

MICROSCALE SYNTHESIS OF VOLATILE,  $^{14}\text{C}$ -LABELLED  
ACID CHLORIDES\*

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SUMMARY

A method for the microscale (one mmole) synthesis of volatile,  $^{14}\text{C}$ -labelled acid chlorides from  $\text{Ba}^{14}\text{CO}_3$  using vacuum line techniques is described. By a judicious choice of reagents, desired intermediates and products may be isolated in high yield by simple vacuum transfer techniques without fractionation.

Key words: Volatile  $^{14}\text{C}$ -acid chlorides, microscale, vacuum line synthesis.

INTRODUCTION

The synthesis of acid chlorides is a simple chemical process. However, the preparation and, in particular, the isolation of volatile, labelled acid chlorides on a micro scale (one mmole or less) presents formidable operational difficulties. In fact, most previously described syntheses of such compounds<sup>1</sup> relied on fractional distillation as the method of product isolation necessitating a relatively large process, ranging in scale from 1 g to as much as 42 grams.<sup>2</sup>

Described, herein, is a vacuum line synthesis which enables one to isolate pure products on a micro scale by direct vacuum transfer techniques. The success of this process is based entirely on a careful choice of reagents.

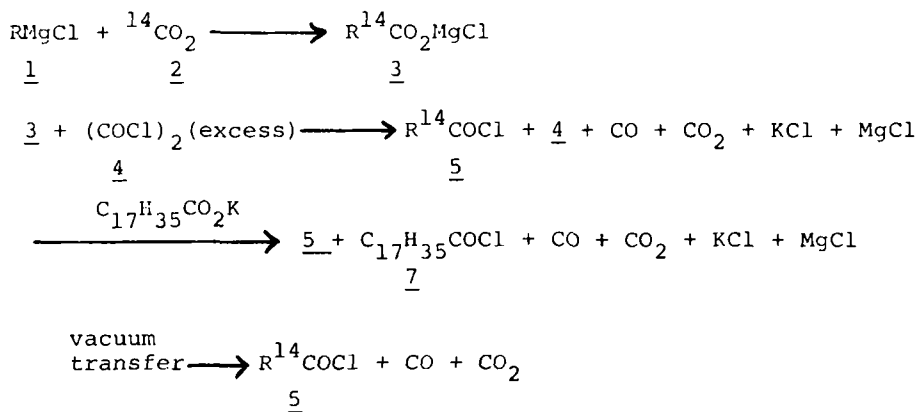
\*Contribution No. 675 from the Institute of Organic Chemistry  
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All experiments were carried out on a one mmole scale making possible the synthesis of carrier free products. However, in the interest of economy, only 3 mCi of BaCO<sub>3</sub> were used per experiment.

### RESULTS AND DISCUSSION

In order to avoid product isolation by fractional distillation, a vacuum line synthesis was devised in which desired products were isolated by a complete vacuum transfer of all volatile materials from the reaction. The desired materials were either transferred as volatiles or left behind as a residue. Scheme 1 describes this process.

A solution of alkyl Grignard 1 in ether was carbonated by injection into a reaction flask connected to a vacuum line containing <sup>14</sup>CO<sub>2</sub>/ether which was frozen in liquid N<sub>2</sub> then warmed to -78°. The labelled carboxylate 3 was obtained in higher yield by this inverse addition method than by the usual



SCHEME 1

procedure in which  $^{14}\text{CO}_2$  is transferred into a solution of Grignard reagent. Furthermore, as the  $^{14}\text{CO}_2$  was always present in excess during the addition, the formation of ketone and alcohol by-products was minimized.\*

Total vacuum transfer of volatile materials left a residue of the magnesium carboxylate 3. Conversion of 3 to the acid chloride 5 was accomplished using excess oxalyl chloride<sup>3</sup> (4). This reagent was chosen because it affords innocuous gases as by-products whose effervescence may be used to monitor the reaction.

When effervescence ceased, the excess oxalyl chloride was destroyed by addition of excess potassium stearate (6). When effervescence ceased again, (indicating complete dissipation of remaining oxalyl chloride) the volatiles containing the desired acid chloride and solvent were vacuum transferred out of the reaction mixture. The excess potassium stearate and the stearyl chloride 7 formed in the previous reaction were left behind as a non-volatile residue.

The labelled acid chlorides prepared in this manner were isolated and characterized as their corresponding anilides. These products required no further purification as demonstrated by radiochromatography and n.m.r. spectroscopy. The yields shown in Table 1 are comparable to those obtained by others in much larger scale reaction.

