

# A New Method for Transcarbamation and Amidation from Benzyl Carbamate

Gondi Sudershan Reddy<sup>1\*</sup>

## Affiliations:

<sup>1</sup> Departments of Chemistry, National Taiwan Normal University, Taipei, Taiwan, 116 (ROC).

Correspondence email: [gondisr@gmail.com](mailto:gondisr@gmail.com)

**Abstracts:** A convenient, and efficient method for Transcarbamation and conversion of benzyl carbamates to amide using potassium carbonate in alcohols under heating condition is described.

**Keywords:** Transcarbamation, Benzyl Carbamate, Amidation, Potassium carbonate, Efficient, Conversion

**Introduction:** Carbamate-bearing molecules play an important role in modern drug discovery and medicinal chemistry<sup>1</sup>. Carbamates are widely utilized as a peptide bond surrogate in medicinal chemistry. This is mainly due to their chemical stability and capability to permeate cell membranes. Furthermore, organic carbamates serve an especially important role as optimum protecting groups for amines and amino acids in organic synthesis and peptide chemistry<sup>2</sup>. Transcarbamation is a process interchange of the alkoxy moiety in carbamate moiety. Transcarbamation increases number of functional group transformations reactions can possibly executed than its mono carbamate, without effecting the other functional groups, which further broaden the scope of using carbamate as protecting group<sup>3</sup>.

Benzyl carbamates are susceptible towards hydrogenation<sup>4</sup>, HBr/AcOH<sup>5</sup>, TMSI<sup>6</sup> where it requires initially cleavage, then the resulted amine need to be protected again.

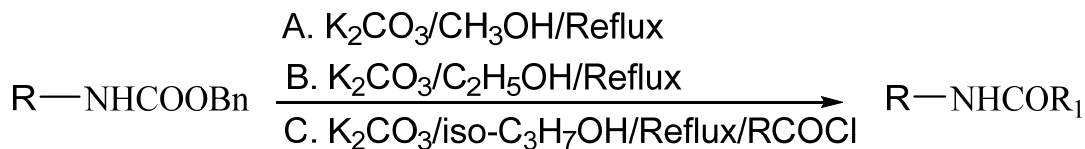
Transcarbamation of benzyl carbamates to alkyl carbamates is very essential. There are few

methods NaOMe<sup>7,8</sup>, NaOH/methanol/65°C<sup>9</sup>, KOH/water/50°C<sup>10</sup>, Dibutyltin maleate<sup>11</sup>, and Tin derivatives<sup>12</sup> were used. So, there is still to need to develop an efficient and convenient method.

Similarly, Amides, like carbamate, they also have long been used in syntheses because they offer the advantage of particularly good stability to a wide range of conditions. there are several routes for the preparation of amides. In most of this reaction, a carboxylic acid is converted into a more reactive intermediate, e.g. an acyl chloride that is then allowed to react with amine in presence of metal<sup>13</sup> or tertiary amine<sup>14</sup>. Attempts have also been made to prepare amide directly from acid using acid activator such as dialkylphosphochloriate<sup>15</sup>, phosphorous-complex<sup>16</sup>, benzoxazole-sulfur dimer<sup>17</sup>, EDC/HOBT<sup>18</sup>. Amides are directly prepared from alcohol<sup>19</sup>, nitrile<sup>20</sup>, oximes<sup>21</sup>, alkane<sup>22</sup>, alkyne<sup>23</sup>, boric acid<sup>24</sup> and thioamide<sup>25</sup>. Transamidation<sup>26-32</sup> is another way to synthesis this class of compounds, Recently conversion of carbamates<sup>33-37</sup> to amides in single step process gaining attention because it is more advantageous than the simple amide synthesis from acid chloride and amine, due to poor solubility of some of amines in organic solvents, whereas the carbamates are commonly soluble in most of the solvents. Some carbamates, especially benzyl carbamates are readily available and thus serve conveniently as starting materials.

**Present work:** In continuation of work to develop new methods for functional transformation using green chemistry protocols or using easily accessible reagents, here we reporting an extremely simple but mild and convenient procedure for Transcarbamation by using Benzyl carbamate and its conversions to Amides, using potassium carbonate in alcohols under heating conditions.

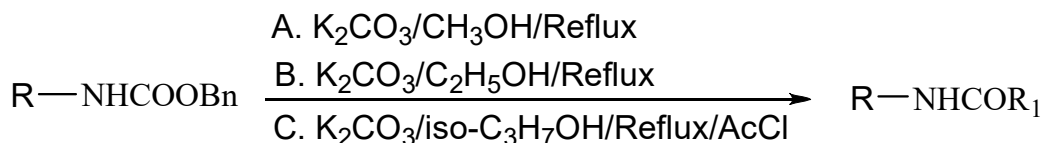
### Scheme-1



R = Alkyl, Aryl, R<sub>1</sub> = OCH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>, CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>

When treated CBZ protected phthalides (**1a** & **1b**) in primary alcohols, methanol (Method-A) or ethanol (Method-B) using potassium carbonate, obtained transcarbamation products **2a,3a,2b** and **3b** in 75-81% yield. Repeated same reactions in secondary alcohol, isopropyl alcohol and obtained the amide **4a** and **4b** respectively in 71-81% yield, by treating acid chloride with corresponding potassium salt obtained, after concentration. When these reactions are repeated in t-butyl alcohol, only recovered starting materials.

