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Synthesis of Carbon-11 Labelled Amides *via* Carbonylation of Lithium Dialkylamides

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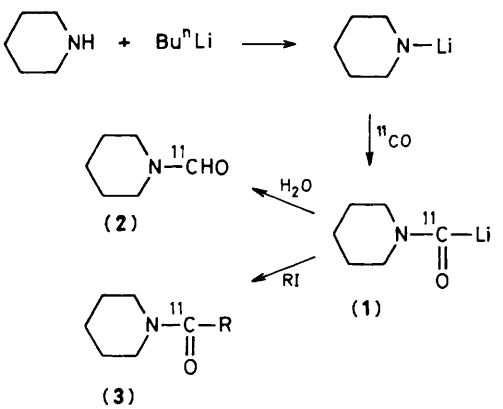
Carbon-11 labelled carboxylic acid amides can be prepared by the carbonylation (^{11}CO) of lithium dialkylamides.

Carbon-11 ($\beta+$ decay, $t_{\frac{1}{2}}$ = 20.4 min) labelled compounds have recently found important application in medical research using Positron Emission Tomography (P.E.T.).[1] There is a growing demand for carbon-11 labelled compounds, and thus a corresponding need for new methods of synthesis of complicated organic molecules labelled with carbon-11. We report here a new method of labelling with carbon-11, the labelling of carboxylic acid amides *via* the carbonylation (with ^{11}CO) of lithium dialkylamides. This synthesis has the novel aspect of forming, *in situ*, a highly reactive radiolabelled intermediate which can be converted into numerous products.

No-carrier-added carbon-11 labelled carbon dioxide was prepared by the $^{14}N(p,\alpha)^{11}C$ and $^{10}B(d,n)^{11}C$ nuclear reactions, using the Washington University Medical School cyclotrons.[2,3] This was reduced to ^{11}CO by passage (helium carrier gas) through a 400 °C furnace packed with zinc adsorbed on asbestos.[3] In this manner large quantities (>100 mCi) of ^{11}CO are readily available.

Bubbling a stream of ^{11}CO in helium into a cold (−78 °C) solution of lithium piperidide in tetrahydrofuran/dimethoxyethane resulted in the trapping of 10—20% of the ^{11}C activity, presumably in the form of the unstable acyl anion salt (**1**),[4] as shown in Scheme 1. Quenching of this intermediate with water or a solution of alkyl iodide resulted in the formation of the formamide (**2**) and the amide (**3**), respectively. In this manner we have prepared [^{11}C]*N*-formylpiperidine (14%), [^{11}C]*N*-acetylpiperidine (12%), and [^{11}C]*N*-propionylpiperidine (15%). Synthesis times (from $^{11}CO_2$ reduction) are very short (5—7 min). The only other carbon-11 labelled product identified (g.l.c. and h.p.l.c.) was a 15—20% yield (of trapped ^{11}C) of [1-^{11}C]pentanoic acid, which arises from reaction of trace amounts of $^{11}CO_2$ with small amounts of n-butyl-lithium left from formation of the lithium dialkylamide.

This synthesis achieves the rapid preparation of ^{11}C-labelled amides in a single step and single reaction vessel. Such a procedure is an alternative to the two step synthesis of ^{11}C-amides *via* carbonation ($^{11}CO_2$) of organolithium or Grignard reagents to form the ^{11}C-acid, followed by amide formation.[5] The ^{11}C-labelled amides are easily separated from the ^{11}C-pentanoic acid by extraction of the latter into dilute aqueous base, and can be separated from the chemical impurities piperidine and/or *N*-alkylpiperidine by extraction of these amines into dilute aqueous mineral acid. Alternatively, the products can be easily separated by reverse-phase h.p.l.c.



Scheme 1

This successful carbonylation of lithium dialkylamides with trace amounts of ^{11}CO is in contrast to other reported carbonylation reactions,[4,6-9] where excess of CO is used either as a continuous flow of pure CO, or a pure (possibly pressurized) CO atmosphere. The synthesis with trace amounts of ^{11}CO eliminates problems, noted by earlier workers, of secondary reactions of the acyl anion salt (**1**) with a second molecule of carbon monoxide.[4,6,7] Such secondary reactions are extremely unlikely in a synthesis involving high specific activity ^{11}CO.

The versatility of a carbonylation reaction is particularly appealing. Variation in structure of dialkylamide and alkylating agent should allow the synthesis of many ^{11}C-labelled

carboxylic acid amides. These amides can be readily reduced to the corresponding ^{11}C-amines; we have prepared [^{11}C]*N*-methylpiperidine in 5% overall yield by diborane reduction[10] of the formamide (**2**). Finally, acyl anion salts such as (**1**) will also add to carbonyl compounds,[4,11,12] providing a method for the synthesis of ^{11}C-labelled α-hydroxycarboxamides.

These results suggest that carbonylation reactions using trace amounts of carbon monoxide may provide the means to label numerous types of compounds with isotopes of carbon (^{11}C, ^{13}C, ^{14}C).

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