

## Greener Protocol for the Synthesis of Carbamates

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Received 4 July 2022, accepted in final revised form 1 December 2022

### Abstract

An efficient and environmentally friendly protocol has been developed for synthesizing carbamates. Carbamate derivatives are frequently used as pesticides (insecticides, fungicides, and herbicides), as starting materials in producing paints and polyurethanes, and as protecting groups of amines in organic synthesis. It is a simple and solvent-free methodology to prepare primary carbamates in high yield and purity from compounds sodium cyanate, Phenol/alcohol, and TCA (Trichloro acetic acid). We reported the application of TCA as a mild, convenient and effective reagent for this transformation.

**Keywords:** Carbamates; Insecticides; Fungicides and herbicides; Sodium cyanate; Phenol/alcohol; Trichloro acetic acid (TCA).

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doi: <http://dx.doi.org/10.3329/jsr.v15i2.60649> J. Sci. Res. 15 (2), 481-488 (2023)

## 1. Introduction

Multi-component reactions (MCRs), by virtue of their flexibility to rapidly assemble three or more reactants and convert them into higher molecular weight compounds in one pot have become very popular in the discovery of biologically active novel compounds due to their experimental simplicity, atom economy and high product yields [1,2]. Heterocyclic compounds have drawn special attention in organic chemistry because of their abundance in natural products and their diverse biological properties [3-6]. The need to develop new green and sustainable methods and processes for chemistry “benign by design” [7-9] has led scientists in both academia and industry to “think chemistry differently”, using safer reagents or solvents, diminishing the generation of toxic and nontoxic waste, and limiting

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solvent use [10]. Mechanochemistry [11-15] is a strong emerging field of research to perform organic reactions in the absence of solvent [16-18].

Carbamate compounds are the esters of carbamic acid that are commonly used as insecticides, fungicides, and herbicides. Carbamates are used as sprays or baits to kill insects by affecting their brains and nervous systems. They are used on crops and in the home to kill cockroaches, ants, fleas, crickets, aphids, whitefly, lace bugs, and mealy bugs. Some carbamates control mosquitoes. When used properly, carbamate pesticides offer significant benefits to society, as they protect and increase agricultural production and human and animal health from insect-vector-mediated diseases. These are also used as starting materials in the production of paints and polyurethanes and as protecting groups of amines in organic synthesis. In recent years, carbamate derivatives have received much attention due to their application in drug design and discovery. The carbamate group is a key structural motif in many approved drugs and prodrugs. There is an increasing use of carbamates in medicinal chemistry, and many derivatives are specifically designed to make drug–target interactions through their carbamate moiety.

In the past few decades, carbamates are growing interest because of their applications in the agrochemicals industry as herbicides, fungicides, and pesticides, in the pharmaceuticals industry as drug intermediates, in the polymer industry, and in the synthesis of polyurethane and peptides [19-25]. These are most commonly prepared from amines and alcohols by carbonylation using phosgene in organic solvents, which are also toxic and flammable [19-21]. These procedures seem to be highly harmful. Many efforts have been made to replace phosgene with carbon dioxide and organic carbonates [26]. However, these methods cannot produce N-unsubstituted (primary) carbamates. Synthesis of N-unsubstituted carbamates from alcohols has also been accomplished by several-pot reaction methods such as; trichloroacetic isocyanate [27,28], chloroformates (starting from toxic phosgene) [29], chlorosulfonyl isocyanate [30] and cyanogen chloride [31,32], activated N-acyl imidazolium [33], *N*-tosylhydrazones [34]. These solvents are toxic and are not eco-friendly; from the standpoint of ‘green chemistry, significant efforts have been made to find an alternative to organic solvents. Here we have reported a simple and solvent-free reaction to synthesize carbamates in high yield and purity from sodium cyanate, Phenol/alcohol and TCA.

