

RAPID REDUCTIVE-CARBOXYLATION OF SECONDARY AMINES. ONE POT SYNTHESIS OF  
TERTIARY N-METHYLATED AMINES

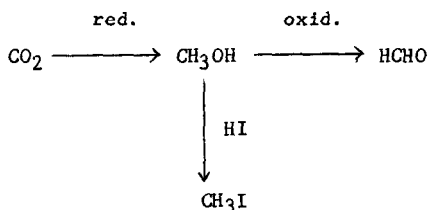
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ABSTRACT

Various tertiary N-methylated amines were synthesized by using a new reductive-carboxylation approach. Secondary amines, on carboxylation with carbon dioxide under moderate reaction conditions, afforded their corresponding carbamate esters, which, on in situ lithium aluminum hydride reduction, gave desired tertiary N-methylated amines in high yield.

N-alkylation of secondary amines is commonly achieved by either reductive methylation with formaldehyde and formic acid derivatives or with methyl iodide.<sup>1-7</sup> In principle, these precursors are derived from the carbon dioxide (Scheme-I). N-alkylation of secondary amines by direct fixation of carbon dioxide is an attractive alternative approach for the above procedures. Recently, a few reports have appeared in the literature<sup>8-9</sup> describing the direct fixation of carbon dioxide by amines, however, these reports have very limited practical value due to the vigorous reaction conditions required and poor yields of the desired final products.

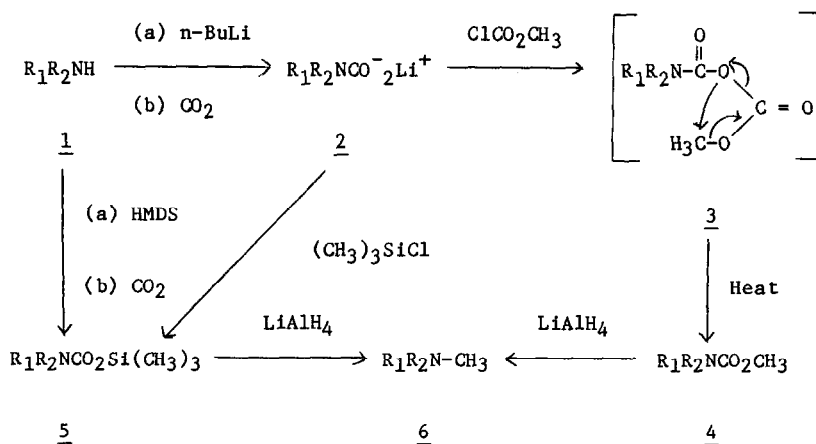
Scheme-I



In our ongoing program, we are interested in the radioisotopic synthesis of <sup>11</sup>C-radiopharmaceuticals (<sup>11</sup>C-half life = 20.4 min) such as N-[<sup>11</sup>C-methyl]-scopolamine, N'-[<sup>11</sup>C-methyl]-imipramine etc. via the readily available <sup>11</sup>C-carbon dioxide labeled precursor for positron emission tomographic (PET) studies. In this paper we wish to report a mild, simple and one pot reductive-carboxylation of secondary amines to the corresponding tertiary N-methylated amines using carbon dioxide under moderate reaction conditions. In this approach, a secondary amine (1) on treatment with n-BuLi, followed by carboxylation with carbon dioxide yielded the lithio salt of a carbamic acid (2), which on reaction with either trimethyl chlorosilane or methyl chloroform-

mate gave trimethylsilyl carbamate 5 and methyl carbamate 4 respectively. Compounds 4 or 5 after *in situ* lithium aluminum hydride reduction<sup>10</sup> afforded tertiary N-methylated amines 6. Compound 5 was alternatively prepared by direct carboxylation of N-TMS derivative of amine (1) 11 (Scheme-II).

## SCHEME-II



A typical experimental procedure for conversion of 1 to 6 is as follows.





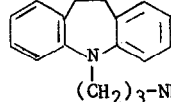
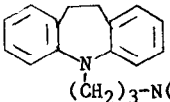
$n\text{-BuLi}$  (7.0 mmole, 6.13 mL solution of 1.55 M  $n\text{-BuLi}$  in hexane) was added under argon to a cold stirred solution of an appropriate secondary amine (6.9 mmole) in dry THF (20 mL) at  $-78^\circ$ . Stirring was continued for 15 min at that same temperature. Bone dry carbon dioxide gas was passed into the above reaction mixture for 10 min at  $-78^\circ$  and 15-20 min at  $55^\circ$ , followed by addition of methyl chloroformate (7.0 mmole) with stirring for an additional 10 min at  $55\text{--}60^\circ$ . To this reaction mixture, lithium aluminum hydride (14.0 mmole) was slowly added and resulting reaction mixture was stirred at reflux temperature for 30 min. The excess of lithium aluminum hydride was decomposed with 20% NaOH solution. The residue was diluted with dry ether (50 mL x 3) and decanted. The combined organic layer was dried over  $\text{Na}_2\text{SO}_4$  and filtered. The filtrate on evaporation, either under reduced or normal pressure, afforded the desired tertiary N-methylated amines (6). The scope of this new reductive-carboxylation is shown in Table I.

