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Chemoselective Synthesis of Carbamates using CO_2 as Carbon Source

Daniel Riemer, Pradipbhai Hirapara, and Shoubhik Das*[a]

Synthesis of carbamates directly from amines using CO_2 as the carbon source is a straightforward and sustainable approach. Herein, we describe a highly effective and chemoselective methodology for the synthesis of carbamates at room temperature and atmospheric pressure. This methodology can also be applied to protect the amino group in amino acids and peptides, and also to synthesize important pharmaceuticals.

Transformation of CO_2 to value-added products is attracting more and more attention from both academia and governmental agencies all over the world, as CO_2 is an easily available and sustainable carbon resource with the advantage of being abundant, nontoxic, nonflammable, and renewable. However, the main drawback of utilizing CO_2 is its high thermodynamic stability and kinetic inertness.[1–3] So far, epoxides, aziridines, and strong nucleophiles, such as Grignard reagents, organo lithium, organo boranes or organo zinc reagents, have been used to cross over this thermodynamic stability through the formation of new C–C bonds using CO_2.[4] Whereas many efforts have already been paid for the C–C bond formation, formation of carbon–heteroatom bonds, especially C–N bonds using CO_2, is also an emerging target to the organic chemists.[5,6] To reach towards the practical summit for the C–N bond formation, reaction conditions need to be mild, preferably at atmospheric pressure and low temperature. For this purpose, finding new methodologies and reaction conditions are always welcome.

C–N bond formation can also be done through the formation of carbamates.[7] In general, organic carbamates are highly important in the field of pharmaceuticals (Figure 1) and agriculture.[8] They also play an important role in the area of synthetic organic chemistry, particularly as synthetic intermediates for the protection of amino groups in peptide chemistry and as linkers in combinatorial chemistry. Traditional synthesis of these organic carbamates requires specialized reagents and an operational complexity owing to the use of either toxic or cumbersome reagents, such as phosgene, its derivatives, and carbon monoxide.[9] Replacing these reagents by CO_2 will be straightforward and highly sustainable.

Different homogeneous and heterogeneous metal catalysts based on Ru, Sn, Al, and Au are well-known for the conversion of amines to carbamates using CO_2 as the carbon source.[10] Macrocyclic polyether and potassium superoxide have also been used to improve the reaction conditions.[11] Except these, various inorganic and organic base-catalyzed or mediated transition metal-free systems have been developed recently.[12] Notably, all of these methodologies include either harsh reaction conditions, like high temperature and pressure, or additional reagents and exhibit poor functional group tolerance. Therefore, development of new, effective, and chemoselective methodology, which works under room temperature (RT) and at atmospheric pressure using CO_2 as the carbon source, remains important.

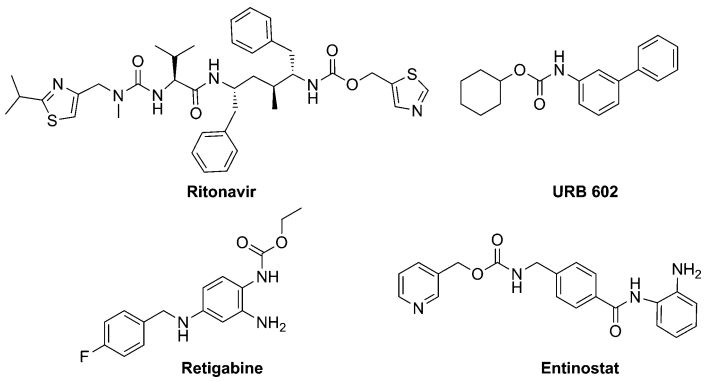

Figure 1. Important drugs having organic carbamate structures.

