REACTION OF $^{14}CO_2$ WITH GRIGNARD REAGENTS TO FORM EITHER CARBOXYLIC ACIDS OR KETONES. A NOVEL CONVENIENT ROUTE TO [2-^{14}C]GLYCEROL AND [1-^{14}C]GLYCOLIC ACID

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SUMMARY

The reaction of CO_2 with GRIGNARD reagents carrying an ether grouping in a sterically suitable position can be directed to afford predominantly either the carboxylic acid or the symmetrical ketone. Thus, the magnesiumorganic compounds prepared from chloromethyl-methyl ether, benzyl-chloromethyl ether and 2-methoxy-bromobenzene, upon treatment with CO_2 under appropriate conditions give the corresponding ketones in excellent yield. An attempt is made to rationalize this finding from a mechanistic viewpoint. The easily accessible 1,3-bis(benzyloxy)-acetone represents a convenient intermediate for an efficient and simple synthesis of glycerol.

Key Words : Carbon-14, GRIGNARD reaction, Ketone synthesis, Glycolic acid, Glycerol

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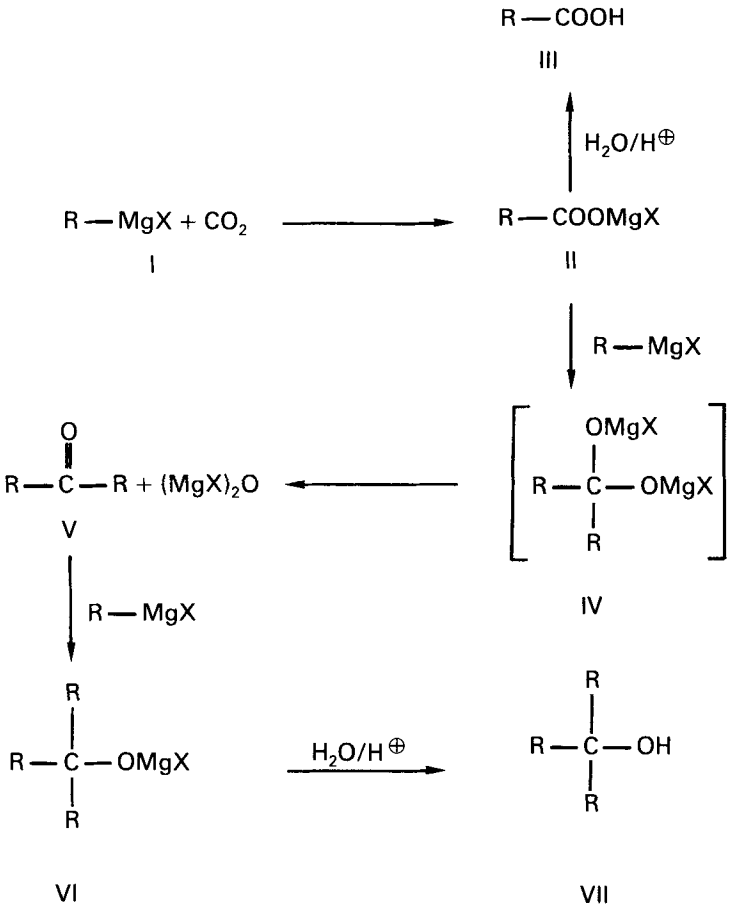
INTRODUCTION

In the course of our preparative work, the need arose for the synthesis of ^{14}C-labelled methoxyacetic acid. As an obvious approach for its preparation, the reaction of methoxymethylmagnesium chloride with carbon dioxide was investigated. Preliminary experiments afforded rather low yields of the desired acid. Instead, a neutral product was formed, which was shown to be the symmetrical ketone, i.e. 1,3-dimethoxy-acetone. Varying the experimental conditions, however, the reaction path could be directed to give either the acid of the ketone as the principal product. This finding initiated the present study to explore the scope and the limitations of these reactions.

