



Base-Promoted Coupling of Carbon Dioxide, Amines, and *N*-Tosylhydrazones: A Novel and Versatile Approach to Carbamates**

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Abstract: A base-promoted three-component coupling of carbon dioxide, amines, and *N*-tosylhydrazones has been developed. The reaction is suggested to proceed via a carbocation intermediate and constitutes an efficient and versatile approach for the synthesis of a wide range of organic carbamates. The advantages of this method include the use of readily available substrates, excellent functional group tolerance, wide substrate scope, and a facile work-up procedure.

Organic carbamates constitute an important class of biologically and pharmaceutically interesting compounds that frequently occur in numerous natural products,^[1] agrochemicals,^[2] and medicines.^[3] Representative examples, namely Prezista,^[4] Lunesta,^[5] and VESIcare,^[6] which are used for the treatment of HIV, insomnia, and overactive bladders, respectively, are shown in Figure 1. Moreover,

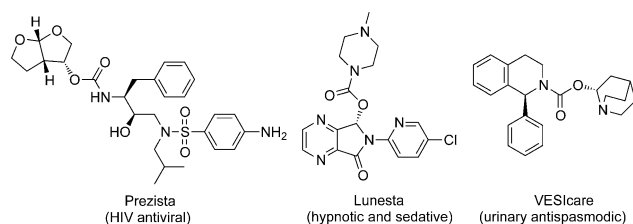


Figure 1. Representative pharmaceuticals containing the carbamate motif.

organic carbamates can also serve as key reagents, target-specific intermediates, and removable protecting groups in organic synthesis.^[7] Conventional methods for accessing such compounds are mainly based on the use of toxic phosgene and isocyanates, which can easily have a detrimental influence on the environment, and their use for the large-scale production

of carbamates is restricted.^[8] Recently, elegant phosgene-free methods, including the catalytic reductive carbonylation of nitro compounds,^[9] the oxidative carbonylation of amines,^[10] the Hofmann and Curtius rearrangements,^[11] and oxidative couplings of formamides with β -ketoesters or 2-carbonyl-substituted phenols,^[12] have also been developed.

From the viewpoints of natural abundance, cost effectiveness, toxicity, and sustainability, the use of carbon dioxide as an alternative to phosgene for the direct synthesis of organic carbamates is highly desirable.^[13] Despite of remarkable advances achieved in the past decades, many of these methods suffer from the use of less environmentally benign halogenated reagents, a limited substrate scope, harsh reaction conditions, and poor chemoselectivity or yields. Therefore, the development of greener methods for the versatile incorporation of CO₂ to yield organic carbamates still remains a demanding goal.

In recent years, *N*-tosylhydrazones have been extensively employed as useful building blocks to construct complex molecules by transition-metal-catalyzed or metal-free cross-coupling reactions.^[14] It is known that the diazo compound, which is generated in situ from the *N*-tosylhydrazone through a Bamford–Stevens process, can decompose to the carbene in aprotic media (Figure 2, path a) or to the carbocation in protic

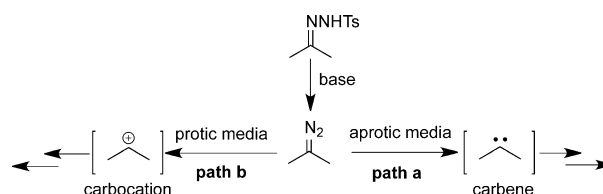


Figure 2. The decomposition of tosylhydrazones and their application in organic synthesis.

media (path b).^[15] Thus far, most of the cross-coupling reactions using *N*-tosylhydrazones as coupling partners are designed to proceed through the former intermediate whereas the corresponding carbocation has been scarcely investigated in organic synthesis. To the best of our knowledge, its application to the fixation of CO₂ has not been explored yet.^[16] As part of our continuing studies on the transformation of CO₂ into useful chemicals,^[17] combined with our interest in the development of new synthetic methods based on *N*-tosylhydrazones,^[18] we herein present an unprecedented strategy for the synthesis of organic carbamates by a three-component coupling reaction of CO₂, amines, and *N*-tosylhydrazones under transition-metal-free conditions.