Inorganic and organic bases have already shown powerful applications for the CO_2 fixation onto organic molecules.[13] Additionally, they have clear advantages of ready availability, low cost, and low toxicity, which provide a direct benefit in the production of pharmaceutical intermediates. Inspired by this information, and also our own interest to develop a mild and chemoselective system for this reaction, we started to develop a transition metal-free system for the synthesis of carbamate derivatives using *p*-anisidine as the model substrate. Several inorganic and organic bases were investigated for the reaction of *p*-anisidine (**1 a**) with a CO_2 balloon and ethyl iodide (EtI) as an alkylating agent for the model system to identify and optimize potential reaction parameters (Table 1). At the end of the reaction, iodide salt formed from EtI and different bases. In the presence of 1 equivalent of Cs_2CO_3 (Table 1) at RT, the corresponding product ethyl (4-methoxyphenyl)carbamate (**1 b**) was

[a] *D. Riemer, P. Hirapara, Dr. S. Das*
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität Göttingen
Tammannstr. 2, 37077 Göttingen (Germany)
shoubhikdas.uni-goettingen.de
E-mail: shoubhik.das@chemie.uni-goettingen.de

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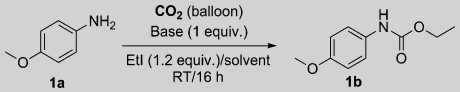
Table 1. Optimization of reaction conditions using 4-methoxyaniline as the model substrate.[a]



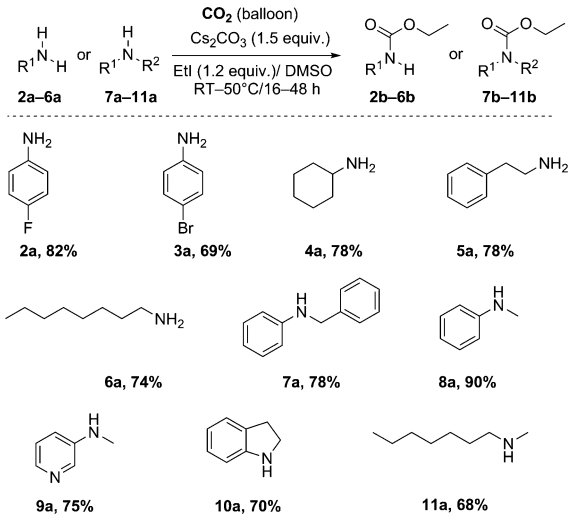
Entry	Base (equiv.)	Solvent	Yield [%][b]
1	Cs_2CO_3 (1.0)	DMSO	62
2	KOH (1.0)	DMSO	1
3	DBN (1.0)	DMSO	54
4	DMAP (1.0)	DMSO	1
5	Et_3N (1.0)	DMSO	0
6	KO*t*Bu (1.0)	DMSO	10
7	Pyridine (1.0)	DMSO	1
8	K_2CO_3 (1.0)	DMSO	57
9	Na_2CO_3 (1.0)	DMSO	22
10	Cs_2CO_3 (1.5)	DMSO	92
11	Cs_2CO_3 (1.5)	DMF	69
12	Cs_2CO_3 (1.5)	THF	0
13	Cs_2CO_3 (1.5)	DMA	68
14	Cs_2CO_3 (1.5)	toluene	0

[a] Reaction conditions: 4-methoxyaniline (0.5 mmol), base, solvent (2.5 mL), EtI (1.2 equiv.), CO_2 (balloon), RT, 16 h. [b] Yield determined by GC using *n*-dodecane as an internal standard.

obtained in 62% within 16 h. Among other carbonates, only K_2CO_3 worked similar to Cs_2CO_3 (Table 1, entries 8–9). After increasing the Cs_2CO_3 loading to 1.5 equivalents, the corresponding yields reached to 92%. We were also pleased to find that the model reaction was easily performed on a 1 g scale without any special precaution and 87% product was isolated. Surprisingly, except 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) and K_2CO_3, no other bases have shown such reactivity in this reaction. The reaction yield was suppressed in *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) and did not show any activity in other solvents, such as tetrahydrofuran (THF) and toluene. We believe, this solvent effect was owing to the fact that nucleophilicity and basicity of the amines were governed by the solvation and polarization in different solvents.[14]

With this optimized conditions in hand, the scope and limitations of this carbamate synthesis protocol were explored (Scheme 1). A number of amines including aromatic, heteroaromatic, alicyclic, and aliphatic were smoothly reacted with high yields up to 90%. Both electron-donating and electron-withdrawing substituents on the aromatic ring at the *para* position reacted well although amines with electron-withdrawing groups had sluggish reaction rate (substrates **1a**–**3a**). Non-symmetric amines also reacted well under the optimized reaction conditions (substrate **7a**). Furthermore, *para*-halogen-substituted amines gave the corresponding products up to 82% yield (substrates **2a**–**3a**) and in none of the cases we observed any reductive dehalogenated product. Interestingly, heterocyclic amines, such as pyridine and indoline (substrates **9a**–**10a**), reacted excellently. Parallel to the primary amines, secondary amines (substrates **8a**–**11a**) also reacted in the similar fashion.

