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Efficient Fixation of CO_2 at Atmospheric Pressure to *N*-propargylamines: Facile Method Promoted by Cu(I)-salts to Obtain 4-substituted-3-alkylideneoxazolidin-2-ones

Nikolina Vidović,[1] Maria Kolympadi Markovic,[2,*] Valerije Vrček,[3] Dean Marković[1,*]

[1] University of Rijeka, Faculty of Biotechnology and Drug Development, Radmile Matejčić 2, 51000 Rijeka, Croatia
[2] University of Rijeka, Faculty of Physics, and Centre for Micro- and Nanosciences and Technologies, Radmile Matejčić 2, 51000 Rijeka, Croatia
[3] University of Zagreb, Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, 10000 Zagreb, Croatia
* Corresponding author's e-mail address: maria.kolympadi@uniri.hr, dean.markovic@uniri.hr

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Abstract: The development of efficient methodologies for carbon dioxide (CO_2) incorporation into value-added compounds remains a key objective in sustainable organic synthesis. Herein, we report the copper(I)-promoted synthesis of (*Z*)-3-benzyl-5-benzylidene-4,4-dimethyloxazolidin-2-one via coupling of propargyl amines with CO_2 under mild conditions. Optimization studies revealed that CuI (1.0 equiv.) in DMF with NaOtBu as base affords the highest yield (90%) of the desired oxazolidinone while combination with palladium additives or using alternative copper sources such as CuBr or CuOAc proved ineffective. This example underscores the significant potential of copper in CO_2 fixation chemistry and emphasizes the crucial role that both the nature and stoichiometry of the metal promoter play in governing the efficiency and selectivity of the transformation.

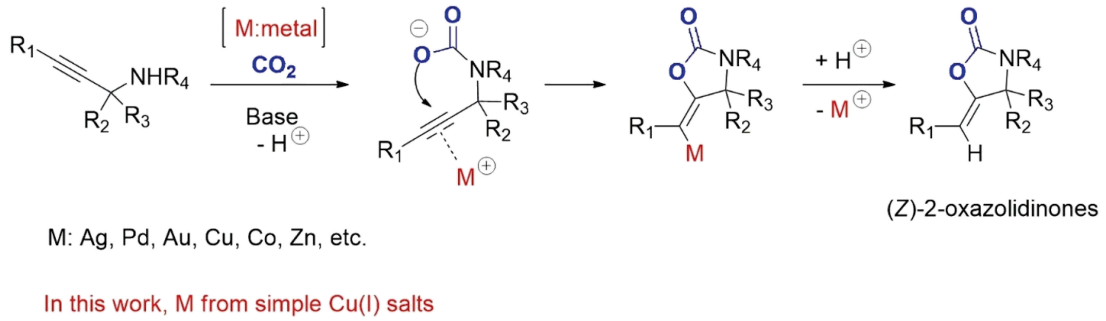
Keywords: oxazolidinone, carbon dioxide, copper, propargyl amine, atmospheric pressure.

INTRODUCTION

CARBON dioxide (CO_2), the most oxidized and thermodynamically stable form of carbon, is widely recognized as a major greenhouse gas and a significant contributor to global warming.[1] At the same time, CO_2 is increasingly valued as a renewable and abundant C1 building block for sustainable chemical synthesis.[2,3] Despite its promise as a feedstock, the chemical utilization of CO_2 remains a considerable challenge due to its inherent thermodynamic and kinetic stability.[4] Effective transformation of CO_2 typically demands highly reactive organometallic reagents or the application of harsh conditions, such as elevated temperatures and high CO_2 pressures, to overcome these barriers.[2]

Over the past three decades, increasing efforts have been directed towards the development of novel CO_2 valorization strategies aligned with the principles of green chemistry. A wide array of value-added chemicals can be synthesized from CO_2, such as carboxylic acids,[5] amides,[6] lactones,[7] organic carbonates and carbamates,[8] as well as their polymeric derivatives.[9] In particular, CO_2 incorporation into epoxides, propargylic alcohols, and propargylamines offers sustainable synthetic pathways to carbonates and carbamates, thereby circumventing the need for hazardous reagents like phosgene traditionally employed in such transformations.[10]