Under similar conditions, the reduction of trimethylsilyl carbamates (5) gave a mixture of tertiary N-methylated amine and starting amine in ratio of 90:10, which was confirmed by spectroscopic and analytical data. The recovery of the starting amine may be due to partial hydrolysis decarboxylation of trimethylsilyl carbamate esters. It should be noted that the reduction of silyl esters has been reported to proceed only with difficulty by Larson et al.<sup>12</sup>

The formation of product 4 can be explained via formation of the thermodynamically unstable intermediate 3, which on heating with loss of  $\text{CO}_2$  (from  $\text{ClCO}_2\text{CH}_3$ ), intramolecularly rearranges to methyl carbamate 4 as suggested by Gutman and Boltanski.<sup>13</sup> This hypothesis was further confirmed by synthesis of N'-(4- $^{11}\text{C}$ -methyl) imipramine<sup>14</sup> (6g) from desimipramine (1g) and  $^{11}\text{C}$ -

carbon dioxide in 84% radiochemical yield. Finally methyl carbamates of diisopropylamine (1a) and desimipramine (1g) were isolated from the reaction before  $\text{LiAlH}_4$  reduction and characterized by IR,  $^1\text{H}$  NMR and analytical data.<sup>15</sup>

TABLE I. Reductive-carboxylation of secondary amines to tertiary N-methylated amines.

No.	Secondary amines ( $\text{R}_1\text{R}_2\text{NH}$ )	Product <sup>b</sup> ( $\text{R}_1\text{R}_2\text{N-CH}_3$ )	Yield <sup>a</sup> %	Relative $R_f$ values of product <sup>d</sup>
a	$[(\text{CH}_3)_2\text{CH}]_2\text{NH}$	$[(\text{CH}_3)_2\text{CH}]_2\text{N-CH}_3^c$	79	1.64
b	$\text{CH}_3(\text{CH}_2)_7\text{NHCH}_3$	$\text{CH}_3(\text{CH}_2)_7\text{N}(\text{CH}_3)_2^c$	82	1.62
c			76	2.65
d			82	1.41
e	$\text{C}_6\text{H}_5\text{CH}_2\text{NHCH}_3$	$\text{C}_6\text{H}_5\text{CH}_2\text{N}(\text{CH}_3)_2$	66	1.31
f	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NHCH}_3$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	99	1.28
g	 $(\text{CH}_2)_3\text{-NHCH}_3$	 $(\text{CH}_2)_3\text{-N}(\text{CH}_3)_2$	79	1.25

<sup>a</sup> Isolated yields based on the single experiment and yields were not optimized.

<sup>b</sup> Products were characterized by comparison with authentic samples (IR,  $^1\text{H}$  NMR, TLC).

<sup>c</sup> These were characterized as HCl-salt.

<sup>d</sup> Relative  $R_f$  value = distance travelled by product chromatogram/distance travelled by starting material chromatogram; in  $\text{CH}_2\text{Cl}_2\text{:MeOH:58\% NH}_4\text{OH}$  (9:1:3-drops) system using Analtech silica gel plates.

These results demonstrate a rapid versatile method for the preparation of tertiary N-methylated amines which is applicable for macro as well as micro scale reactions, and radiochemical applications as well.

#### ACKNOWLEDGEMENTS

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- 15) N'-Carbomethoxydiisopropylamine (4a), yield 98%, IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2963, 1705, 1670, 1310, 1365, 1290,  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.23 [d,12H,4x(CH<sub>3</sub>)], 3.67(s,3H,-OCH<sub>3</sub>), 3.70-4.28(m,2H, 2xCH). Anal (C<sub>8</sub>H<sub>17</sub>NO<sub>2</sub>) Calcd. C,60.34; H,10.76; N,8.796; Found C,60.46; H,10.65; N,8.73. N'-(4-carbomethoxy)desimipramine (4g), yield 93%, IR (Neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2950-2920, 2840, 1705, 1595, 768, 750;  $^1\text{H NMR}(\text{CDCl}_3)$   $\delta$  1.74(t,2H,C-CH<sub>2</sub>-C), 2.72(s,3H,N-CH<sub>3</sub>), 3.17(s,3H,OCH<sub>3</sub>), 3.2-4.0(m, 8H,N-CH<sub>2</sub>-C, H<sub>2</sub>C-N-C, CH<sub>2</sub>-CH<sub>2</sub>), 6.9(bs,8H,Ar-H); Anal(C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>) Calcd. C,74.05; H,7.46; N,8.63; Found C,73.94; H,7.36; N,8.71.

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