Already in his pioneer work GRIGNARD (1, 2) has described the principal reactions of organomagnesium halides with carbon dioxide as outlined in SCHEME 1. While the first reaction step, i.e. the formation of the carboxylate II and subsequent hydrolysis to the carboxylic acid III, represents a key route for the introduction of isotopic carbon, the side-reactions yielding the ketone V or the tertiary alcohol VII, have found little application for preparative purposes (3). Only some aromatic GRIGNARD reagents are described, from which upon treatment with carbon dioxide, favourably at elevated temperature, considerable amounts of ketones were obtained (4). For most aliphatic GRIGNARD

reagents, however, the tertiary alcohol is the principal by-product and little or no ketone is formed.



SCHEME 1: The principal reactions of organomagnesium halides with CO_2

The high yield of 1,3-dimethoxy-acetone obtained by the reaction of methoxymethylmagnesium chloride with carbon dioxide, therefore, was a surprising finding. Stimulated by this observation and the original goal, i.e. to prepare methoxyacetic acid, the present study was carried out with two objectives : On one hand to find the optimal experimental conditions for the ketone formation (ketone route) including the scope for its application, and on the other hand to optimize the transformation to the acid (acid route).

METHODS AND RESULTS

In TABLE 1 various halides are listed which were transformed into the GRIGNARD reagents in tetrahydrofuran according to CASTRO (5).

Favourable prerequisits to the ketone route are elevated temperature (4), application of an excess of the GRIGNARD reagent and extended reaction time. The organometallic reagents were used in a threefold excess and stirred with carbon dioxide at room temperature for approximately 15 hours. The reaction mixtures were analysed quantitatively by GLC for the potential products: acid, ketone and tertiary alcohol.

	Halides	% acid	% ketone	% alcohol
[1]	CH_3OCH_2Cl	1	89.5	< 5
[2]	$CH_3OCH_2CH_2Cl$ *)	-	-	-
[3]	$CH_3OCH_2CH_2CH_2Cl$	33	45	14
[4]	$CH_3CH_2CH_2CH_2Cl$	32	24	12
[5]	$(CH_3)_3CCl$	76	0	0
[6]	$C_6H_5CH_2OCH_2Cl$	< 2	89	< 5
[7]	$C_6H_5CH_2SCH_2Cl$	70	0	0
[8]	C_6H_5Br	44	12	0.1
[9]	$2\text{-}(CH_3O)C_6H_4Br$	7	89	1.6
[10]	$4\text{-}(CH_3O)C_6H_4Br$	73	8.4	2
[11]	$C_6H_5CH_2Cl$	98	0	0

TABLE 1 : Products formed by the reaction of GRIGNARD reagents with CO_2 using the 'ketone route'.

*) no GRIGNARD reagent formed (6)

The respective yields indicated in TABLE 1 are calculated on the basis of the applied carbon dioxide. Regarding the ketone formation the striking examples are the GRIGNARD reagents prepared from chloromethyl-methyl ether [1], benzyl-chloromethyl ether [6] and 2-methoxy-bromobenzene [9] with yields of al-

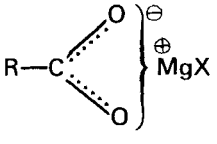
most 90%. HOLMBERG (7) has already reported on the unexpected behaviour of 2-methoxy-phenylmagnesium bromide upon reaction with carbon dioxide. This author indicated 2,2'-bis(methoxy)-benzophenone as the main product, representing 34% based on the GRIGNARD reagent. In our experiments almost 50% of ketone was achieved from 1-chloro-3-methoxy-propane [3], whereas the other halides afforded only minor amounts of the carbonylation product.

In order to optimize the GRIGNARD reaction regarding the acid formation (acid route), the reaction must be stopped at the stage of the carboxylate II. This can be achieved applying a small excess of the GRIGNARD reagent only and by operation at low temperature for a relatively short reaction period. Observing these reaction conditions, methoxyacetic acid and benzyloxyacetic acid were synthesized by stirring the reaction mixture at a temperature range of -70° to 0° for 80 minutes to give yields of 76% and 83%, respectively.

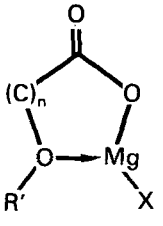
MECHANISTIC CONSIDERATIONS

An examination of the results compiled in TABLE 1 reveals the striking feature of a predominant ketone formation with organomagnesium halides carrying a neighbouring ether-oxygen.