## **2. Experimental**

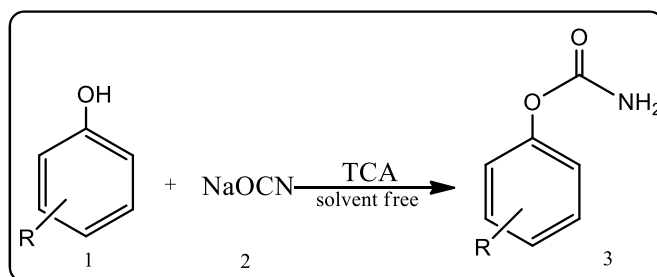
### **2.1. Materials and Instruments**

All chemicals were purchased from commercial sources and used without further purification. Analytical samples were dried at room temperature. The melting points were recorded on a Buchi B2540 microscopic melting apparatus. Infrared (IR) spectra were obtained on a Bruker-Equinox 55 spectrophotometer in KBr pellets. The <sup>1</sup>H-NMR spectra were measured on a Bruker 400 NMR spectrometer in CDCl<sub>3</sub> solution using TMS as an internal standard. Chemical shifts (δ) were reported in parts per million (ppm). Mass spectra were measured with an API 2000 spectrometer.

## 2.2. Methodology

### 2.2.1. Procedure for the synthesis of carbamate derivatives

Primary carbamates **3a-j** were prepared in high yields and in high purity from a reaction of either alcohol or phenol **1** with sodium cyanate **2** in the presence of TCA at 55° C for the appropriate time, as shown in Table 1 and Scheme 1.



Scheme 1. Synthesis of carbamate derivatives.

## 2.3. Characterization

### 2.3.1. Spectral data of the synthesized carbamate derivatives

**Phenyl carbamate 3(a):** White solid, M.P. = 155-156 °C; IR (KBr)  $\text{cm}^{-1}$ : 2143.97 (N-H str), 1606(C=O Str), 1541 (Aromatic, C=C Str),  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.09 (m, 2H), 7.44-7.24 (m, 3 H), 6.13 (m, 2 H). ESI-MS  $m/z$ (%): 138  $[\text{M}+\text{H}]^+$  (100).

**p-tolyl carbamate 3(b):** White solid, M.P. = 162-163 °C; IR (KBr)  $\text{cm}^{-1}$ : 2212.16 (N-H str), 1664 (C=O Str), 1450 (Aromatic, C=C Str),  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.67-7.63 (m, 2H), 7.44-7.42 (m, 2 H), 7.16-7.14(m, 2 H), 3.07 (s, 3 H) . ESI-MS  $m/z$  (%): 152  $[\text{M}+\text{H}]^+$  (100).

**2-methoxyphenyl carbamate 3(c):** White solid, M.P. = 187-188 °C; IR(KBr)  $\text{cm}^{-1}$ : 2127.13 (N-H str), 1624 (C=O Str), 1552 (Aromatic, C=C Str),  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08-8.04 (m, 2H), 7.44-7.28 (m, 2 H), 6.89-6.87 (m, 2 H), 1.59 (s, 3 H). ESI-MS  $m/z$  (%): 168  $[\text{M}+\text{H}]^+$  (100).

**4-nitrophenyl carbamate 3(d):** White solid, M.P. = 184-185 °C; IR (KBr)  $\text{cm}^{-1}$ : 2132.86 (N-H str), 1636(C=O Str), 1496 (Aromatic, C=C Str),  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.24-8.22 (m, 2H), 7.56-7.39 (m, 2 H), 4.96 (m, 2 H). ESI-MS  $m/z$  (%): 183  $[\text{M}+\text{H}]^+$  (100).

**4-chlorophenyl carbamate 3(e):** White solid, M.P. = 165-166 °C; IR (KBr)  $\text{cm}^{-1}$ : 2111.47 (N-H str), 1627 (C=O Str), 1565 (Aromatic, C=C Str),  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.67-7.63 (m, 2H), 7.28-7.24 (m, 2 H), 6.89-6.87(m, 2 H). ESI-MS  $m/z$  (%): 172  $[\text{M}+\text{H}]^+$  (100).

**2-hydroxyphenyl carbamate 3(f):** White solid, M.P. = 197-198 °C; IR (KBr)  $\text{cm}^{-1}$ : 2142.77 (N-H str), 1676(C=O Str), 1572 (Aromatic, C=C Str),  $^1\text{H NMR}$  (400 MHz,

$\text{CDCl}_3$ ):  $\delta$  8.86 (m, 2H), 7.24-7.13 (m, 2 H), 6.29-5.73 (m, 2 H). ESI-MS  $m/z(\%)$  :154  $[\text{M}+\text{H}]^+$  (100).