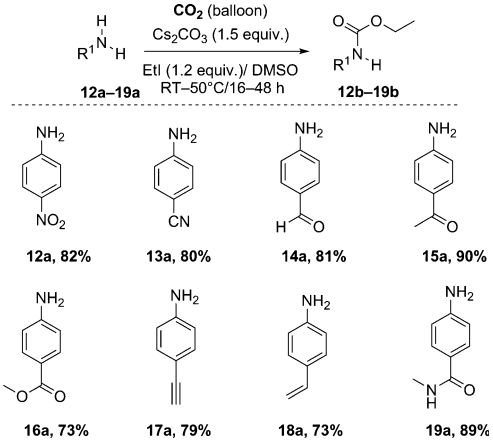
Functional group tolerance in chemical reactions is highly important to find its application for the synthesis of natural



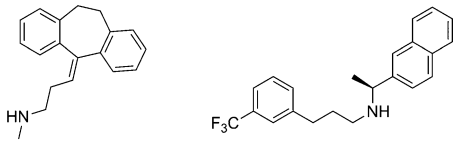
Scheme 1. Synthesis of carbamates using CO_2 as the carbon source. [a] Reaction conditions: Substrates (0.5 mmol), Cs_2CO_3 (1.5 equiv.), DMSO (2.5 mL), EtI (1.2 equiv.), CO_2 (balloon), RT–50 °C, 16–48 h. [b] All are isolated yield.

products and pharmaceuticals.[15] The chemoselective nature of this reaction system was investigated in the presence of different reducible functional groups (Scheme 2). Under our optimized reaction conditions, nitrile-, nitro-, double-bond-, triple-bond-, amide-, ester-, and carbonyl-substituted amines were well tolerated, and thereby provided the corresponding carbamate products in good to excellent yield. It should be noted that in all of the cases no additional reaction of the different functional groups was observed, and thereby demonstrated the excellent chemoselectivity of this reduction process. To the best of our knowledge there is no other example of this type of selectivity for the carbamate synthesis.

Organic carbamates have cardinal role in modern drug discovery and in medicinal chemistry owing to their structural similarity with the amide-ester hybrid features and exhibit excellent chemical and proteolytic stabilities. Additionally, form-



Scheme 2. Functional group tolerance for the carbamate synthesis using CO_2 as the carbon source. [a] Reaction conditions: Substrates (0.5 mmol), Cs_2CO_3 (1.5 equiv.), DMSO (2.5 mL), EtI (1.2 equiv.), CO_2 (balloon), RT–50 °C, 16–48 h. [b] All are isolated yields.



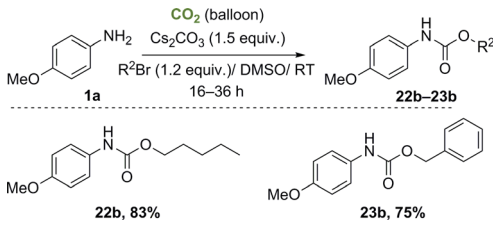
nortriptyline (**20a**), **86%** cinacalcet (**21a**), **82%**

Figure 2. Pharmaceuticals underwent carbamate synthesis using CO_2 as a carbon source. [a] Reaction conditions: substrates (0.5 mmol), Cs_2CO_3 (1.5 equiv.), DMSO (2.5 mL), EtI (1.2 equiv.), CO_2 (balloon), RT, 16 h. [b] All are isolated yields.

ing hydrogen bonds through the carboxyl group and amine moiety allow them to enhance biological as well as pharmacokinetic properties.[8,16] For this purpose, we have chosen nortryptyline and cinacalcet (Figure 2) under our optimized reaction conditions. It should be noted that both of the substrates reacted excellently, up to 86% yield was obtained and again selective transformation occurred in presence of the double bond (Figure 2, **20a**). Owing to the purification, no special precaution was needed to purify these products by column chromatography.

