ARTICLE IN PRESS

Tetrahedron Letters xxx (2014) xxx-xxx

Contents lists available at ScienceDirect



Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

DBU and copper(I) mediated carboxylation of terminal alkynes using supercritical CO₂ as a reactant and solvent

Fa-Wang Li, Quan-Ling Suo*, Hai-Long Hong, Ning Zhu, Ya-Qi Wang, Li-Min Han*

Chemical Engineering College, Inner Mongolia University of Technology, Hohhot 010051, PR China

ARTICLE INFO

Article history: Received 22 January 2014 Revised 19 April 2014 Accepted 8 May 2014 Available online xxxx

Keywords: Carboxylation Terminal alkyne ScCO₂ DBU and copper Propiolic acid

ABSTRACT

An organic solvent free, DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene)-mediated and copper(I)-catalyzed C—H activating carboxylation of terminal alkynes in supercritical CO₂ (ScCO₂) was developed in this work. Terminal alkynes react with ScCO₂ in the presence of CuI/DBU and produce the corresponding functionalized propiolic acids in excellent yields. Under the optimized conditions, carbon dioxide can act as both reactant and solvent for the reaction. DBU serves as a ligand of copper catalyst, nucleophile, and base during the reaction. DBU alone can also mediate the direct C—H carboxylation in the absence of transit metal catalyst. But the reaction requires a higher reaction temperature and pressure to obtain desired yields.

© 2014 Elsevier Ltd. All rights reserved.

etrahedro

Carbon dioxide is known as one of greenhouse gases that cause global climate warming. It is highly desirable to use CO_2 as C1 feedstock in the preparation of valuable chemical products because of the abundance and low cost of CO_2 .¹ The carboxylation of terminal alkynes with CO_2 is one of various chemical reaction pathways for converting CO_2 to functionalized propiolic acids. This reaction is low cost and environmentally friendly.² In addition, propiolic acids have attracted tremendous interest in medicinal chemistry³ and fine-chemicals.⁴

It has been reported that highly reactive organolithium and Grignard reagents can be carboxylated with CO₂. However, these reactions are often restricted to organometallic reagents and require harsh reactive conditions, which limits the synthesis of various functionalized propiolic acids and their derivatives. The transition-metal-catalyzed carboxylation of less-reactive nucleophiles with CO₂ has been achieved, in which more reaction substrate can be used. However, it usually requires expensive and sensitive organometallic reagents such as organozinc,⁵ organoboron,⁶ and organotin.⁷

Recently, direct carboxylation of C—H bond with CO₂ has been developed, which is more economic and effective.⁸ Goossen⁹ and Zhang¹⁰ reported the copper(I)-catalyzed direct carboxylation of terminal alkynes with CO₂, in which diamine or N-heterocyclic carbene ligands were used as shown in Scheme 1. Lu reported a simple ligand-free Ag(I)-catalyzed carboxylation pathway for the

* Corresponding authors. Tel./fax: +86 471 6575796. E-mail address: szj010062@163.com (Q.-L. Suo).

http://dx.doi.org/10.1016/j.tetlet.2014.05.024 0040-4039/© 2014 Elsevier Ltd. All rights reserved.



Scheme 1. Direct carboxylation of terminal alkynes with CO₂.

reaction of terminal alkynes with CO₂.¹¹ Goossen further found that a good catalytic selectivity and efficiency for the carboxylation of terminal alkynes with CO₂ was obtained with only 500 ppm silver salt as a catalyst.¹² Interestingly, direct carboxylations of terminal alkynes with CO₂ can also be mediated by strong bases alone such as Cs₂CO₃.¹³ Moreover, Saito and co-workers reported that alkynes were carboxylated by CO₂ in the presence of Ni(cod)₂ and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) to produce the carboxylic acid in good yields under mild conditions.¹⁴ TBD (1,5,7-Triazabicyclo[4.4.0]dec-1-ene)-mediated reactions of alkynes with CO₂ can produce succinate salts through Pd/C-catalyzed hydrogenation. Most reactions occur at 100 °C with DMAc as a solvent.¹⁵ The synthesis of propiolic acid esters via the coupling of CO₂ with terminal alkynes and allylic chlorides has been also achieved using a copper-based catalytic system.¹⁶

All these reactions can give good yields of the desired product under mild reaction conditions. However, expensive and moisture-sensitive cesium salt and toxic organic solvents such as DMF and DMSO are needed for the reactions. Thus the immediate question is: can CO_2 be used as both solvent and reactant for the carboxylation reaction under supercritical conditions? In the pres-

ARTICLE IN PRESS

F.-W. Li et al./Tetrahedron Letters xxx (2014) xxx-xxx

ent work, a new environment-friendly pathway for the carboxylation of terminal alkynes in supercritical CO_2 (ScCO₂) was developed, in which ScCO₂ functions as both a reactant and solvent.

The carboxylation of phenylacetylene in ScCO₂ was chosen as a model reaction to optimize the reaction conditions and the optimized results are listed in Table 1. The reactions were conducted at 50 °C under 8 MPa unless stated otherwise. The effect of bases on the yields of desired products was evaluated by using 5 mol % copper(I) salt as a catalyst. No desired product was obtained using NEt₃ and Cs₂CO₃ alone in ScCO₂ (entries 1 and 2). Poor but promising yields of 20% and 25% were obtained with 10 mol % DBU plus NEt₃ or Cs₂CO₃, respectively in the reaction system (entries 3 and 4). The yield was significantly increased to 62% when the amount of DBU increased to 120 mol % (entry 5). Interestingly, it was also found that 120 mol % DBU alone gave 41% yield in the absence of copper catalyst (entry 6).