**4-bromophenyl carbamate 3(g):** White solid, M.P. = 167-168 °C; IR (KBr)  $\text{cm}^{-1}$ : 2413.91 (N-H str), 1646 (C=O Str), 1514 (Aromatic, C=C Str),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.72-8.60 (m, 2H), 7.26-7.21 (m, 2 H), 6.22-5.93 (m, 2 H). ESI-MS  $m/z(\%)$  :217  $[\text{M}+\text{H}]^+$  (100).

**2-nitrophenyl carbamate 3(h):** White solid, M.P. = 175-176 °C; IR (KBr)  $\text{cm}^{-1}$ : 2134.17 (N-H str), 1660(C=O Str), 1538 (Aromatic, C=C Str),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96-7.82 (m, 2H), 7.22-7.09 (m, 2 H), 6.19-5.83 (m, 2 H). ESI-MS  $m/z(\%)$  :183  $[\text{M}+\text{H}]^+$  (100).

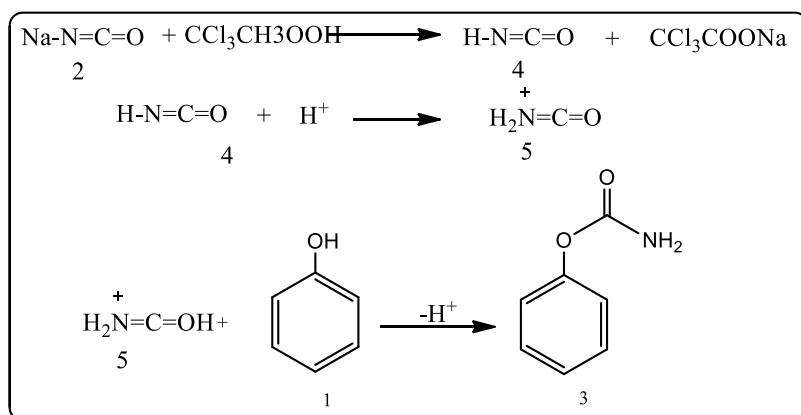
**2-chlorophenyl carbamate 3(i):** White solid, M.P. = 162-163 °C; IR (KBr)  $\text{cm}^{-1}$ : 2431.43 (N-H str), 1636(C=O Str), 1525 (Aromatic, C=C Str),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.56-8.27 (m, 2H), 7.29-7.23 (m, 2 H), 6.29-5.72 (m, 2 H). ESI-MS  $m/z(\%)$  :172  $[\text{M}+\text{H}]^+$  (100).

**4-methoxyphenyl carbamate 3(j):** White solid, M.P. = 185-186 °C; IR (KBr)  $\text{cm}^{-1}$ : 2137.65 (N-H str), 1676(C=O Str), 1572 (Aromatic, C=C Str),  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.24 (m, 2H), 7.29-7.23 (m, 2 H), 5.97-5.73 (m, 2 H), 3.32 (s, 3 H). ESI-MS  $m/z(\%)$  :168  $[\text{M}+\text{H}]^+$  (100).

### 3. Result and Discussion

#### 3.1. Plausible mechanism for the formation of carbamate

The present feasible reaction mechanism resembles the recently reported one [33-35] illustrated in Scheme 2. The reaction of sodium cyanate **2** with TCA to produce isocyanic acid **4** could be the first step. Next, for the generation of intermediate **5**, the proton of TCA is added to isocyanic acid **4** that the proton is perfectly added to nitrogen rather than oxygen. Finally, carbamate **3** is likely to be formed when either alcohol or phenol **1** attacks the carbon of intermediate **5** (Scheme 2).

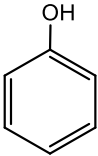
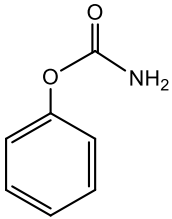
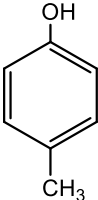
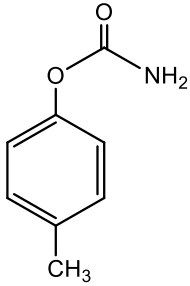
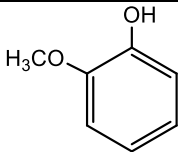
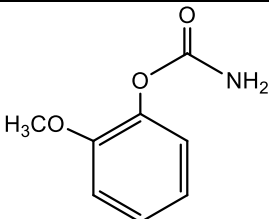
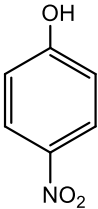
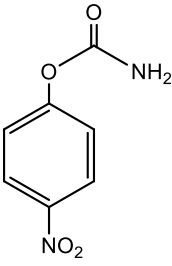