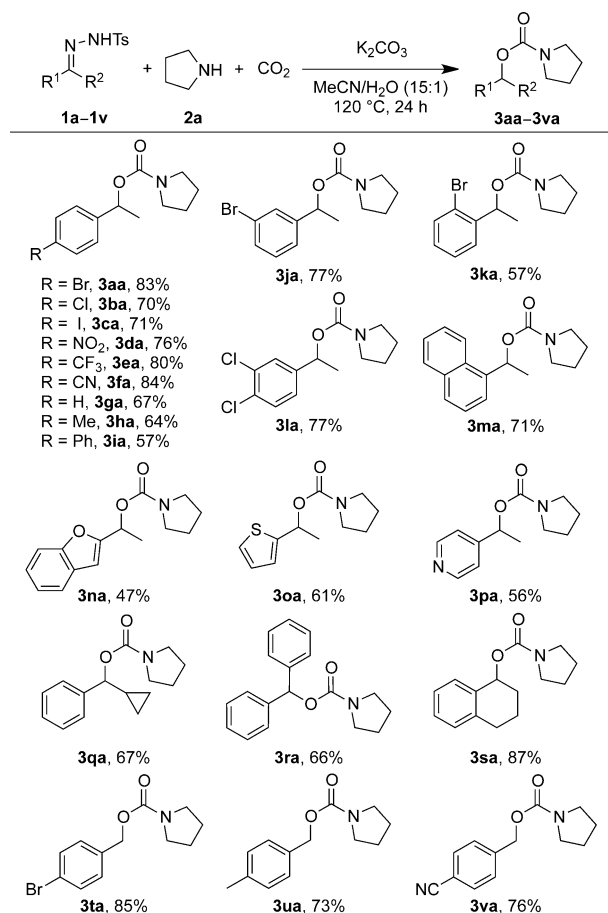
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At the outset of this investigation, we explored the coupling of *N*-tosylhydrazone **1a**, pyrrolidine (**2a**), and CO₂ for the synthesis of **3aa** under different reaction conditions,^[19] and the optimized reaction conditions included the use of K₂CO₃ as the base in a mixed MeCN/H₂O (15:1) solvent system at 120 °C under CO₂ atmosphere (4 MPa) for 24 hours (Scheme 1).

With the optimized reaction conditions in hand, we turned our attention to the scope and limitations of this base-promoted transformation. Gratifyingly, a wide range of *N*-tosylhydrazones with different substitution patterns could be used in this reaction, affording the corresponding organic carbamates in moderate to excellent yields (Scheme 1).

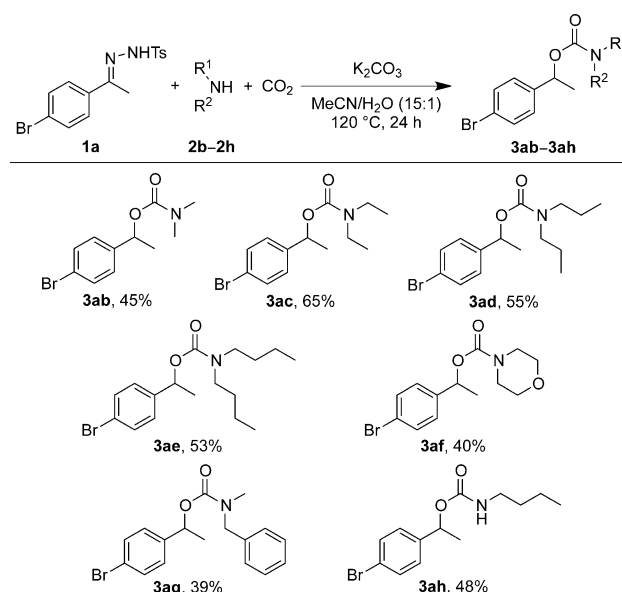


Scheme 1. Synthesis of organic carbamates from a variety of *N*-tosylhydrazones. Reaction conditions: *N*-Tosylhydrazone **1** (0.5 mmol), pyrrolidine (**2a**) (5 mmol), K₂CO₃ (1.5 mmol), CO₂ (4 MPa), MeCN/H₂O (3 mL, 15:1 v/v), 120 °C, 24 h. Yields of isolated products are given. Ts = *para*-toluenesulfonyl.