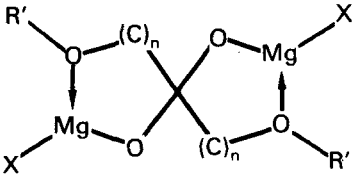
This fact suggests the hypothesis that the reaction is assisted by the presence of the oxygen function. Searching for a possible mechanistic cause of the finding, it is reasonable to assume two factors responsible for the high yields of ketones from the above compounds: First, enhancement of the reactivity of the carboxylate II towards the addition of another GRIGNARD reagent, and, second, stabilization of the intermediate IV and thus preventing the subsequent conversion to the tertiary carbinol.



VIII



IX



X

FIGURE 1: Complexes of GRIGNARD reagents with CO_2

The lack of reactivity of carboxylates II to GRIGNARD reagents is believed to be attributable to the tendency to form a resonance hybrid VIII, in which neither C-O bond has true carbonyl character (8).

Reagents carrying an ether grouping in a sterically suitable position, however, may form a coordination complex as indicated in formula IX. Apparently, this is especially favoured, if a five- or six-membered ring is formed (n = 1 or 2; examples [1], [6] and [9] in TABLE 1). The intramolecular interaction establishes the carbonyl character of the compound and allows the nucleophilic attack by a second molecule of the organomagnesium reagent.

The addition product of complex IX with another molecule of the GRIGNARD reagent once formed, in analogy, may constitute the bicyclic complex X. Contrary to the increasing effect of the reactivity in IX, in the spirane X the reactivity is decreased; the otherwise high tendency to split off halomagnesium oxide is cancelled, and therefore the reaction path blocked at the ketone stage.

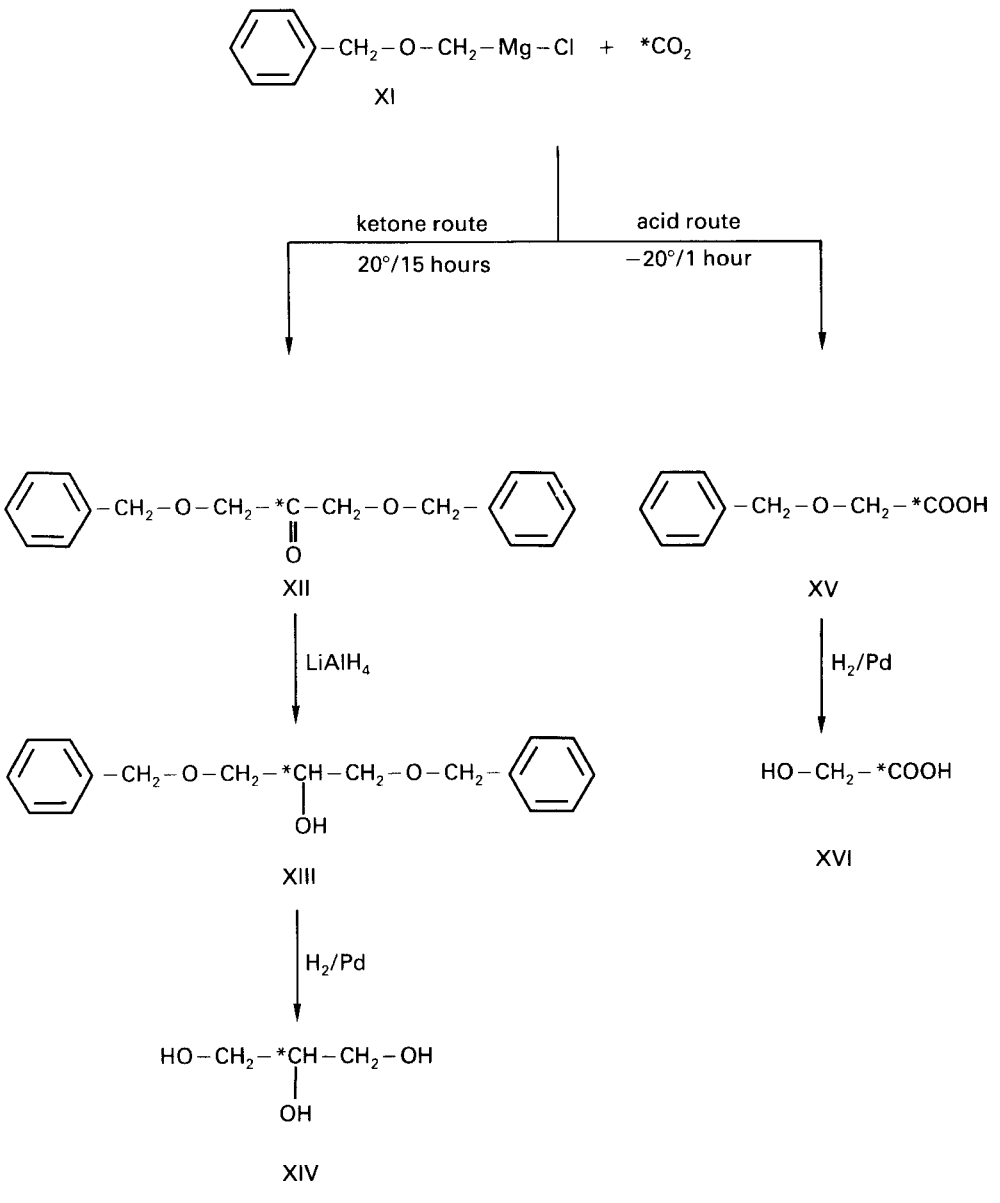
The postulated protecting action on carbonyl compounds by formation of intramolecular coordination complexes is supported by various reports describing the transformation of GRIGNARD reagents into aldehydes (9) or ketones (10, 11, 12).

