A METHOD FOR THE PREPARATION OF ^{14}C-LABELED CARBOXYLIC ACIDS. SYNTHESIS OF 6,11-DIHYDRO[b,e]THIEPIN-11-ONE-3-YL ACETIC ^{14}C-ACID*

Howard Parnes
Institute of Organic Chemistry, Syntex Research, 3401 Hillview Avenue, Palo Alto, California 94304

SUMMARY

An example of a potentially general method for the preparation of ^{14}C-carboxylic acids based on the carbonation of an α-lithiated carboxylate is described. This procedure requires only the unlabeled analog of the desired ^{14}C-acid as the precursor. The possibility of carrying out the selective decarboxylation of a malonic acid derivative with loss of only the unlabeled carboxyl group is described.

Key Words: α-Lithiated Carboxylate, Carbonation, Selective Decarboxylation

INTRODUCTION

A problem often encountered in radiochemical synthesis is the unavailability of a precursor which, when reacted with a labeled reagent, affords the desired product in a reasonable number of steps. The need to prepare the title compound (4) presented such a problem. However, the fact that (4) is a carboxylic acid made its preparation possible using only (1) [the unlabeled analog of (4)] as the starting material by what is essentially an exchange reaction, so that no precursor was needed.

DISCUSSION

Generation of anions α to carboxylic acids or esters and their subsequent reaction with a variety of electrophiles is a well known process.[1,2,3,4,5] Such

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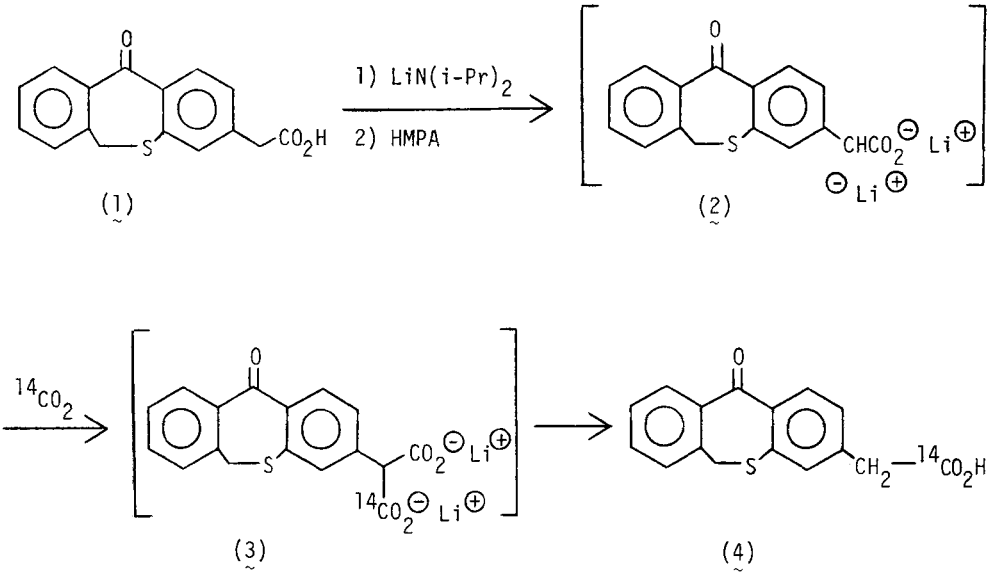
a process is conceptually attractive for the preparation of carboxylic-[^{14}C] acids since no precursor (other than the unlabeled analog of the desired acid) is needed. If the dilithium salt of an unlabeled acid can be generated and then quenched with $^{14}CO_2$, then decarboxylation of the resulting malonic acid would yield the labeled acid (see Scheme 1) having a specific activity equal to one half of that of the $^{14}CO_2$ used.

Scheme 1



(1) (2) (3) (4)

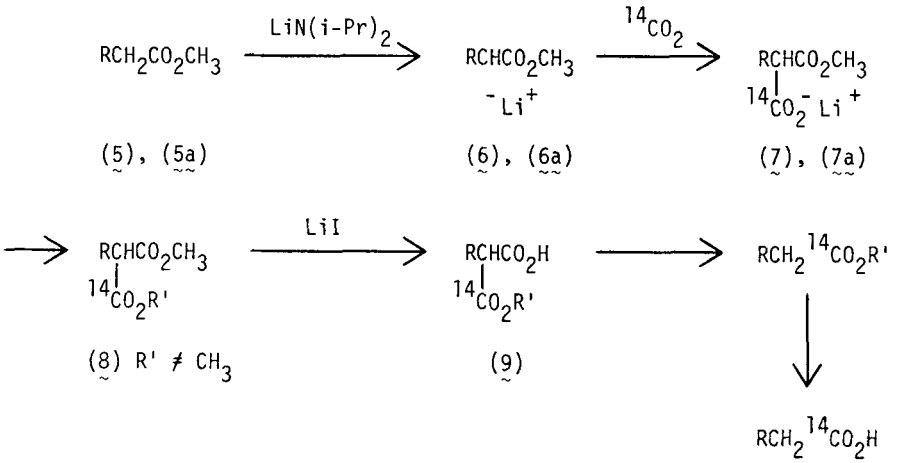
Treatment of (1) with lithium diisopropylamide (LDA)/hexamethylphosphoramide (HMPA) in THF generated the red-purple dianion (2) instantly. HMPA was added because it is thought to solvate acid and ester enolates,[3,7] thus preventing self-condensation. Since (1) contains a ketone function which could react with (2) it was important to moderate the reactivity of this enolate.

