the methylbenzylmagnesium halides. Conclusions of this sort have found their way into standard reference texts[6].

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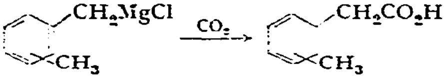
[*] We have corroborated this finding. When we carbonated *o*-methylbenzylmagnesium bromide (the *o*-methylbenzyl bromide was prepared from *o*-xylene and NBS), a 46% yield of crude *o*-tolylacetic acid was obtained melting at 87-8°. The literature[12] m.p. of the pure acid is 88°. Conversion of the crude acid to its methyl ester with diazomethane followed by analysis (v.p.c.) showed the complete absence of any "abnormal" acids.

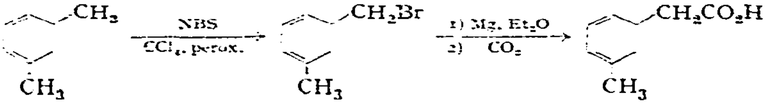
Upon a reinvestigation of these reactions, we have found that the abnormal carbonation products reported previously were very likely the result of impurities in the starting methylbenzyl halides. The Grignard reagents prepared from pure samples of the methylbenzyl halides were found to form only the "normal" acids upon carbonation.

EXPERIMENTAL RESULTS

It was found, that when the three isomeric methylbenzyl chlorides were prepared from the corresponding xylene through the use of sulfuryl chloride and peroxide, only the expected methyl substituted phenylacetic acids were obtained by carbonation of their respective Grignard reagents.



Two methods were employed in the synthesis of *m*-methylbenzyl bromide, since it was the Grignard reagent derived from this compound which reportedly gave an abnormal product upon carbonation. In method I, *m*-xylene was treated with N-bromosuccinimide and peroxide in a solvent of carbon tetrachloride. Analysis of the methylbenzyl bromide obtained from this reaction by vapor phase chromatography showed that it was almost exclusively *m*-methylbenzyl bromide uncontaminated with ring substitution products:



Carbonation of the Grignard reagent prepared from this pure sample of halide produced *m*-tolylacetic acid as the only acid product. To establish the latter point conclusively, a sample of the crude acid was converted to its methyl ester with diazomethane. This ester, when analyzed by vapor phase chromatography, was shown to be methyl *m*-tolylacetate exclusively.

In order to test the validity of the analytical method employed, a synthetic mixture of *m*-tolylacetic acid, 2,4-dimethylbenzoic acid and 2,6-dimethylbenzoic acid was prepared. This was esterified with diazomethane and the methyl esters analyzed by v.p.c. The results for each isomer were accurate to ± 0.1 %.

A second method (Method II) was devised to prepare *m*-methylbenzyl bromide which, it was hoped, would approximate the procedure used by the earlier workers*. In this method, *m*-xylene was heated with bromine in the absence of solvent and in the presence of artificial light source. Analysis (v.p.c.) of the "*m*-methylbenzyl

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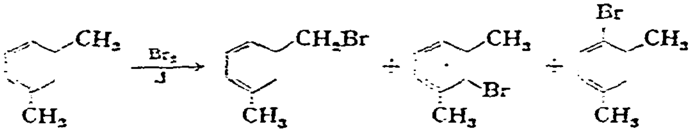
* Mousseron and Du[4] do not indicate how they prepared their *m*-methylbenzyl bromide, nor do they record any physical constants for this starting material. It seems likely that they resorted to some type of photochemical bromination of *m*-xylene as described very sketchily by Schramm[7]. Moser and Sause[5] state that they used the method of Schramm except for substituting a tungsten light source for sunlight.

bromide" produced by this method showed that it was badly contaminated with 4-bromo-*m*-xylene as well as with smaller amounts of 2-bromo-*m*-xylene*.



It was not surprising to find that a Grignard reagent prepared from such a mixture gave "abnormal" products in addition to the expected *m*-tolylacetic acid. Depending upon the isolation techniques used, one could conceivably isolate *either* the 2,6- or 2,4-dimethylbenzoic acid. This might explain the discrepancy between the findings in refs.** 4 and 5.

Likewise we have found, that when *p*-methylbenzyl bromide is prepared from *p*-xylene and N-bromosuccinimide, the resulting halide (after purification by crystallization) is essentially free of any 2-bromo-*p*-xylene. Grignard formation from halide prepared by this method, followed by carbonation, produced only *p*-tolylacetic acid and no "abnormal" 2,5-dimethylbenzoic acid as was originally claimed[4] ***.