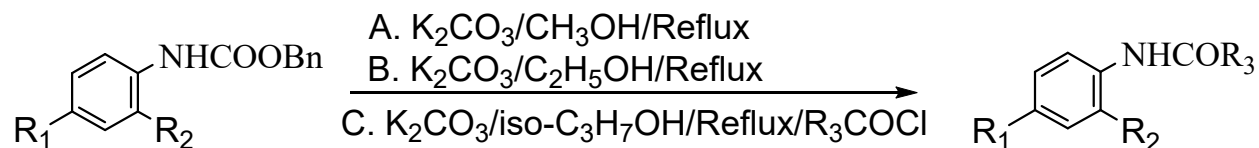
Table-1



Entry	Substrate	R	R <sub>1</sub>	Method	Time (h)	Yield (%)
1	1a	7-IsoBenzofuranyl	OCH <sub>3</sub>	A	18	2a,78
2	1a	7-IsoBenzofuranyl	OC <sub>2</sub> H <sub>5</sub>	B	18	3a,76
3	1a	7-IsoBenzofuranyl	CH <sub>3</sub>	C	18	4a,81
4	1b	4-IsoBenzofuranyl	OCH <sub>3</sub>	A	24	2b,75
5	1b	4-IsoBenzofuranyl	OC <sub>2</sub> H <sub>5</sub>	B	24	3b,81
6	1b	4-IsoBenzofuranyl	CH <sub>3</sub>	C	24	4b,71
7	1c	Cyclohexyl	OCH <sub>3</sub>	A	18	2c, 80
8	1c	Cyclohexyl	OC <sub>2</sub> H <sub>5</sub>	B	18	3c, 82
9	1c	Cyclohexyl	CH <sub>3</sub>	C	18	4c, 73

Encouraged by this result, various structurally diverse benzyl carbamates (1c in table-1 and 1d-1g in table-2) have been successfully converted into their corresponding methyl, ethyl carbamates and amides in moderate to good yields. The scope of this general procedure is shown in table-2. The products from table-1 and 2 shows that chloro, methoxy, phthalide were sustained in these conditions.

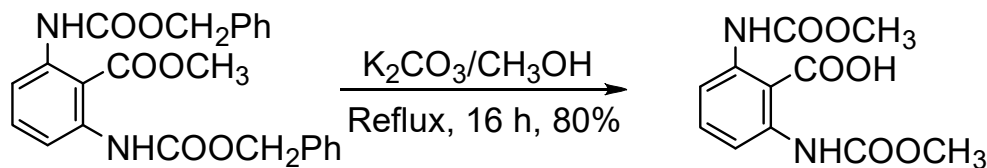
Table-2



Entry	Substrate	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Method	Time(h)	Yield (%)
1	1d	Cl	H	OCH <sub>3</sub>	A	18	2d, 85
2	1d	Cl	H	OC <sub>2</sub> H <sub>5</sub>	B	16	3d, 88
3	1d	Cl	H	CH <sub>3</sub>	C	16	4d, 71
4	1d	Cl	H	C <sub>2</sub> H <sub>5</sub>	C	16	5d, 75
5	1e	OCH <sub>3</sub>	H	OCH <sub>3</sub>	A	16	2e, 80
6	1e	OCH <sub>3</sub>	H	OC <sub>2</sub> H <sub>5</sub>	B	16	3e, 83
7	1e	OCH <sub>3</sub>	H	CH <sub>3</sub>	C	16	4e, 65
8	1e	OCH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	C	16	5e, 73
9	1f	H	OCH <sub>3</sub>	OCH <sub>3</sub>	A	18	2f, 83
10	1f	H	OCH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	B	18	3f, 81
11	1f	H	OCH <sub>3</sub>	CH <sub>3</sub>	C	18	3f, 66
12	1g	H	H	OCH <sub>3</sub>	A	24	2g, 84
13	1g	H	H	OC <sub>2</sub> H <sub>5</sub>	B	24	2g, 82
14	1g	H	H	CH <sub>3</sub>	C	16	2g, 76

When dibenzyl carbamate (scheme-2) under this condition (Method-A), obtained the acid product, **2i** where the esters group are hydrolyzed. Mild reaction condition, simplicity, ease of workup and the low toxicity and environmental impact of metal carbonates in contrast to the hazardous reagents reported in the literature are some of the noteworthy features of this methods. Though this reagent, potassium carbonate is extensively employed in organic synthesis, this new finding further broadens its versatility.

Scheme-2



In conclusion, we have provided a new efficient as well as straight forward procedure for Transcarbamation by using benzyl carbamate in primary alcohols, and conversion of benzyl

carbamates to amide in isopropyl alcohol by employing potassium carbonate, which is relatively inexpensive materials, involves simple workup and afforded Transcarbamation products and Amides in excellent yields.

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■ **Competing interests:** There is no Competing Interests pending.

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