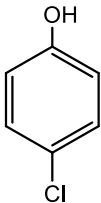
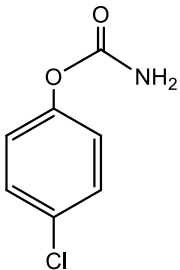
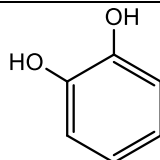
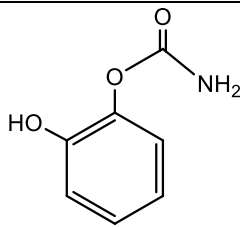
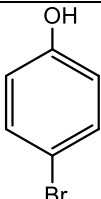
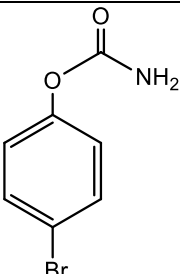
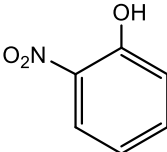
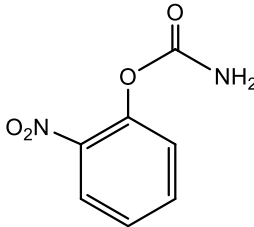
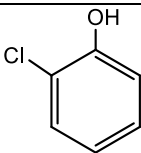
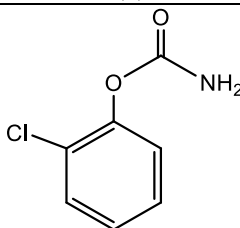
Scheme 2. A plausible mechanism for the formation of carbamate derivatives.

### 3.2. Effect of temperature on synthesis of carbamate derivatives

The reaction temperature for carbamate formation with TCA is 55 °C, presented in Table 2. It is observed that at below 55 °C temperature, the product yield is low, and the reaction time is high. So we have confirmed 55 °C is a suitable temperature for this reaction.

Table 1. Synthesis of carbamate derivatives.

Sl. No.	Phenol	Carbamate (Product)	Time (min)	Yield (%)
1	 1(a)	 3(a)	30	96
2	 1(b)	 3(b)	35	96
3	 1(c)	 3(c)	35	95
4	 1(d)	 3(d)	30	96

5	 1(e)	 3(e).	30	96
6	 1(f)	 3(f)	35	95
7	 1(g)	 3(g)	35	96
8	 1(h)	 3(h)	35	95
9	 1(i)	 3(i)	35	96

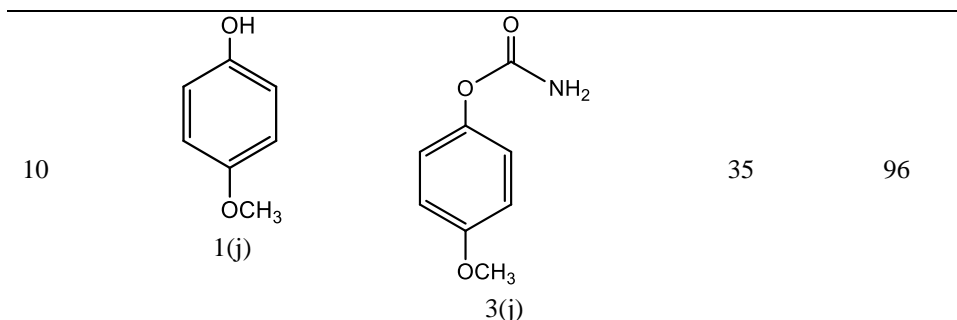


Table 2. Effect of temperature on the formation of carbamate derivatives.

Sl. No.	Catalyst	Temperature (°C)	Time (min)	Yield (%)
1	TCA	R.T.	180	60
2	TCA	35	120	75
3	TCA	40	50	80
4	TCA	55	30	96

#### 4. Conclusion

In conclusion, this simple solvent-free method affords various primary carbamates at normal temperatures in short reaction times, with high yields and purity, with nontoxic reagents, and inexpensive starting materials, without the formation of any undesirable by-products. Also, we have revealed that trichloroacetic acid is a highly effective reagent for synthesizing primary carbamates. However, to our knowledge, there has been no report on the use of TCA for primary carbamates synthesis.

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