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NOTES

USE OF SOLVENT VAPOUR PRESSURE TO EVACUATE THE INSTALLATION IN CARBONATIONS OF GRIGNARD REAGENTS

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Abstract. An installation is described for the carbonation of organomagnesium reagents with $^{13}CO_2$ or $^{14}CO_2$. The obtained vacuum results by sweeping all permanent gases with solvent vapour (ethyl ether or tetrahydrofuran) at room temperature under moderate vacuum. Specific steps in the carbonation procedure are indicated, leading to good yields of carboxyl-labelled acids.

INTRODUCTION

The usual procedure in the preparation of carboxylic acids labelled with ^{13}C or ^{14}C (denoted by $^{*}C$) at the carboxyl group involves the carbonation of an organometallic reagent (Grignard reagent or organolithium derivative) using costly high vacuum lines with diffusion pump.[1-9] We propose an inexpensive alternative based on the idea that the vapour pressure of the solvent (anhydrous diethyl eter or tetrahydrofuran) can be put to use for displacing all the air or the inert permanent gas from the system so that the variable vacuum is controlled only by the lowest temperature in any part of the installation, according to the principle of the coldest wall.

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In the literature, as far as we are aware, this idea has not been applied, except for Eberson's apparatus [10] for the carbonation of Grignard reagents with $^{14}CO_2$ (in that apparatus, cooling was effected with dry ice at which temperature diethyl ether has a vapour pressure of about 1 Torr).

The installation, depicted in Fig. 1, is made from high quality glass which withstands temperature variations, and from good, well lubricated conical or spherical ground-glass joints (for conical ones : 14, 19, or 29 mm outer diameter) and stopcocks. Flask *1* contains the labelled barium carbonate and, in side-arm *2*, diethyl ether (introduced by means of a pipette with curved tip). In the dropping funnel *3* with 100-ml capacity equipped with pressure equalizer, concentrated sulfuric acid is placed. The preparation of the Grignard reagent had taken place earlier in the three-necked flask *6* which had been disconnected from the installation and fitted with reflux condenser and normal dropping funnel ; then the flask *6* with the ethereal solution of the organomagnesium derivative is attached to the installation as indicated in Fig. 1. An important condition is that the free volume above the ethereal solution in flask *6* should be 25-30% greater than the volume occupied at room temperature and normal pressure by the carbon dioxide generated in *1-4* (otherwise gaseous $^*CO_2$ would bubble through mercury in *7*,*8* and escape). This condition is respected by the amount of Ba^*CO_3 and the volume indicated below : if other flask capacities are used, the present ratio between the amount of Ba^*CO_3 and the volume should be maintained.