\*In one experiment using  $\text{EtMgBr}$ , the residue of Grignard carboxylate was acidified with p-TSA in THF and all volatiles were distilled into a receiver. G.C. analysis (Poropak Q; 1 meter x 3 mm;  $130^\circ\text{C}$ ) showed, in addition to propanoic- $^{14}\text{C}$ -acid, less than 2% 3-pentanone and no tertiary carbinol.

TABLE 1  
 Carbonation of RMgX with  $^{14}\text{CO}_2$  and  
 Direct Conversion to  $\text{R}^{14}\text{COCl}$

RMgX	$\text{R}^{14}\text{COCl}$ Yield*
MeMgCl	82
EtMgCl	88
EtMgBr	85
PrMgCl	78
t-BuMgCl	57

\*Yields determined as the corresponding anilides are based on  $\text{Ba}^{14}\text{CO}_3$ .

The entire sequence may be carried out in about 5 hours by a person experienced in vacuum line techniques. Furthermore, this process has three additional important advantages. First of all, the acid chloride is prepared directly from the crude magnesium carboxate. There is no need to either isolate the free acid or convert 3 to the potassium salt prior to chlorination as others have done! Secondly, the entire sequence is conducted in a closed system. The very real hazard of exposure to volatile radioactive materials is, thus, eliminated. Finally, since the synthesis is performed on a very small scale, and materials are isolated without fractional distillation, it is possible to prepare carrier-free products.

#### EXPERIMENTAL

Carrier free  $\text{Ba}^{14}\text{CO}_3$  was obtained from Amersham Corporation. Alkyl magnesium halide solutions were obtained from Aldrich Chemical Co. and titrated prior to use.<sup>4</sup> Reagent

grade solvents were dried over  $3\text{\AA}$  molecular sieves prior to use. Radiochemical purity of the anilide derivatives was determined by radio-tlc using a Berthold Model 276 Radiochromatography scanner. Radioassays were obtained using a Packard Tri-Carb Model 574 Scintillation Counter. Proton nmr spectra were recorded on a Varian EM-390 spectrometer. Gas chromatography was performed on a Hewlett Packard Model 402 gas chromatograph.

#### General Procedure for Vacuum Line Synthesis of Volatile $^{14}\text{C}$ -Acid Chlorides

A round bottom flask with a side arm containing a rubber septum was charged with  $\text{Ba}^{14}\text{CO}_3$  (1 mmol; 199 mg; 3 mCi/mmol), connected to a vacuum manifold and evacuated. Concentrated  $\text{H}_2\text{SO}_4$  was injected through the rubber septum and the liberated  $^{14}\text{CO}_2$  was condensed into a similar flask which had been previously evacuated and cooled in liquid  $\text{N}_2$ . Injection of 3 ml of anhydrous ether onto the frozen  $\text{CO}_2$  was followed by injection of one equivalent alkyl Grignard in ether. The liquid  $\text{N}_2$  bath was replaced with a dry ice-acetone bath and the reaction was stirred for one hour then allowed to slowly warm to ambient temperature. All volatile materials were transferred out of the reaction flask into an evacuated, liquid  $\text{N}_2$  cooled receiver leaving the dry  $^{14}\text{C}$ -labelled carboxylate salt. Dichloromethane (5 ml) was injected, and the stirred, ice cooled suspension was treated with 1.15 equivalents of oxalyl chloride. The ice bath was removed and the reaction was stirred at ambient temperature until effervescence ceased (about 2 hrs). Excess oxalyl chloride was destroyed by addition solid potassium stearate by means of a Kontes powder addition funnel (part #K-299400). The

desired  $^{14}\text{C}$ -acid chloride was isolated by vacuum transfer into a cooled receiver ( $-78^\circ$ ) leaving behind the non-volatile stearyl chloride along with magnesium and potassium salts.

## REFERENCES

1. Murray A. and Williams D.L. - Organic Synthesis with Isotopes, Interscience Publishers, Inc., New York, 1958, p. 308. This reference mentions a one mmole scale preparation of acetyl- $^{14}\text{C}$  chloride from sodium acetate- $^{14}\text{C}$ . It is, in our opinion, rather inconvenient, hazardous (since an open system is apparently used), and does not demonstrate the purity of the product.

Other micro-scale synthesis of volatile labelled acid chlorides may exist in the literature, although a fairly thorough search has failed to uncover such processes.

2. Some representative synthesis of  $^{14}\text{C}$ -labelled acid chlorides are:
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4. We wish to thank Messrs. A. Holstein and M. Sparacino for performing the Grignard titrations.