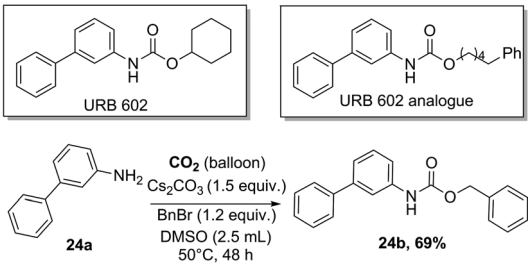
Structural diversifications of organic carbamates represent an important step in pharmaceutical research.[17] This variation of the carbamate scaffold provides a bigger platform for the identification of new bioactive compounds with greater efficiency. To attain this, both the nitrogen and oxygen end of the carbamate structure can be varied. Therefore, parallel to the amines, different other alkyl partners have also been varied to generate a chemical library based on this carbamate structures (Scheme 3). Notably, not only alkyl iodides, but also alkyl bromide can be applied under the optimized reaction conditions. *n*-Pentyl bromide and benzyl bromide were investigated as the alkyl partner along with our model substrate, and a maximum of 83% yield was achieved after stirring with the *n*-pentyl bromide for 4 h.

URB 602 is a selective inhibitor of monoacylglycerol lipase (MAGL), which is involved in the hydrolysis of 2-arachidonylglycerol (2-AG) in the brain.[18] This selective inhibition of MAGL avoids the direct activation of CB1 receptors and leads to less psychoactive side effects. Whereas the selectivity remains excellent in vivo, it completely changes in vitro.[19] Therefore, structural modification of URB 602 is necessary to make it a powerful inhibitor. This modification can be done through isosteric replacement, substitution in the aromatic ring, or by



Scheme 3. Different alkyl bromides used for the synthesis of carbamates. [a] Reaction conditions: substrates (0.5 mmol), Cs_2CO_3 (1.5 equiv.), DMSO (2.5 mL), R^2Br (1.2 equiv.), CO_2 (balloon), RT, 16–36 h. [b] All are isolated yields.

changing the substitution in the oxygen part. Different synthetic routes for this modification have been designed, but by using our direct synthetic protocol, URB 602 derivatives can be synthesized in a single step with a good yield of 69% (Scheme 4). Moreover, with our protocol in hand, a chemical library of this structure can be obtained easily.

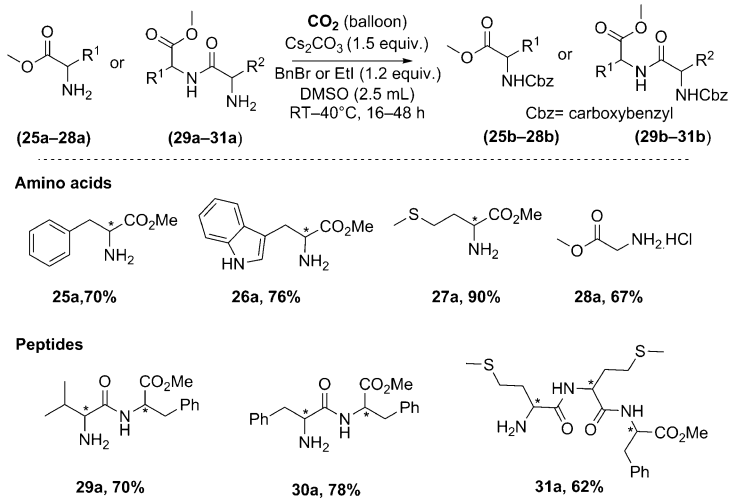


Scheme 4. Synthesis of URB 602 derivative using CO_2 as a carbon source. [a] Reaction conditions: substrates (0.5 mmol), Cs_2CO_3 (1.5 equiv.), DMSO (2.5 mL), BnBr (1.2 equiv.), CO_2 (balloon), 50 °C, 48 h. [b] Isolated yield.