Organic carbamates are especially attractive due to their prevalence in pharmaceuticals and agrochemicals.[11] Notable examples include the antibiotic linezolid,[12,13] the



Scheme 1. Proposed mechanism of CO_2 fixation into *N*-propargylamines, as suggested by Yamada et al.[15,16] and Ikariya et al.[17]

antiviral drug efavirenz,[13] and their role as key intermediates in polyurethane production.[14] In addition, the oxazolidinone moieties are also at the core of direct Factor Xa inhibitors such as rivaroxaban, an orally bioavailable anticoagulant, which underscores the scaffold's versatility beyond antimicrobial applications, extending into critical roles in thrombosis management.[11] Cyclic organic carbamates, particularly five-membered 2-oxazolidinones, can be efficiently accessed via CO_2 fixation on *N*-propargylamines followed by intramolecular cyclization. Yamada et al.[15,16] and Ikariya et al.[17] proposed a general mechanism for this transformation, in which a metal catalyst facilitates cyclization of a transient organic carbamic acid intermediate in the presence of a base (Scheme 1). This process is initiated by coordination of the metal ion to the alkyne moiety, followed by proton abstraction at the alkylidene position to promote ring closure.

A wide range of metal catalysts have been employed for this transformation, including noble metals such as Ag,[15,16] Pd,[18–20] and Au,[17] as well as more earth-abundant alternatives like Cu,[21–24] Co,[25] and Zn,[26] often in combination with suitable organic ligands. In recent years, advanced heterogeneous systems, such as immobilized metal catalysts,[23] metal-organic frameworks (MOFs),[26,27] ionic liquids,[28] and organocatalysts,[29–31] have also demonstrated excellent efficacy for the synthesis of 2-oxazolidinones. Furthermore, multicomponent reaction strategies have been developed for the one-pot construction of complex cyclic carbamates, offering streamlined access to structurally diverse products.[19,32–34]

We report herein a simple method for the synthesis of (*Z*)-3-benzyl-5-benzylidene-4,4-dimethyloxazolidin-2-one starting from a *N*-benzyl-2-methyl-4-phenylbut-3-yn-2-amine and CO_2 at atmospheric pressure. The use of a trialkylated propargylamine is essential to the success of the transformation, as the geminal R^2 and R^3 substituents exert a Thorpe–Ingold (*gem*-dialkyl) effect, which promotes favourable conformational preorganization and enhances the intramolecular cyclization leading to the oxazolidinone core. Screening of simple copper(I) sources in combination with Pd catalysts, which are expected to complex the C≡C bond and facilitate the CO_2 insertion and cyclization of intermediate, did not afford any product. Instead, it was found the common CuI salt could promote the CO_2 capture and cyclization with medium to excellent yields without the use of additives or ligands.

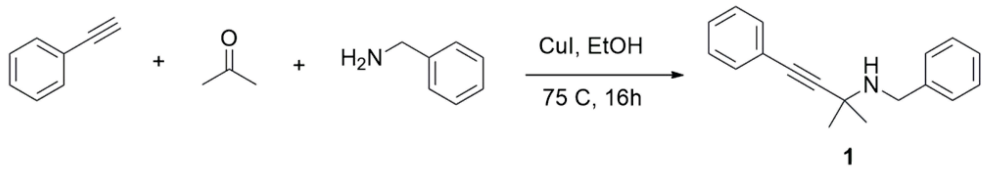
EXPERIMENTAL

Reagents

All solvents and reagents were purchased from Sigma-Aldrich, Merck, VWR, Gram Mol, Alfa Aeser and Carlo Erba and were used without further purification. Analytical Thin Layer Chromatography (TLC) was performed on silica gel 60 F254 precoated aluminium sheets (0.2 mm layer; Macherey-Nagel, Düren, Germany); components were detected under an UV lamp (λ = 254 nm) and by dipping into an aqueous $KMnO_4$ solution (1 % (*w*/*v*) $KMnO_4$ with 6 % K_2CO_3, 0.1 % NaOH) followed by heating. Silica gel 60, 63–200 µm (Macherey-Nagel, Düren, Germany) was used for gravimetric column chromatography. NMR spectra were acquired by means of a Varian Inova 400 spectrometer (Varian, Palo Alto, USA) in $CDCl_3$. Chemical shifts (δ) are given in ppm and are referenced to solvent signals. IR spectra were recorded on an Agilent Cary 630 FTIR instrument.