CONCLUSIONS

It now becomes apparent that carbonation of the benzyl and methylbenzyl Grignard reagents produces only the normal acids *provided* the starting halides are pure.

While the immediate result of the present work is simply to offer an explanation for the anomalies formerly associated with the carbonation products of the methylbenzyl Grignard reagents, it should also serve as a caution for the blind acceptance of other so-called "anomalous products" of benzyl-type Grignard reagents. While many of these products are undoubtedly valid and may well arise through some type of cyclic mechanism[10], one might do well to consider the purity of the starting halides as an undetermined variable in many of the examples cited.

EXPERIMENTAL

Methylbenzyl chlorides

All three isomeric methylbenzyl chlorides were prepared by the method described by Kharasch and Brown[11]. The preparation of *m*-methylbenzyl chloride can be considered typical of the method.

m-Methylbenzyl chloride. To a 500 ml flask was added a mixture of *m*-xylene (212 g, 2.0 mole), sulfuryl chloride (94.5 g, 0.7 mole) and 0.48 g benzoyl peroxide. The

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* The refractive index of the "*m*-methylbenzyl bromide" prepared by this method was n_D^{27} = 1.5595. The refractive index (n_D^{27}) of the *m*-methylbenzyl bromide prepared from NBS (Method I) was 1.5632. The *m*-methylbenzyl bromide used in ref. 5 (n_D^{27}) was 1.5547. The refractive index listed for 4-bromo-*m*-xylene (corrected to 27°) is 1.5453. (See ref. 8).

** It might also be noted that *chlorination* of the side chain of *m*-xylene with chlorine gas and sunlight is accompanied by the formation of at least 10% 4-chloro-*m*-xylene even under the most favorable conditions[9].

*** Since no mention was made in ref. 4 as to how the *p*-methylbenzyl bromide was made which gave 10% "abnormal" acid upon carbonation of the Grignard reagent, we were obviously not able to attempt a duplication of their preparation.

mixture was refluxed until evolution of gases ceased. It was then distilled to give 53 g (50 %) *m*-methylbenzyl chloride boiling 96–8°/30 mm. The literature[11] b.p. is 101–2°/30 mm.

Preparation of authentic samples of o-, m- and p-tolylacetic acids

All three of these acids were prepared by similar methods involving the metalation of the corresponding xylene with *n*-amylsodium followed by carbonation. The preparation of *o*-tolylacetic acid described below is typical.

o-Tolylacetic acid. *n*-Amylsodium was prepared by the addition of *n*-amyl chloride (21.3 g, 0.2 mole) in 30 ml dry *o*-xylene to a sodium dispersion (13.8 g, 0.6 g-atom) covered by 225 ml *o*-xylene in a 500 ml Morton flask at —10° with high speed stirring. A dry nitrogen atmosphere was maintained at all times. High speed stirring was continued one hour at —10° and 24 h at room temperature.

The mixture was then carbonated by pouring onto a Dry Ice–ether slurry. After the mixture had warmed to room temperature, the excess metal was decomposed by the addition of 80 % aqueous *tert*-butanol. Water was added until two clear layers resulted. These were separated and the organic layer was washed once with 50 ml water. The wash was added to the aqueous layer, which, in turn, was washed once with 50 ml ethyl ether. The aqueous layer was acidified with dilute hydrochloric acid and the organic acid was extracted with five 50-ml portions of ether. The extractions were combined and dried over Drierite. After solvent removal under vacuum, the solid acid obtained was recrystallized from water to give 11.8 g (39 %) *o*-tolylacetic acid melting at 88–90° (lit.[12] m.p. 88–9°). A second fraction (2.5 g) of solid was obtained melting at 85–8°. Total yield was therefore 47 %.

m-Tolylacetic acid (22 % yield, m.p. 61–2°) and *p*-tolylacetic acid (37 % yield, m.p. 91–2°) were prepared in analogous fashion from the corresponding xylenes.

Dimethylbenzoic acids

2,6-Dimethylbenzoic acid was prepared in the usual fashion by carbonating the Grignard reagent derived from 2,6-dimethyliodobenzene (purchased from Eastman Kodak Company) (30 g, 0.13 mole). A 51 % yield (10 g) of 2,6-dimethylbenzoic acid melting at 114–115° was realized. The literature[13] m.p. is 116°.