In synthetic organic chemistry, protecting groups play a pivotal role to prevent the formation of undesired side products.[20] Protection of the α-amino group in amino acids and in peptides is also important to prevent polymerization once they are activated for forming peptide bond. These protecting groups should prevent epimerization during peptide bond coupling, be stable enough for the reaction conditions, and deprotection methods should be easy and fast. The most common α-amino protecting groups for the peptide coupling reactions are the carboxybenzyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), and *tert*-butyloxycarbonyl (Boc). Among these Cbz is the most widely used protecting group for peptide synthesis in solution. These protecting groups form the carbamate structures after combing with the α-amino group of amino acids and peptides. Therefore, using our protocol, CO_2 can easily be used as a protecting reagent for the amine functionality in synthetic organic chemistry as well as in peptide chemistry (Scheme 5). Different amino acids, such as phenylalanine, tryptophan, and methionine, reacted well under the optimized conditions. In fact, the corresponding Cbz protected glycine was obtained in good yield from glycine salt (**28a**) using excess of Cs_2CO_3 (2.5 equiv.).

Extension of using CO_2 as the protecting reagent was achieved by applying on three different peptides that were synthesized by combining corresponding amino acid precursors (Scheme 5, entries **29a**–**31a**). In all cases, peptides reacted well, and up to 78% yield of Cbz-protected peptides was achieved. We did not observe any other by-products. In all cases, products were recovered after washing with excess dichloromethane followed by column purification. We expect that this protection procedure of peptides can easily be applied to other higher series of peptides, and thereby can open up new avenues in peptide-based chemistry and in protecting reagents.

In summary, we have demonstrated an efficient carbamate synthesis protocol starting from amines and using CO_2 as a C1 source. Notably, our methodology has shown a broad sub-



Scheme 5. Protection of amino group in amino acids and peptides using CO_2 as a carbon source. [a] Reaction conditions: substrates (0.5 mmol), Cs_2CO_3 (1.5 equiv.), DMSO (2.5 mL), alkyl halide (1.2 equiv.), CO_2 (balloon), RT–40 °C, 16–48 h. [b] All are isolated yields. [c] Except entry **28 a**, in every cases benzyl bromide was added.

strate scope and an excellent functional-group tolerance, such as nitro, nitrile, ester, double bond, triple bond, amide, and even carbonyl functional groups in the reaction. Furthermore, selective carbamate formation of nortriptyline and cinacalcet was also achieved together with the synthesis of a URB 602 derivative. Finally, this methodology was also applied to the amino acids and peptides to replace the traditional protecting reagents. We believe this methodology could find interest in the synthesis of highly functionalized molecules, natural products, and pharmaceuticals.

Experimental Section

Full details are provided in the Supporting Information.

General procedure for the carbamate synthesis: DMSO (2.5 mL) was transferred into a dry three-neck flask (after three vacuum- and CO_2-purge cycles) charged with the amine (0.5 mmol), Cs_2CO_3 (1.5 equiv.), and connected to a CO_2 balloon. The reaction was monitored by thin layer chromatography and GC–MS. Upon completion, alkyl halide (1.2 equiv.) was taken under nitrogen atmosphere, added to the reaction mixture, and stirred for 2–4 h at RT. The reaction mixture was washed with dichloromethane and ethyl acetate, respectively, and an aqueous workup was performed, the solution was dried with anhydrous sodium sulfate, and the product was purified using column chromatography (eluent: ethyl acetate/hexane and 1% triethyl amine). All yields are isolated yields unless otherwise stated.

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Keywords: carbamates · carbon dioxide · chemoselective · peptides · protecting group

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*D. Riemer, P. Hirapara, S. Das**

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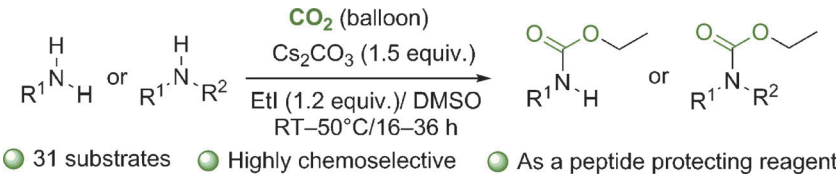
Chemoselective Synthesis of Carbamates using CO_2 as Carbon Source



Diverse tolerance: An efficient carbamate synthesis protocol starting from amines and using CO_2 as a C1 source is demonstrated. The methodology shows a broad substrate scope and excellent functional-group tolerance. The methodology was also applied to amino acids and peptides, replacing the traditional protecting reagents, and could find interest in the synthesis of highly functionalized molecules, natural products, and pharmaceuticals.