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Copper-Catalyzed Four-Component Coupling between Aldehydes, Amines, Alkynes, and Carbon Dioxide

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Abstract: A simple and efficient synthesis of oxazolidinones was developed through a copper-catalyzed coupling of aldehydes, amines, and terminal alkynes under atmospheric pressure of carbon dioxide.

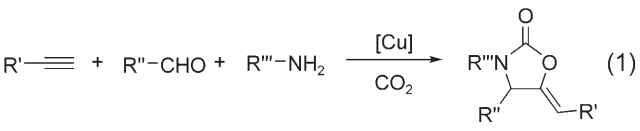
Keywords: carbon dioxide fixation; copper catalysis; multicomponent reactions; oxazolidinone; tandem reactions

With increasing awareness of the elevated CO_2 levels in the atmosphere, there has been great effort placed into the development of strategies towards its potential use as an abundant and inexpensive C_1 feedstock.[1] A method in which CO_2 has been utilized as a substrate is through the carboxylative cyclization of propargylic amines to generate oxazolidinones bearing exocyclic alkenes. A variety of protocols has been reported for the carboxylative cyclization reaction. Propargylic amines have reacted with CO_2 in the presence of organometallic complexes of ruthenium[2] and palladium.[3] Catalyst-free versions of the carboxylative cyclization of propargylamines with CO_2 have been achieved using strong bases,[4] in supercritical CO_2,[5] and under electrochemical conditions.[6] However, these protocols are often limited by high CO_2 pressure and/or restricted to propargylamines bearing terminal alkynes.

A simple and effective entry into propargylic amines is through a three-component coupling reaction between aldehydes, amines, and alkynes (A^3-coupling).[7] Recently, we and others have demonstrated that a variety of metal salts and organometallic complexes can catalyze the A^3-coupling reaction to generate the corresponding propargylamines in good yields.[8] As a natural extension of the A^3-coupling reaction, we have begun to explore the possibility of incorporating the A^3-coupling methodology into tandem processes. With respect to this goal, we have recently reported a five-component double A^3-coupling[9] and a six-component double A^3-coupling/[2+2+2] cycloaddition reaction.[10]

While a great deal of progress has been achieved in the A^3-coupling reaction, there exist some limitations to the current methodology. Thus far, the A^3-coupling reactions have been restricted to secondary and aromatic amines. Aliphatic primary amines are challenging substrates that are often not viable for the A^3-coupling reaction. Although it is unclear why aliphatic amines are poor substrates, we hypothesize that these electron-rich amines may poison the A^3-coupling catalyst. We propose a potential solution to this problem by utilizing CO_2 as an antidote. Since primary aliphatic amines are known to readily form carbamic acids in the presence of CO_2,[11] this cheap and readily available gas could ultimately reduce the amount of free amine in solution and promote the A^3-coupling reaction. In turn, we also envisioned the newly formed propargylic amine to undergo a carboxylative cyclization *in situ* to generate oxazolidinones bearing exocyclic alkenes.

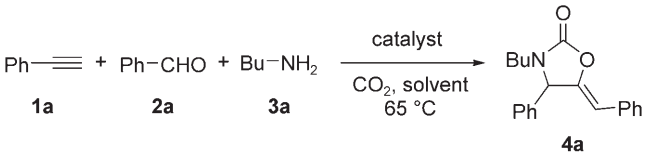
Herein, we report an efficient copper-catalyzed four-component, tandem A^3-coupling/carboxylative cyclization between aldehydes, amines, terminal alkynes, and CO_2 in which CO_2 serves as both promoter and reagent for the facile synthesis of synthetically important oxazolidinone products [Eq. (1)].



(1)

We began the optimization process by using a modified version of the CuBr/$RuCl_3$ system for the A^3-coupling between phenylacetylene **1a**, benzaldehyde **2a**, and butylamine **3a** under an atmospheric pressure of CO_2 (Table 1).[12]

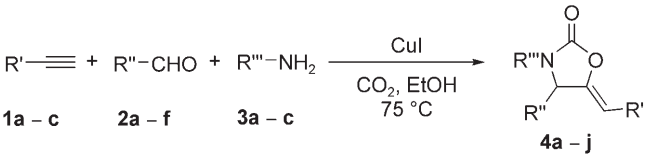
Table 1. Optimization of the four-component coupling between alkyne, aldehyde, amine, and CO_2.[a]