Notably, the reaction system tolerates a variety of valuable functional groups on the aryl ring of the *N*-tosylhydrazones, including Cl, Br, I, NO₂, CF₃, and CN substituents (products **3aa–3ia**), providing ample potential for further synthetic elaborations. The electronic nature of the substituents on the aryl ring of the *N*-tosylhydrazone influences the product yields significantly. In general, *N*-tosylhydrazones with electron-withdrawing groups furnished the desired products

(**3aa–3fa**) in higher yields than those with electron-neutral or electron-donating substituents (**3ga–3ia**). Interestingly, 3- and 4-substituted substrates gave better yields than 2-substituted substrates (products **3aa**, **3ja**, and **3ka**), which might be attributed to steric hindrance effects. Both disubstituted and 1-naphthyl-substituted *N*-tosylhydrazones smoothly underwent the coupling reaction to afford the desired products **3la** and **3ma** in 77% and 71% yield, respectively. Interestingly, organic carbamates with heterocyclic substituents, such as benzofuryl, thiophenyl, or pyridyl groups (**3na–3pa**), could also be obtained from the corresponding *N*-tosylhydrazones, albeit in moderate yields. *N*-Tosylhydrazones derived from cyclopropyl-(phenyl)methanone, benzophenone, and 3,4-dihydronaphthalen-1(2*H*)-one were also suitable substrates for this transformation, giving the desired products in good to excellent yields (**3qa–3sa**). Pleasingly, *N*-tosylhydrazones derived from various benzaldehydes were compatible with the reaction conditions and were efficiently converted into the corresponding products **3ta–3va** in good yields. However, *N*-tosylhydrazones derived from aliphatic ketones or aldehydes failed to yield even a trace of the desired products; presumably, the lack of a stabilizing group disfavors the formation of essential reaction intermediates.

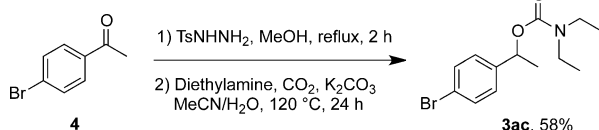
Subsequently, we turned our attention to the utilization of various secondary and primary aliphatic amines (Scheme 2).



Scheme 2. Synthesis of organic carbamates from a variety of amines. Reaction conditions: *N*-Tosylhydrazone **1a** (0.5 mmol), amine (**2b–2h**) (5 mmol), K₂CO₃ (1.5 mmol), CO₂ (4 MPa), MeCN/H₂O (3 mL, 15:1 v/v), 120 °C, 24 h. Yields of isolated products are given.

To our delight, all of the coupling reactions proceeded smoothly and furnished the corresponding products in moderate to good yields under the standard reaction conditions. However, the reaction using aniline as a coupling partner gave rise to a complex mixture, and the desired product was not observed, which could be ascribed to the low basicity and nucleophilicity of aniline.

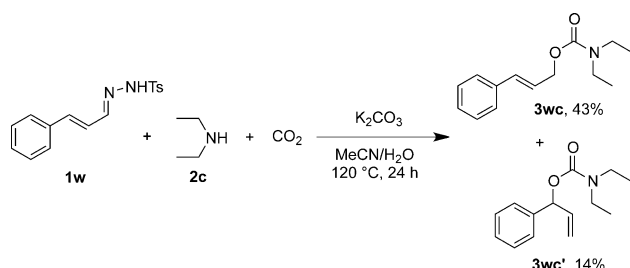
Considering that the *N*-tosylhydrazones are easily obtained by condensation reactions between tosylhydrazides and carbonyl compounds, we then wished to develop a one-pot synthesis of the organic carbamates through the use of *N*-tosylhydrazones generated in situ (Scheme 3). Therefore,