3,4-Dimethylbenzoic acid was prepared by carbonating the Grignard reagent derived from 4-bromo-*o*-xylene. It melted at 164–5° (lit.[14] m.p. 165–6°).

2,3-Dimethylbenzoic acid was prepared in low yield from the reaction of *o*-methylbenzylmagnesium chloride and paraformaldehyde followed by oxidation of the product with potassium permanganate in aqueous acetone. After several crystallizations from dilute ethanol it melted at 139–142° (lit.[13] m.p. 142–3°).

2,4- and 2,5-Dimethylbenzoic acids were commercial products (Eastman Kodak Co.) and were used without further purification.

Methylbenzyl bromides

m-Methylbenzyl bromide (*Method I*). *m*-Xylene (63.5 g, 0.60 mole), *N*-bromosuccinimide (88.5 g, 0.50 mole), 150 ml carbon tetrachloride and 0.2 g benzoyl peroxide were placed together in a 500 ml flask and heated to reflux. After the first 10 min of reflux another 0.2 g of benzoyl peroxide was added. The mixture was refluxed for 6 h. It was then cooled in ice and filtered to remove the precipitated succinimide. The precipitate was washed with carbon tetrachloride and the washings added to the filtrate. The carbon tetrachloride was removed under vacuum and the residue was distilled to give 55.3 g (60 %) *m*-methylbenzyl bromide boiling at 133–7° at water aspirator vacuum. Redistillation of this material on a Todd column gave 40 g *m*-methylbenzyl bromide boiling at 109–110°/24 mm; $n_D^{27} = 1.5632$ (lit.[5] $n_D^{27.5} = 1.5545$). Analysis of this material by v.p.c. (4 ft. diethylene glycol succinate column at 85°) showed it to be essentially pure *m*-methylbenzyl bromide.

m-Methylbenzyl bromide (*Method II*). Bromine (113 g, 0.71 mole) was added dropwise to refluxing *m*-xylene (106 g, 1 mole). The reaction was carried out in a hood illuminated with a tungsten light. After an additional one hour of reflux, distillation yielded 76 g (58 %) of material boiling at 100–109° under water aspirator vacuum. The index of refraction of this material (n_D^{27}) was 1.5595. Analysis of this material by v.p.c. (same conditions as described for Method I) showed that it was seriously contaminated with 4-bromo-*m*-xylene and contained, in addition, small amounts of 2-bromo-*m*-xylene.

p-Methylbenzyl bromide was prepared from NBS and *p*-xylene as described under Method I for *m*-methylbenzyl bromide. It was distilled at 90–100° (10 mm) and then recrystallized from absolute ethanol. It melted sharply at 35–6°. (Lit.[15] m.p. 35.5°).

Preparation of methylbenzyl Grignard reagents and their carbonation

o-Methylbenzylmagnesium chloride was prepared by the addition of *o*-methylbenzyl chloride (40.0 g, 0.28 mole) in 200 ml, dry ethyl ether to magnesium turnings (8.4 g, 0.35 g-atom) in 50 ml dry ethyl ether with stirring under a dry nitrogen atmosphere. The Grignard reagent was formed in 71 % yield as determined by titration.

A portion of the above solution (60 ml, 0.066 mole Grignard) was poured onto a Dry Ice–ether slurry. After warming to room temperature, dilute hydrochloric acid was added until two clear layers resulted. The ether layer was washed with water and these washings added to the aqueous layer. The latter was washed with ether and then acidified with dilute hydrochloric acid. The liberated acids were then extracted with five 50-ml portions of ether. The combined extracts were then dried over Drierite. Removal of the solvent (Rinco evaporator) gave 8.7 g (88 %) of *o*-tolylacetic acid melting at 88–9°.

A small portion of this acid was treated with excess diazomethane prepared by the method of De Boer[16]. Excess diazomethane was destroyed by the addition of formic acid. The etheral solution was then washed with water, sodium bicarbonate solution, and again with water. After drying over Drierite, the solvent was removed and the residue was analyzed by v.p.c. (2-meter Column "R", 180°, 15 p.s.i. He). The material proved to be 100 % methyl *o*-tolylacetate by comparison of its retention time with an authentic sample. The analytical conditions employed were quite adequate to detect any isomeric acids which might have formed. A synthetic mixture of authentic samples of methyl *o*-tolylacetate, methyl 2,3-dimethylbenzoate and methyl 3,4-dimethylbenzoate could be separated with ease under identical analytical conditions.

m-Methylbenzylmagnesium chloride. This Grignard reagent was prepared in 85 % yield as determined by titration from 21.5 g (0.153 mole) of *m*-methylbenzyl chloride and 7.2 g (0.30 g-atom) of magnesium. The carbonation and work up procedure were identical to that employed with the *ortho*-isomer described above. An 84% yield of acid (14.9 g) was obtained melting at 62–64°.