Entry	Catalyst	Solvent	Yield [%][b]
1	$RuCl_3$[c], CuBr		41
2	CuBr		38
3	CuCl		34
4	CuI		86
5	CuSCN		6
6	$CuBr_2$		37
7	CuI	THF	59
8	CuI	H_2O	62
9	CuI	EtOAc	80
10	CuI	EtOH	78
11	CuI	MEG	67
12	CuI	EtOAc	78[d]
13	CuI	EtOH	89[d]

[a] Phenylacetylene (1.0 equiv.), benzaldehyde (2.0 equiv.), butylamine (2.0 equiv.), and copper catalyst (30 mol%) in solvent (*c* 5.0 M) under CO_2 (1 atm.).
[b] Reported yields based on **1a** and determined by NMR using an internal standard.
[c] 3.0 mol% of $RuCl_3$.
[d] 75 °C.

Table 2. Copper-catalyzed four-component coupling between alkyne, aldehyde, amine, and CO_2.[a]



Entry	R′	R″	R‴	Yield [%][b]
1	Ph	Ph	Bu	85
2	Ph	4-MeC_6H_4	Bu	78
3	Ph	4-$NMe_2C_6H_4$	Bu	55
4	Ph	4-CNC_6H_4	Bu	38
5	Ph	4-BrC_6H_4	Bu	71
6	Ph	Pentyl	Bu	56
7	Ph	Ph	$Ph(CH_2)_3$	58
8	Ph	Ph	Allyl	70
9	4-MeC_6H_4	Ph	Bu	91
10	4-MeOnaphthyl	Ph	Bu	58
11	Hexyl	Ph	Bu	0

[a] Alkyne (1.0 equiv.), aldehyde (2.0 equiv.), amine (2.0 equiv.), and CuI (30 mol%) in EtOH (*c* 5.0 M) under CO_2 (1 atm.).
[b] Isolated yields based on the alkyne.

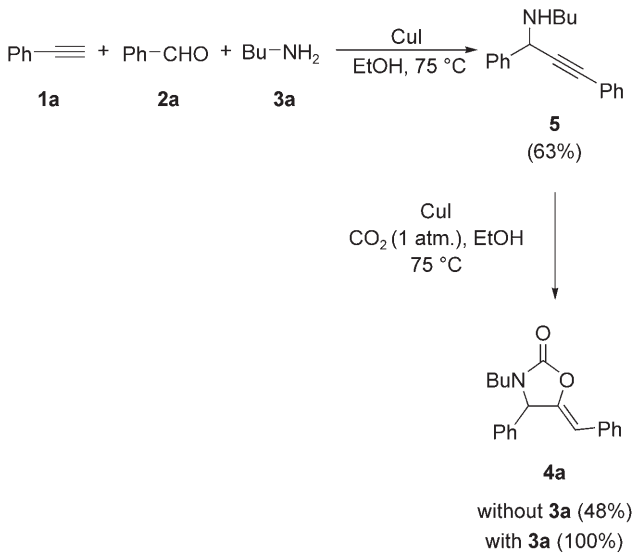
The initial reaction between alkyne **1a**, aromatic aldehyde **2a**, and aliphatic amine **3a** provided the desired oxazolidinone **4a** with a modest yield (Table 1, entry 1). It was determined that $RuCl_3$ was not an essential co-catalyst for the successful synthesis of the desired product (Table 1, entry 2). In fact, we were quite surprised by this result since in the original A^3-coupling involving aromatic amines, $RuCl_3$ provided a substantial increase in yield (60%) for the aromatic propargylamine when used as a co-catalyst with CuBr. Screening various copper salts revealed CuI to be an excellent catalyst for the four-component coupling reaction (Table 1, entries 3–6). Although the reaction proceeded well under neat conditions, we felt that a solvent was necessary since we anticipated that some starting materials and products generated from the tandem A^3-coupling/carboxylative cyclization reaction would be solids. While most solvents decreased the yield, EtOAc and EtOH were found to be the best solvents (Table 1, entries 7–11). Finally, increasing the reaction temperature slightly improved the yield of the reaction when EtOH was used as the solvent (Table 1, entry 10).

With the optimized reaction conditions in hand, we began to examine the scope of the tandem A^3-coupling/carboxylative cyclization reaction (Table 2).