PREPARATION OF [2-^{14}C]GLYCEROL AND [1-^{14}C]GLYCOLIC ACID

The facile access to 1,3-bis(benzyloxy)-acetone (XII) offered its use for a novel synthesis of [2-^{14}C]glycerol. Although various methods are described for the preparation of ^{14}C-labelled glycerol (13, 14), many of them suffer from the drawback to involve tedious extraction procedures of the readily water soluble product.

The present approach is outlined in SCHEME 2. Reduction of XII with $LiAlH_4$ afforded the carbinol XIII which upon catalytic hydrogenolysis in ethanol gave the glycerol XIV. Isolation of the latter easily was achieved by removal of the catalyst, evaporation of the volatile by-products and distillation under reduced pressure, yielding a radiochemically pure product. The radiochemical yield was 74.8% based on the $Ba^{14}CO_3$.

In analogy, [1-^{14}C]glycolic acid (XVI) was obtained by hydrogenolysis of the benzyloxyacetic acid XV. Calculated on the carbonate, the radiochemical yield was 83%.



SCHEME 2: Preparation of [2–^{14}C]glycerol and [1–^{14}C]glycolic acid

EXPERIMENTAL

The analyses of the products were performed by GLC using a PACKARD chromatograph, Model 427, equipped with a flame ionization detector and a gas proportional counter for simultaneous detection of the compounds and the inherent radioactivity.

A. Acid route

Methoxy-[1-^{14}C]acetic acid

Due to the instability of the GRIGNARD reagent prepared from chloromethyl-methyl ether, the strict observance of the experimental conditions as described by CASTRO (5) is crucial for its preparation.

In a separate flask, a solution of 2.82 g (35 mmoles) of freshly distilled chloromethyl-methyl ether in 18 ml of anhydrous tetrahydrofuran was prepared, while in the reaction flask, under a dry atmosphere of N_2, 850 mg (35 m-atoms) of Mg-turnings and 10 mg of $HgCl_2$ were stirred with a magnetic stirrer for 5 minutes. To initiate the reaction, 2 ml of the above tetrahydrofuran solution were added into the reaction flask at room temperature. With-

in one minute the reaction started exothermically. Then, the reaction flask was immersed in a dry-ice acetone bath at -30° and the remaining tetrahydrofuran solution added dropwise within one hour. Stirring was continued for 3 additional hours in the cooling bath kept between -30° and -20°. From the clear reaction solution, 5 ml were withdrawn and decomposed with water. The released dimethyl ether was measured volumetrically, indicating the presence of approximately 8 mmoles of the reagent.