The dianion was carbonated with one half equivalent of $^{14}CO_2$ (to ensure maximum utilization of labeled reagent) and then quenched completely with a large excess of unlabeled CO_2. The intermediate dilithium malonate (3) decarboxylated spontaneously so that the product (4) was obtained directly after workup. Chromatographic purification of crude (4) afforded the pure product in 48% radiochemical yield (70% chemical yield) at a specific activity of

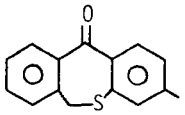
9.12 mCi/mmol.[8] Higher specific activities may, of course, be obtained by limiting the excess of (2).

A variation of this method may, in principle, be used to prepare [^{14}C]-carboxylic acids having a specific activity equal to that of the $^{14}CO_2$ used. Scheme 2 illustrates this concept.

Scheme 2



(5), (6), (7): R = alkyl, aryl

(5a), (6a), (7a): R = 

Carbonation of the α-anion (6) of a methyl ester (5) followed by esterification of the monomethyl malonate (7) would yield the mixed diester (R' ≠ Me) (8). Selective hydrolysis of the methyl ester with LiI,[6] for example, would reveal the unlabeled carboxyl as the free acid while the labeled carboxyl would still be protected as an ester (9). Decarboxylation would result in loss of the unlabeled carboxyl exclusively. The effect would be an exchange of unlabeled CO_2 for $^{14}CO_2$ without dilution of specific activity.

We attempted to implement this idea using the methyl ester (5a). Addition of a THF solution of (5a) to a THF solution of lithium diisopropylamide at -78° gave a red solution of the ester enolate (6a). $^{14}CO_2$ was distilled into the reaction and after 15 minutes the remaining (6a) was quenched with cold CO_2.

When the reaction was worked up, only the starting material (5a) was isolated (80%). There was no trace of the expected monomethyl malonate (7a). Apparently, the malonic acid derivatives of (5a) are too unstable to isolate.* However, this method should be quite useful with more stable methyl malonates. Furthermore, if maximum specific activity is not essential, then the carbonation/decarboxylation procedure described here for the preparation of ^{14}C-carboxylic acids from α-lithiated carboxylates should be a useful addition to the radiochemist's repertoire, especially when convenient precursors are not readily available.

EXPERIMENTAL

Barium carbonate-^{14}C (53.7 mCi/mmol) was purchased from Amersham Corp. All solvents were reagent grade, except as noted, and were used without purification. Radiochemical purity was determined by radio-TLC using a Packard Model 7201 Radiochromatogram Scanner. Radioactivity was determined using a Packard Tricarb Model 574 Liquid Scintillation Counter.

6,11-Dihydrodibenzo[b,e]thiepin-11-one-3-yl acetic-[^{14}C] acid (4)

A round bottom flask with side-arm and rubber septum was connected to a vacuum line and evacuated. Tetrahydrofuran (20 ml) was vacuum distilled from $LiAlH_4$ into the reaction flask and cooled to 0°. Diisopropylamine (.360 ml, 2.7 mmol) was injected through the side-arm followed by n-BuLi (1.6 ml of 1.6 M hexane solution, 2.56 mmol) and the reaction was stirred for 15 minutes. After cooling to -78° HMPA (0.60 ml, 3.3 mmol) was injected and stirring was continued for an additional 30 minutes. Injection of a THF solution of (1) (426 mg, 1.5 mmol) resulted in instantaneous formation of the red-purple dianion (2). Barium carbonate-^{14}C (40 mCi, 0.745 mmol, 53.7 mCi/mmol, Amersham Corp.), contained in a side-arm round bottom flask and connected to the vacuum line via a Drierite

*Two attempts to trap the monomethyl malonate (7a), first using i-propylbromide/DMF and then the much more reactive trifluoromethanesulfonate, resulted only in recovery of starting material (5a). In each case the alkylating agent was injected into the reaction mixture at -78° after the enolate (6a) had been quenched with CO_2. The reaction was then allowed to come to room temperature, stirred overnight and worked up.

tower, was acidified with H_2SO_4. The $^{14}CO_2$ thus generated was distilled into the reaction vessel containing (2). After 15 minutes, excess unlabeled CO_2 was distilled (through the Drierite tower) into the reaction vessel. Stirring was continued until the dianion (2) had completely reacted (as evidenced by the disappearance of the red-purple color). The reaction mixture was treated with saturated NH_4Cl (5 ml), degassed, and poured into 10% HCl (100 ml). Extraction with ethyl acetate afforded the crude product (27 mCi) which was purified by column chromatography (SiO_2; ethyl acetate-hexane-acetic acid, 30:70:1). The fractions containing pure (4) were washed with water to remove acetic acid, then dried over Na_2SO_4 and taken to dryness yielding the product as a white crystalline solid (9.57 mCi, 9.12 mCi/mmol, 298 mg, 1.05 mmol).

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8. We can offer no obvious explanation for the lower than expected specific activity of the product. Two possible reasons, however unlikely, may be (a) incomplete transfer of $^{14}CO_2$ to the reaction vessel and (b) a low n-BuLi titre. Since we did not titrate the n-BuLi and it was not a fresh bottle, (b) may have some credibility.