We began by examining the effect of varying the aldehyde component of the reaction (Table 2, entries 1–6). In general, it appears that the four-component reaction is very sensitive to the electronic properties of the aldehyde. Deviation from the phenyl substituent to a more electron-rich or electron-poor aromatic aldehyde decreased the yield. An aliphatic aldehyde such as hexanal was also a viable substrate and provided the desired oxazolidinone in modest yield. Next, we examined the amine component of the tandem reaction (Table 2, entries 7 and 8). Basic primary amines were good substrates, but once again, varying the substrate from the optimized reaction conditions to other types of aliphatic amines proved to diminish the yield. Finally, the alkyne component of the tandem reaction was examined (Table 2, entrie 9–11). When aromatic alkynes were used as substrates, the corresponding oxazolidinones were obtained. However, aliphatic alkynes were poor substrates. This was expected to be the case since aliphatic alkynes have yet been established as a substrate amenable in the A^3-coupling reactions.

Although we were quite confident that the oxazolidinones generated from the four-component coupling reaction between aldehydes, amines, alkynes, and CO_2 proceeded *via* a tandem A^3-coupling/carboxylative cyclization, we examined the individual steps of this reaction (Scheme 1).

Under the optimized reaction conditions excluding CO_2, the expected propargylamine **5** was synthesized with a moderate yield of 63% (isolated yield of 55%). Subsequently, the A^3-coupling product **5** was subjected to the optimized reaction conditions to furnish ox-



Scheme 1. Stepwise synthesis of oxazolidinone **4a**.

azolidinone **4a** with a yield of 48%. Only when butylamine was introduced into the system was a high yielding carboxylative cyclization achieved. From these results, it appears that a symbiotic relationship exists between the amine and CO_2. For the one-pot tandem A^3-coupling/carboxylative cyclization reaction, oxazolidinone **4a** was obtained with a yield of 85%, which translates to an average of 92% per step. Thus, it appears that CO_2 promotes the A^3-coupling reaction.[13] We speculate that the electron-rich butylamine poisons the copper catalyst and CO_2 reacts with the primary amine to form carbamic acid that ultimately reduces the amount of the amine in solution. Conversely, the formation of the carbamic acid essentially increases the effective concentration of CO_2 in solution and aids the carboxylative cyclization step.[14]

In summary, we have successfully demonstrated a facile synthesis of oxazolidinones bearing exocyclic alkenes *via* a copper-catalyzed four-component coupling between aldehydes, amines, alkynes, and CO_2 under atmospheric pressure. We have also demonstrated a rare example in which CO_2 acts as both a promoter and substrate for the tandem A^3-coupling/carboxylative cyclization reaction. Further investigation into the synthetic applications of this methodology is now in progress.

Experimental Section

General Procedure for the Copper-Catalyzed Four-Component Coupling Reaction

In a sealable test tube equipped with a magnetic stir bar was charged CuI (51.0 mg, 0.268 mmol). The reaction vessel was sealed and flushed with CO_2. The tube was attached with a balloon of CO_2 and charged with EtOH (0.18 mL), aldehyde **2a** (0.18 mL, 1.8 mmol), and amine **3a** (0.18 mL, 1.8 mmol). The reaction mixture was allowed to stir slowly at room temperature for approximately 30 sec (***caution:*** reaction is slightly exothermic and will release CO_2) and then alkyne **1a** (0.100 mL, 0.892 mmol) was added. The test tube was placed in an oil bath set at 75 °C and was allowed to stir overnight. The reaction mixture was allowed to cool to room temperature and was passed through a plug of silica gel. The crude reaction mixture was further purified by silica gel column chromatography (hexane/EtOAc) to provide the desired oxazolidinone **4a**.