Scheme 3. One-pot synthesis of **3ac**. Reaction conditions: 1) **4** (0.5 mmol), tosylhydrazide (0.5 mmol), reflux, 2 h; 2) diethylamine (5 mmol), K_2CO_3 (1.5 mmol), CO_2 (4 MPa), MeCN/ H_2O (3 mL, 15:1 v/v), 120 °C, 24 h.

a solution of 1-(4-bromophenyl)ethanone (**4**) and tosylhydrazide in methanol was heated to reflux and stirred for two hours, followed by removal of the solvent, and the remaining crude mixture was then treated with K_2CO_3 , pyrrolidine, and CO_2 under the standard reaction conditions. Gratifyingly, the desired product **3ac** could also be obtained in a similar yield to that described in Scheme 2. This reaction demonstrates the potential of this method for the convenient synthesis of various carbamates directly from readily available carbonyl compounds.

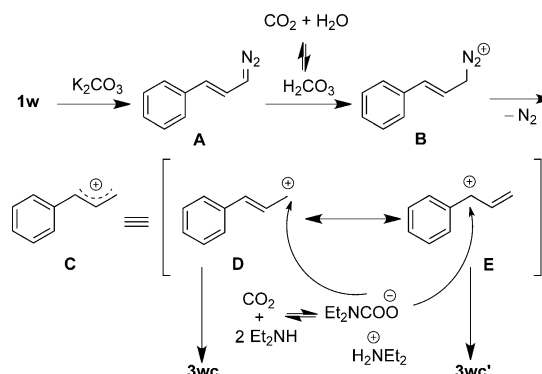
To gain further insights into the nature of this transformation, we conducted the three-component reaction of *N*-tosylhydrazone **1w**, diethylamine (**2c**), and CO_2 under the optimized reaction conditions. Upon isolation, two regioisomers (**3wc** and **3wc'**) were obtained in 43 % and 14 % yield, respectively (Scheme 4).^[20] These results indicate that the



Scheme 4. The three-component reaction of *N*-tosylhydrazone **1w**, diethylamine, and CO_2 . Reaction conditions: 1) **1w** (0.5 mmol), diethylamine (5 mmol), K_2CO_3 (1.5 mmol), CO_2 (4 MPa), MeCN/ H_2O (3 mL, 15:1 v/v), 120 °C, 24 h.

reaction should proceed through the formation of an allylic carbocation intermediate. Moreover, several control experiments and deuterium-labeling experiments were performed, and the results revealed that the reaction between water and CO_2 to form carbonic acid may contribute to the formation of the carbocation (for more details, see the Supporting Information).

Although the mechanism of this carbamate formation has not been fully elucidated at this point, on the basis of the above-described observations as well as related transforma-



Scheme 5. Proposed reaction mechanism.

tions, a plausible mechanism is proposed in Scheme 5. Initially, *N*-tosylhydrazone **1w** undergoes thermal decomposition in the presence of K_2CO_3 to generate diazo compound **A**, which could be protonated by carbonic acid formed from water and CO_2 to provide diazonium ion **B**. Then, the thermodynamically favorable liberation of dinitrogen gives allylic carbocation species **C**,^[15b] which can be described by a resonance hybrid of **D** and **E**. Finally, the carbamate anion, which is generated from the reaction of the amine with CO_2 ,^[13] undergoes nucleophilic attack to **C**, which affords the desired products **3wc** or **3wc'**. It should be pointed out that the final step could also be promoted by K_2CO_3 .^[13e]

In summary, we have developed a novel and versatile reaction of CO_2 with *N*-tosylhydrazones and amines to yield organic carbamates, offering an attractive method for the straightforward synthesis of various carbamates, a privileged motif found in a number of natural and synthetic compounds with extraordinary biological and pharmaceutical properties. Further investigations to extend the substrate scope of this reaction and to deepen our mechanistic understanding of this transformation are ongoing in our laboratory.

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- [19] See the Supporting Information for details.
- [20] 5-Phenyl-1H-pyrazole as the major side product was also isolated in 30% yield.