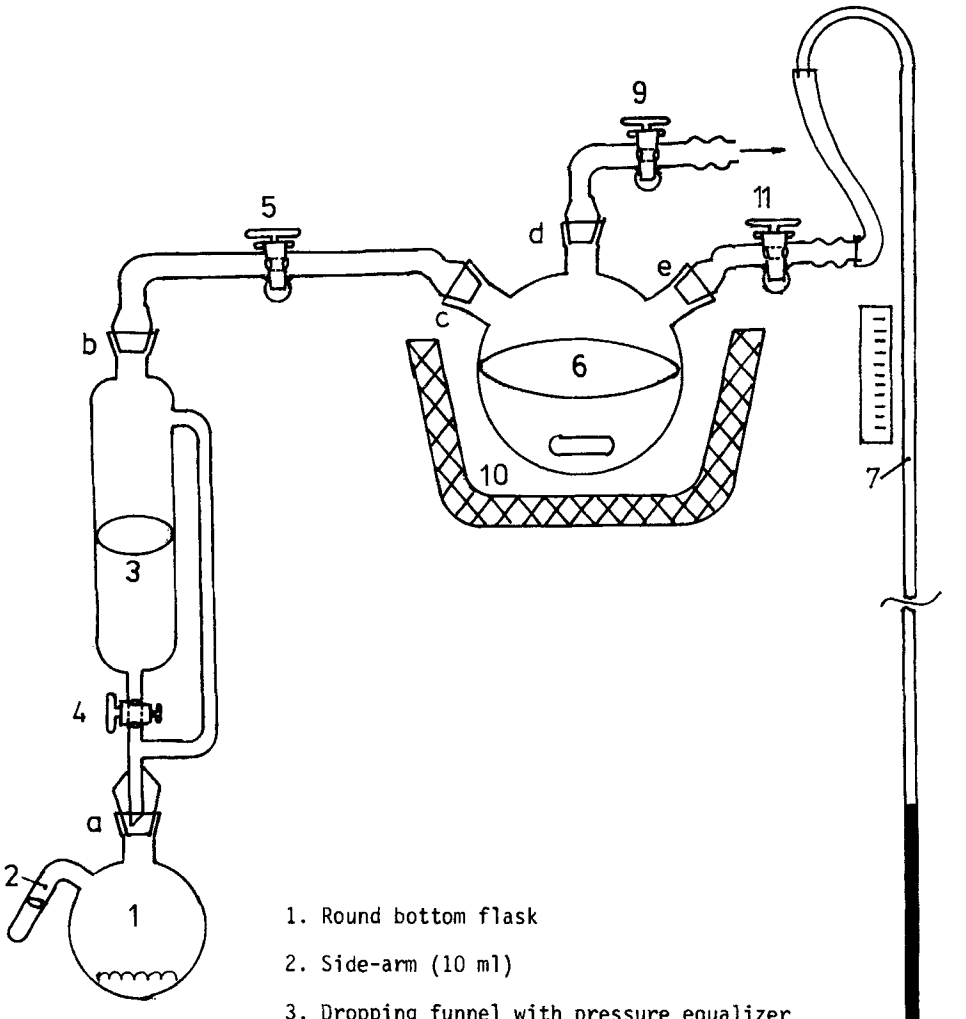
PROCEDURE

The order of operations indicated below should be strictly observed.

1) Flask *6* (100 ml capacity) is removed by separating junctions *c*, *d*, *e*, stoppering *c*, and attaching a reflux condenser and a normal dropping funnel to junctions *d* and *e*, respectively. All glassware should be rigorously dried.

2) Into the flask *6* are introduced : a magnetic stirrer, 0.50 g dry magnesium turnings (21 mmol), 5 ml anhydrous diethyl ether, and an iodine crystal.

3) From the dropping funnel a solution of 18 mmol halogen derivative in 10 ml of diethyl ether is added dropwise under gentle reflux till the reaction is complete. If an organolithium derivative is prepared, the reaction should be run in an inert gas atmosphere.



1. Round bottom flask
2. Side-arm (10 ml)
3. Dropping funnel with pressure equalizer
4. Stopcock for liquid
5, 9, 11. Vacuum stopcock for gases
6. Three-necked flask (100 ml)
7. Barometric tube
8. Round-bottom mercury reservoir
10. Thermally insulated cooling bath made from aluminium

Fig. 1. Scheme of the installation

4) Flask *6* with the solution of the organometallic derivative (in excess relative to $Ba^{*}CO_3$) is attached to the installation as in Fig. 1. Junction *d* is attached to a stopcock connected with a vacuum pump, and junction *e* to a barometric tube of about 1 m length and about 7 mm internal diameter whose lower end is introduced in flask *8* having a sufficient amount (about 0.5 kg) of mercury.

5) The carbon dioxide ($^{*}CO_2$) generator is flask *1* containing 1.80 g (9.10 mmol) of $Ba^{*}CO_3$, 6-7 ml diethyl ether in the side-arm *2* and 20 ml conc. H_2SO_4 in the dropping funnel *3*.

6) Junctions *b* and *c* are assembled as in Fig. 1. Stopcock *5* is opened.

7) Flask *6* is cooled for 15-20 minutes under stirring with an ice-salt mixture for reducing evaporation of the solvent.

8) Stopcock *9* is closed and the vacuum pump is started (alternatively one may use a water jet pump, protecting the installation against moisture via a calcium chloride connector). Stopcock *9* is carefully opened and the rise of the mercury level in the barometric tube *7* is observed. At a certain moment the diethyl ether in the side-arm *2* begins to boil, and its vapours sweep out all permanent gases. Some ether spillage into flask *1* is of no consequence.

9) When all the solvent in side-arm *2* has evaporated and the mercury level in *7* has became stationary, stopcock *9* is closed again.

10) The cooling bath *10* (a Dewar flask or an externally insulated aluminium bath) is filled with liquid nitrogen. Diethyl ether condenses in flask *6*. The pressure in the installation now corresponds to the vapour pressure of diethyl ether at -190°C, i.e. less than 10^{-2} Torr. The level of mercury in *7* attains a maximum.

11) The generation of $^{*}CO_2$ is started by adding dropwise sulfuric acid onto the $Ba^{*}CO_3$ via stopcock *4*, avoiding excessive foaming in flask *1*. Since the installation is under high vacuum, the carbon dioxide diffuses rapidly and condenses in flask *6* as dry ice over the solidified ethereal solution of the organometallic compound. The mercury level in 7 indicates a pressure rise of at most 1 Torr. When the acid has been added, the carbon dioxide evolution is completed by heating flask *1* at about 100°.