Acknowledgements

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References

[1] For recent reviews, see: a) M. Shi, Y.-M. Shen, *Curr. Org. Chem.* **2003**, *7*, 737–745; b) T. Sakakura, J.-C. Choi, H. Yasuda, *Chem. Rev.* **2007**, *107*, 2365–2387.
[2] T. Mitsudo, Y. Hori, Y. Yamakawa, Y. Watanabe, *Tetrahedron Lett.* **1987**, *28*, 4417–4418.
[3] M. Shi, Y.-M. Shen, *J. Org. Chem.* **2002**, *67*, 16–21.
[4] a) M. Costa, G. P. Chiusoli, M. Rizzardi, *Chem. Commun.* **1996**, 1699–1700; b) M. Costa, G. P. Chiusoli, D. Taffurelli, G. J. Dalmonego, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1541–1546.
[5] Y. Kayaki, M. Yamamoto, T. Suzuki, T. Ikariya, *Green Chem.* **2006**, *8*, 1019–1021.
[6] M. Feroci, M. Orsini, G. Sotgiu, L. Rossi, A. Inesi, *J. Org. Chem.* **2005**, *70*, 7795–7798.
[7] For reviews on multi-component reactions, see: a) *Multicomponent reactions*, (Ed.: J. Zhu. H. Bienaymé), Wiley-VCH, Weinheim, **2005**; for reviews on the A^3-coupling reaction, see: b) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472–1483; c) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263–4275.
[8] For recent examples, see: a) S. Orlandi, F. Colombo, M. Benaglia, *Synthesis* **2005**, 1689–1692; b) X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395–4398; c) B. Sreedhar, P. S. Reddy, B. V. Ravindra, *Tetrahedron Lett.* **2005**, *46*, 7019–7022; d) M. L. Kantam, B. V. Prakash, C. R. V. Reddy, B. Sreedhar, *Synlett* **2005**, 2329–2332; e) N. Gommermann, P. Knochel, *Tetrahedron* **2005**, *61*, 11418–11426; f) N. Gommermann, P. Knochel, *Synlett* **2005**, 2796–2798; g) V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8*, 1529–1532; h) S. Sakaguchi, T. Mizuta, Y. Ishii, *Org. Lett.* **2006**, *8*, 2459–2462; i) N. Gommermann, P. Knochel, *Chem Eur. J.* **2006**, *12*, 4380–4392; j) W. Yan, R. Wang, Z. Xu, J. Xu, L. Lin, Z. Shen, Y. Zhao, *J. Mol. Catal. A: Chem.* **2006**, *255*, 81–85; k) B. Huang, X. Yao, C.-J. Li, *Adv. Synth. Catal.* **2006**, *348*, 1528–1532; l) F. Colombo, M. Benaglia, S. Orlandi, F. Usuelli, *J. Mol. Catal. A: Chem.* **2006**, *260*,

128–134; m) P. Li, L. Wang, *Tetrahedron* **2007**, *63*, 5455–5459; n) M. Kidwai, V. Bansal, A. Kumar, S. Mozumdar, *Green Chem.* **2007**, *9*, 742–745; o) L. M. Kantam, V. Balasubrahmanyam, K. B. S. Kumar, G. T. Venkanna, *Tetrahedron Lett.* **2007**, *48*, 7332–7334; p) P. R. Likhar, S. Roy, M. Roy, M. S. Subhas, M. L. Kantam, R. L. De, *Synlett* **2007**, 2301–2303; q) B. Sreedhar, P. S. Reddy, C. S. V. Krishna, P. V. Babu, *Tetrahedron Lett.* **2007**, *48*, 7882–7886.

[9] E. R. Bonfield, C.-J. Li, *Org. Biomol. Chem.* **2007**, *5*, 435–437.

[10] E. R. Bonfield, C.-J. Li, *Adv. Synth. Catal.* **2008**, *350*, 370–374.

[11] Primary amines are known to form carbamic acids in the presence of CO_2, see: D. B. Dell′Amico, F. Calderazzo, L. Labella, F. Marchetti, G. Pampaloni, *Chem. Rev.* **2003**, *103*, 3857–3897.

[12] Based on the first example of the A^3-coupling reaction reported by our group, see: C.-J. Li, C. Wei, *Chem. Commun.* **2002**, 268–269.

[13] Very few examples have been reported in which CO_2 acts as a catalyst, see: a) R. Vaidyanathan, V. G. Kalthod, D. P. Ngo, J. M. Manley, S. P. Lapekas, *J. Org. Chem.* **2004**, *69*, 2565–2568; b) Y. Sugawara, W. Yamada, S. Yoshida, T. Ikeno, T. Yamada, *J. Am. Chem. Soc.* **2007**, *129*, 12902–12903.

[14] A common additive in synthetic protocols with CO_2 is 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). It is presumed that DBU promotes reactions involving CO_2 by trapping it as a carbamate or bicarbonate, see: a) E. R. Pérez, R. H. A. Santos, M. T. P. Gambardella, L. G. M. De Macedo, U. P. Rodrigues-Filho, J.-C. Launay, D. W. Franco, *J. Org. Chem.* **2004**, *69*, 8005–8011; b) D. J. Heldebrant, P. G. Jessop, C. A. Thomas, C. A. Eckert, C. L. Liotta, *J. Org. Chem.* **2005**, *70*, 5335–5338.