The remaining solution containing roughly 25 mmoles of the GRIGNARD reagent, was diluted with 30 ml of anhydrous tetrahydrofuran and chilled with liquid N_2. Attached to a vacuum-line, in the evacuated system, 20 mmoles (100 mCi) of $^{14}CO_2$, generated from $BaCO_3$ with H_2SO_4, were frozen into the reaction flask.

The carboxylation reaction was effected by vigorous stirring, first at -70° for 20 minutes followed by two warm up periods from -70° to -20° and subsequently from -20° to 0° for 30 minutes each.

At room temperature, the white suspension was diluted with 25 ml of diethyl ether and decomposed with 10 ml of conc. NH_4Cl solution and 10 ml of 4N HCl. In a separatory funnel, the two layers were separated and the aqueous

phase extracted with three portions of diethyl ether 60 ml each. From the combined organic layers, the acidic product was removed with 1N NaOH. The aqueous alcaline solution, finally, was acidified with 10N HCl and extracted continuously with diethyl ether in a KUTSCHER STEUDEL apparatus for 15 hours. The ether solution was dried with Na_2SO_4, the solvent evaporated and the residue distilled at 110°/20 mm Hg to give 1.43 g (76.3 mCi) of methoxyacetic acid, radiochemical yield 76.3%. Analysis of the product by GLC (Carbowax 20 M/150°) revealed a chemical purity of 98%.

Benzyloxy-[1-^{14}C]acetic acid (XV)

Starting from 1.41 g (9 mmoles) benzyl-chloromethyl ether in 6 ml of tetrahydrofuran, 233 mg (9.6 matoms) of magnesium and 10 mg of $HgCl_2$ the GRIGNARD reagent was prepared as described above at a temperature of 0 - 10°. The solution was diluted with 6 ml of tetrahydrofuran and 6 ml of diethyl ether. Under vacuum, 6 mmoles (53.3 mCi) of $^{14}CO_2$ were transferred into the reaction flask. The reaction mixture was stirred at -20° for one hour. The following processing was performed in analogy to the preparation of the methoxyacetic acid. After dilution of the white suspension with 15 ml of diethyl ether, hydrolysis was achieved with 6 ml of conc. NH_4Cl solution and 3 ml of 4N HCl.

To remove unreacted $^{14}CO_2$, a stream of $N_2$was kept running through the reaction flask and an adapter with aqueous NaOH. In this adapter 6.9 mCi (12.9%) of $^{14}CO_2$ could be recovered. Separation of the neutral and acidic products as described above afforded 1.5 mCi (2.8%) of ketone XII and 827 mg (44.2 mCi) of the oily benzyloxyacetic acid XV, or 83% based on the CO_2. The identity and purity of the product were established by GLC (OV 17/130°). The acid was transformed into the methyl ester with CH_2N_2 prior to the analysis.

B. Ketone route

1,3-Dimethoxy-acetone

The GRIGNARD reagent was prepared from 2.42 g (30 mmoles) of chloromethyl-methyl ether in 20 ml of tetrahydrofuran, 754 mg (31 matoms) of Mg-turnings and 10 mg of $HgCl_2$ under careful exclusion of moisture, as described above for the synthesis of methoxyacetic acid. The CO_2 generated from 1.97 g (10 mmoles) of $BaCO_3$ with 25 ml of conc. H_2SO_4 was frozen into the reaction mixture, chilled in liquid N_2. The reaction flask was separated from the vacuum-line and placed in a dry-ice bath at -70°. Under magnetic stirring the bath was allowed to warm up to 20° within 4 hours. Stirring was

continued overnight at room temperature. After dilution of the fine suspension with 20 ml of diethyl ether, the mixture was cooled to 0° and hydrolyzed with 10 ml of conc. NH_4Cl solution and 10 ml of 4 N HCl. The two layers were transferred into a KUTSCHER STEUDEL apparatus and extracted continuously with diethyl ether for 20 hours. After drying of the organic phase with Na_2SO_4, the solvent was evaporated and the residue distilled at 80°/15 mm Hg to give 1.09 g of dimethoxyacetone. GLC analysis (OV 17/80°) indicated a purity of 97% and the presence of 3% tertiary alcohol. The actual yield of ketone based on the applied CO_2, consequently, was 89.5%.