Synthesis of *N*-benzyl-2-methyl-4-phenylbut-3-yn-2-amine (1)

Copper(I) iodide (2.85 g, 0.015 mol) was suspended in EtOH (25 mL) under the N_2 atmosphere. Phenylacetylene (5.48 mL, 0.05 mol), acetone (3.7 mL, 0.05 mol) and benzylamine (5.45 mL, 0.05 mol) were added and so obtained mixture was stirred overnight at 75 °C. Solvents were then removed on rotary evaporator. The pure product was isolated by column chromatography on silica gel (10 % EtOAc/cyclohexane) as a yellowish oil (1.75 g, 7.00 mmol, 14 %).



Scheme 2. Synthesis of *N*-benzyl-2-methyl-4-phenylbut-3-yn-2-amine (**1**).[35,36]

General procedure for the synthesis of (*Z*)-3-benzyl-5-benzylidene-4,4-dimethyloxazolidin-2-one (2)

Inside the glovebox, one vial was charged with Cu-salt (1 mmol), base (3 mmol), and in some cases additive (0.1 mmol) (see Table 1). In another vial, substrate **1** (1 mmol) was dissolved in anhydrous acetonitrile (2.5 mL). Both vials were then purged with CO_2 and bubbled for 5 mins. The solution of substrate was then transferred to the vial containing solids and heated at 60 °C. The reaction mixture was stirred at 60 °C for 22 h under CO_2 (1 atm). The reaction was quenched with H_2O (4 mL) and diluted with EtOAc (4 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 4 mL). The combined organic layers were washed with brine (2 × 12 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel (10 % EtOAc/petroleum ether) to afford **2** in various yields according to Table 1, as a whitish solid.

RESULTS AND DISCUSSION

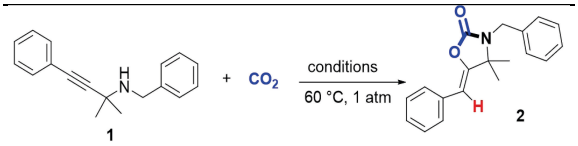
Initial experiments were carried out using inexpensive and readily available CuI (1 equiv.), along with the addition of Pd catalysts (0.1 equiv.) under atmospheric pressure of CO_2. In total, three different Pd catalysts were tested, but none yielded the desired cyclic products (Table 1, Entries 2–4). Even after changing the solvent and base, the target products were not detected (Table 1, Entry 5).

When the reaction was carried out by using copper wire alone (Entry 6), without any additional additives, 2-oxazolidinone **2** was obtained in 15 % yield. This result indicates that copper can independently promote the reaction and that Pd-complexes do not act synergistically with Cu in this system. The structure of product **2** was confirmed by IR and NMR spectroscopy. A comparable yield was obtained when copper wire was replaced with copper(I) acetate (Entry 7), likely due to its lower reactivity. In contrast, the addition of CuBr (Entry 8) resulted in no product formation. However, switch to CuCN and CuI (Entries 9 and 10) led to significantly improved the yields of product **2**, indicating that the halide identity and electronic properties of the copper salt play a critical role in the modulation of reactivity.