Treatment of a small portion of this acid with excess diazomethane and analysis of the product by v.p.c. (20 ft. column; 20% Craig polyester succinate on firebrick; 180°; 15 p.s.i. He) indicated 100% methyl *m*-tolylacetate. An authentic sample of methyl *m*-tolylacetate had an identical retention time. An authentic mixture of the three most likely isomers, methyl *m*-tolylacetate, methyl 2,4-dimethylbenzoate and methyl 2,6-dimethylbenzoate were completely separated by the analytical conditions employed.

p-Methylbenzylmagnesium chloride. Was prepared from 23.0 g (0.164 mole) of *p*-methylbenzyl chloride and 7.2 g (0.3 g-atom) of magnesium. Carbonation gave 16.6 g (68%) of acid melting at 90–2°.

Treatment with diazomethane and analysis by v.p.c. (same conditions as for *meta*-isomer) showed 100% methyl *p*-tolylacetate. An authentic mixture of methyl *p*-tolylacetate and methyl 2,5-dimethylbenzoate was easily separated by the analytical conditions used.

m-Methylbenzylmagnesium bromide. (a) Bromide prepared by Method I. *m*-Methylbenzylmagnesium bromide was prepared by the addition of *m*-methylbenzyl bromide (27.8 g, 0.15 mole) (prepared by Method I) in 175 ml dry diethyl ether to magnesium turnings (7.2 g, 0.3 g-atom) in 50 ml dry ethyl ether, with stirring under an atmosphere of dry nitrogen. Carbonation and work up under identical conditions to those described above, gave 14.5 g (65%) of *m*-tolylacetic acid melting at 60–2°. Treatment with diazomethane and analysis by v.p.c. indicated 100% methyl *m*-tolylacetate.

(b) Bromide prepared by Method II. The Grignard reagent was prepared from 27.8 g (0.15 mole) of "*m*-methylbenzyl bromide" prepared by Method II and 7.2 g (0.3 g-atom) of magnesium turnings. The usual carbonation and work up procedure gave 14.6 g of acid (65%) melting at 48–53°. Treatment of a small portion of this product with diazomethane and analysis by v.p.c. indicated that it was a mixture of methyl *m*-tolylacetate (83%), methyl 2,4-dimethylbenzoate (13%) and methyl 2,6-dimethylbenzoate (4%).

p-Methylbenzylmagnesium bromide. The preparation and carbonation of the Grignard reagent from *p*-methylbenzyl bromide was essentially identical in all respects to that described above for *m*-methylbenzyl bromide. The crude acid (55%) melted at 90–1° after preliminary drying in a desiccator over Drierite. When a portion of this crude acid was converted to the methyl ester with diazomethane and the latter analyzed by v.p.c. (4 ft. diethylene glycol succinate column, 150°) only methyl *p*-tolylacetate was present. An authentic mixture of methyl *p*-tolylacetate and methyl 2,5-dimethylbenzoate could be separated easily by the analytical conditions used.

Determination of accuracy of analytical method

A synthetic mixture of the following acids was prepared:

m-tolylacetic acid	1.61 g (55.2%)
2,4-dimethylbenzoic acid	0.947 g (32.5%)
2,6-dimethylbenzoic acid	0.360 g (12.5%)

An ethereal solution of this mixture was then treated with diazomethane, worked up and analyzed by v.p.c. under the same conditions described above. The following results were obtained:

methyl *m*-tolylacetate	55.1 %
methyl 2,4-dimethylbenzoate	32.6 %
methyl 2,6-dimethylbenzoate	12.3 %

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SUMMARY

Contrary to previous literature reports, it has been found that Grignard reagents prepared from *pure* methylbenzyl halides yield only the expected normal acids upon carbonation. Thus, *m*- and *p*-methylbenzylmagnesium bromides, upon carbonation, yield only *m*- and *p*-tolylacetic acids respectively when the starting methylbenzyl halides are prepared by N-bromosuccinimide treatment of the corresponding xylene. The dimethylbenzoic acids reported as "abnormal" products from these reactions arise from contamination of the methylbenzyl halides with dimethylbromobenzenes.

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