12) Stopcock *5* is closed so that all $^{*}CO_2$ is trapped in flask *6*.The cooling bath *10* is removed, and the rotating magnetic stirrer is brought under flask *6*.

13) The stirrer is started allowing flask *6* to reach gradually room temperature. The mercury level sinks by about 250-350 mm.

14) When the temperature in *6* reaches -120°C, the ethereal solution thaws, and carbonation begins. The mercury level in *7* is observed to rise due to the rapid consumption of the $^{*}CO_2$.

15) A second freeze-thaw cycle is started by opening stopcock *5* and repositioning the cooling bath *10* with liquid nitrogen. The mercury level in *7* should rise to practically the same height as before (in step 10) (otherwise an air leak may have occurred, the outcome of synthesis is doubtful). The stopcock *5* is closed and the cooling bath is removed. On warming, the mercury level drops a few mm, and the stirrer is started again. On thawing, in some cases a new upward jump of the mercury level in *7* is observed indicating that some more $^{*}CO_2$ had been generated in *1*.

Finally stirring is maintained for 2-3 hrs to ensure completion of the reaction.

16) Stopcock *5* is opened, then the connection to the vacuum pump is removed and stopcock *9* is cautiously opened to let air into the installation.

Flasks are disconnected, and after reassembling flask *6* with the usual dropping funnel and reflux condenser, the labelled magnesium carboxylate is decomposed with dilute acid under stirring and cooling. The acid is extracted with diethyl ether and purified in the usual manner.

It is recommended to perform several trial runs with non-labelled $BaCO_3$ and with simple Grignard reagents, then with the Grignard reagent under study, before the run with labelled $Ba^{*}CO_3$.

RESULTS

The results of a series of carbonations are shown in Table 1. [1-^{13}C]--naphthalene, [3-^{13}C]-phenanthrene, and [1-^{13}C]-phenanthrene were prepared in order to study the catalytic automerization [11] of the condensed polycyclic benzenoid hydrocarbons under the influence of an $AlCl_3 \cdot NaCl$ melt at about 200°.

In Table 1, Nph means α-naphthyl, yields are relative to $Ba^{*}CO_3$.

Table 1.

No.	Grignard reagent	Product	Yield %
1	$PhCH_2MgCl$	$PhCH_2{}^{13}COOH$	90
2	$Ph(CH_2)_3MgBr$	$Ph(CH_2)_3{}^{13}COOH$	92
3	$NphCH_2MgCl$	$NphCH_2{}^{13}COOH$	90
4	$Nph(CH_2)_3MgBr$	$Nph(CH_2)_3{}^{13}COOH$	94

REFERENCES

1. Murray A. III and Williams D.L.-*"Organic Syntheses with Isotopes"*, Part I, Interscience, New York, p. 86, 1958.
2. Weygand F. and Simon H., in *"Methoden der Organischen Chemie" (Houben-Weyl)"*, vol. IV, Part 2, Georg Thieme Verlag, Stuttgart, p. 643, 1985.
3. Calvin M, Heidelberger C., Reid J.C., Tolbert B.M. and Yankuich P.M.-*"Isotopic Carbon"*, Wiley, New York, p. 178, 1949.
4. Balaban A.T., Galateanu I., Georgescu G. and Simionescu L.-*"Labelled Compounds and Radiopharmaceuticals Applied in Nuclear Medicine"*, Wiley, Chichester, pp. 220, 294, 1986.
5. Catch J.R.-*"Carbon-14 Compounds"*, Butterworths, London, 1961.
6. Raaen V.F., Ropp G.A. and Raaen H.P.-*"Carbon-14"*, McGraw-Hill, New York,1968.
7. Bubner M. and Schmidt L.-*"Die Synthese Kohlenstoff-14 markierter organischer Verbindungen"*, Georg Thieme Verlag, Stuttgart, p. 542, 1955.
8. Ott D.G.-*"Syntheses with Stable Isotopes of Carbon, Nitrogen, and Oxygen"*, Wiley-Interscience, New York, 1981.
9. Baret C. and Pichat L.-*Bull. Soc. Chimique France* 18, 580 (1951).
10. Eberson L.-*Acta Chem. Scand.* 16, 781 (1962).
11. Balaban A.T., Gheorghiu M.D., Schiketanz A. and Necula A.-*J. Amer. Chem. Soc.* (in press).