The most effective copper source was CuI (1.0 equiv., Entry 10), which delivered the highest yield (90 %) of product **2**. CuCN (Entry 9) also afforded a substantial yield (65 %) of **2**, indicating that copper(I) salts with halide or pseudohalide contraions can effectively promote this transformation. Notably, when CuI was used in a catalytic amount instead of 1.0 equiv., under otherwise identical reaction conditions, the yield dropped significantly from 90 % to 34 % (entry 10 *vs.* 11). However, the present study, as well as previous reports,[23,34,38] demonstrates that CuI can be particularly useful in promoting CO_2 chemistry due to its solubility and stability of Cu(I) species.

To determine whether copper is essential for achieving high yields, the reaction was performed in the

Table 1. Optimization of reaction conditions for a synthesis of *(Z)*-3-benzyl-5-benzylidene-4,4-dimethyloxazolidin-2-one (**2**).



Entry	Cu-source	Additive (0.1 equiv.)	Solvent	Base (3 equiv.)	Yield % 2
1	None	none	DMF	NaOtBu	0
2	CuI[(a)]	[$PdCl_2$ (dppf)]	DMSO	DABCO	0
3	CuI[(a)]	$PdCl_2$ [p(*O*-Tol)$_3$]$_2$	DMSO	DABCO	0
4	CuI[(a)]	Pd(dppe)$_2$	DMSO	DABCO	0
5	CuI[(a)]	$PdCl_2$ [p(*O*-Tol)$_3$]$_2$	DMF	Cs_2CO_3	0
6	CuI-wire, 100 mg	None	DMF	NaOtBu	15
7	Cu(CH_3COO)[(b)]	None	DMF	NaOtBu	15
8	CuBr[(b)]	None	DMF	NaOtBu	0
9	CuCN[(b)]	None	DMF	NaOtBu	65
10	CuI[(b)]	None	DMF	NaOtBu	90
11	CuI[(a)]	None	DMF	NaOtBu	34
12	CuI[(a)]	None	DMF	NaH	0

[(a)] 0.1 equiv.;
[(b)] 1,0 equiv. of Cu-salt.
DABCO: 1,4-diazabicyclo[2.2.2]octane

absence of any copper source (Entry 1). No formation of product **2** was observed, confirming that a copper promoter is essential to conduct the reaction. NaO*t*Bu was used in most experiments and consistently correlated with product formation when paired with an appropriate Cu source. Substituting NaO*t*Bu with NaH (Entry 12) led to a complete loss of reactivity, likely due to differences in base strength and its steric and electronic properties. Therefore, NaO*t*Bu is the preferred base, as it helps to stabilize the carbamic anion and enhance the nucleophilicity of the carbamate intermediate.

^{1}H and ^{13}C NMR spectra of the starting material **1** (Supplementary Figures 1 and 2) and final 2-oxazolidinone **2** (Supplementary Figures 3 and 4) illustrate the successful carboxylative cyclization reaction. A new peak appears at 5.41 ppm ^{1}H NMR of **2** is characteristic of the alkylidene hydrogen, and two new peaks at 153.3 and 154.7 ppm of ^{13}C NMR of **2** correspond to the new quarternary carbons. Moreover, Supplementary Figures 5 and 6 show the differences in IR spectra of two compounds: 1782 and 1685 cm^{-1} are indicative of the carbonyl –C=O and *exo*-double bond in the structure of final cyclic carbamate **2**.[15,16,22,24,28,30,31,34,37]

CONCLUSION

Under the tested conditions, the reaction between propargyl amine **2** and CO_2 exclusively yielded 2-oxazolidinone **2**, resulting from CO_2, cyclization and proton abstraction. The nature and stoichiometry of the copper source significantly influenced the outcome, with stoichiometric CuI (1.0 equiv.) proving to be the most effective. Pd-additives were found to inhibit the reaction, emphasizing the necessity of copper for this transformation. NaO*t*Bu was identified as the optimal base, facilitating key deprotonation and activation processes. Under these optimized conditions, product **2** was obtained in 90 % yield, underscoring the importance of precise control over both the Cu-source and base to achieve high selectivity and efficiency.

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Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: https://doi.org/10.5562/cca4186.

PDF files with attached documents are best viewed with Adobe Acrobat Reader which is free and can be downloaded from Adobe's web site.

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