1,3-Bis(benzyloxy)-[2-^{14}C]acetone (XII)

To the analogous GRIGNARD solution prepared at 0 - 10°, using benzyl-chloromethyl ether instead of chloromethyl-methyl ether, 10 mmoles (155 mCi) of $^{14}CO_2$ were added. Reaction and hydrolysis were performed exactly as described for the 1,3-dimethoxyacetone. The two phases obtained after hydrolytic decomposition were separated and the organic layer was washed with water, 1 N NaOH and water again. The crude product obtained after drying with Na_2SO_4 and evaporation was distilled in a bulb-tube at 160°/0.01 mm Hg affording 3.1 g (137.5 mCi) of an oily

compound. Analysis by GLC (SE 30 on Gas Chrom Q/200°) revealed a radiochemical purity of 99% and a chemical purity of 77%. The radiochemical yield was 88.7%.

This product was used without further purification for the preparation of glycerol.

In a preliminary study with non-radioactive material the product was purified by careful fractionating distillation. The identity of the ketone XII was established by IR, NMR and MS, b.p. 150°/0.01 mm Hg, m.p. 37 - 38°.

All the halides listed in TABLE 1 were treated and analyzed in the same way as described for the two examples above.

C. Preparation of glycerol and glycolic acid

[2-^{14}C]Glycerol-1,3-dibenzyl ether (XIII)

To the suspension of 380 mg (10 mmoles) of $LiAlH_4$ in 20 ml of anhydrous diethyl ether, cooled in an ice bath, the above chemically crude 1,3-bis(benzyloxy)-acetone (XII) (3.1 g, 137.5 mCi) in 20 ml of diethyl ether was added dropwise under magnetic stirring. Subsequently,

the reaction mixture was refluxed for one hour, the excess hydride decomposed at 0° by careful addition of 1.08 ml (60 mmoles) of water and the mixture refluxed again for 30 minutes. Approximately 5 g of Na_2SO_4 were added and mixed thoroughly with the formed hydroxides. The precipitate easily could be removed by filtration and was washed with diethyl ether. The combined ether solution was evaporated and the residual oil distilled in a bulb-tube at 160°/0.01 mm Hg, yielding 3.0 g (127 mCi) of crude XIII.

[2-^{14}C]Glycerol (XIV)

The crude product XIII (3.0 g, 127 mCi) was dissolved in 15 ml of ethanol and 600 mg of palladium 10% on charcoal were added. The mixture was hydrogenated at room temperature and atmospheric pressure. Within 2 hours the theoretical volume of H_2 was absorbed. After removal of the catalyst by filtration, the clear solution was evaporated under reduced pressure. The residual oil was washed three times with pentane and then transferred into a bulb-tube.

To remove volatile impurities, the crude product was stirred at 60°/0.5 mm Hg for one hour. Distillation was performed at 150°/0.5 mm Hg, yielding 716 mg (116 mCi) of glycerol.

The product was identical with a reference sample of glycerol and had a radiochemical purity greater than 99% as ascertained by TLC (silica gel, acetone) and GLC (Carbowax 20 M/170°). The radiochemical yield was 74.8% based on the $^{14}CO_2$.

[1-^{14}C]Glycolic acid (XVI)

The above described benzyloxy-[1-^{14}C]acetic acid (XV) (827 mg, 44.2 mCi) dissolved in 10 ml of tetrahydrofuran was hydrogenated at room temperature and atmospheric pressure in the presence of 300 mg of palladium 5% on charcoal. After 4 hours the theoretical volume of H_2 was absorbed. The catalyst was removed by filtration and the filtrate evaporated under reduced pressure to give 388 mg (44.2 mCi) of pure glycolic acid XVI.

The radiochemical purity of the product was 99% as found by TLC and GLC. TLC was performed with two solvent systems (silica gel, chloroform - methanol - formic acid, 80 : 15 : 5) and ethanol - chloroform - conc. NH_3 - water, 53 : 30 : 15 : 2). Prior to the analysis by GLC (OV 17/70°) the acid was converted to the trimethylsilyl derivative with N,O-bis(trimethylsilyl)-acetamide in tetrahydrofuran. The radiochemical yield based on the $^{14}CO_2$ was 82.9%.

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