Using 120 mol % DBU as base, the yield of product **1b** could be improved to 72% by changing the catalyst from CuCl to Cul (entry 7). The yield of the reaction increased from 72% to 84% with the increase of DBU amount from 120 mol% to 200 mol% (entries 7 and 8). The yield remained unchanged when the amount of DBU was further increased to 300 mol% (entry 9). An excellent yield of 92% was obtained with 0.02 equiv Cul (entry 10) but the yield decreased to 65% with the further decreasing of Cul amount from 0.02 equiv to 0.01 equiv (entry 11). Furthermore, a higher reaction temperature (100 °C) resulted in a lower yield under same conditions (entry 12). It indicates that the decarboxylative function of copper(I) salt under high temperature conditions.⁹

Notably, organic solvents, such as DMF and THF, can be used as a co-solvent of $ScCO_2$ for the reaction but give lower yields. As shown in entries 13 and 14, the yields decreased to 82% and 75% with adding DMF and THF, respectively. It might be explained that organic solvents reduce the CO_2 capturing capability of DBU during the reaction. The yield of product **1b** (entry 15) was increased to 95% using TMEDA as a ligand under the same reaction conditions. In a word, the yield of carboxylation could be enhanced by the reaction of terminal alkynes with $ScCO_2$ (Supplementary data, Table S1).

As mentioned above, DBU itself can promote the direct carboxylation of terminal alkynes with CO_2 in the absence of copper(I)

HCI /=>

Table 1

=\

Cu(I)-catalyzed carboxylation of phenylacetylene with CO2^a

a catalyst base

$H + CO_2 \text{Output, Output, Output,$							
	1a	1b)				
Entry	Catalyst (mol %)	Base (mol %)	Yield ^b (%)				
1	CuCl(5)	NEt ₃ (120)	0				
2	CuCl(5)	Cs ₂ CO ₃ (120)	0				
3 ^c	CuCl(5)	NEt ₃ (120)	20				
4 ^c	CuCl(5)	Cs ₂ CO ₃ (120)	25				
5	CuCl(5)	DBU(120)	62				
6	None	DBU(120)	41				
7	CuI(5)	DBU(120)	72				
8	CuI(5)	DBU(200)	84				
9	CuI(5)	DBU(300)	82				
10	CuI(2)	DBU(200)	92				
11	CuI(1)	DBU(200)	65				
12 ^d	CuI(2)	DBU(200)	70				
13 ^e	CuI(2)	DBU(200)	82				
14 ^f	CuI(2)	DBU(200)	75				
15 ^g	CuI(2)	DBU(200)	95				

^a Reaction conditions: phenylacetylene (2.0 mmol), CO₂ (8 MPa), 50 °C.

^b Isolated yield.
 ^c DBU (10 mol %) was added.

^d 100 °C.

^e 5 mL DMF was added.

^f 5 mL THF was added.

^g In the presence of 5 mol % TMEDA.

Table 2

DBU-mediated direct carboxylation of phenylacetylene with CO₂^a

1a			1b				
Entry	Pressure (MPa)	T (°C)	Time (h)	Yield ^b (%)			
1	8	60	24	64			
2	8	70	24	78			
3	8	80	24	84			
4	8	90	24	71			
5	6	80	24	73			
6	12	80	24	86			
7	12	80	16	90			
8 ^c	12	80	16	72			

^a Reaction conditions: phenylacetylene (2.0 mmol), DBU (200 mol %), CO₂.

^b Isolated yield.

^c In the presence of 1 mol % Cul.

salt catalyst. Moreover, DBU was proved to be the optimum base among those bases examined (Supplementary data, Table S2). To exclude the potential copper contamination in the reactor, we carried out the experiments in clean autoclave with special Teflon lining and stirrer bars. The Cu metal contents in reaction reagents including terminal alkynes and DBU were analyzed by flame atomic absorption and found negative. Subsequently, the reaction conditions for the direct carboxylation of terminal alkynes with CO₂ in the presence of DBU alone were optimized as shown in Table 2. The yields of phenylpropiolic acid were dramatically increased from 64% to 84% with the increasing of reaction temperature from 60 °C to 80 °C (entries 1–3) but dropped to 71% with the further increasing of reaction temperature to 90 °C (entry 4). It was found that the yield of phenylpropiolic acid increased from 73% to 86% with increasing the CO₂ pressure from 6 MPa to 12 MPa at 80 °C (entries 3, 5, 6). The highest yield was obtained with a reaction time of 16 h under 12 MPa at 80 °C (90%, entry 7). Notably, the addition of CuI (1 mol %) has a negative effect (entry 8) on carboxylation reaction mediated by DBU alone, which is caused by the decarboxylative function of copper(I) salt at higher temperatures.

The reaction conditions optimized above were further tested for the carboxylation of various terminal alkynes with CO₂ in the presence of CuI/DBU as shown in Table 3. Aromatic alkynes containing electron-donating or electron-withdrawing groups at the paraposition afforded the corresponding propiolic acid products in moderate to excellent yield from 81% to 96% (entries 1-5, column A) under the optimized conditions. Among of them, 4-Fluorophenylacetylene gave the highest yield of 96%, which might be ascribed to the good solubility of fluoro-substituent in ScCO₂. The carboxylation reactions of aliphatic alkyne (1-octyne) and the terminal alkyne of heterocycle (2-ethynylthiophene) with CO2 generated the corresponding propiolic acid products in good yields of 90% and 83%, respectively (entries 6 and 7, column A). The carboxylation reactions of cyclopropyl acetylene with CO₂ gave lower yields of 70% (entry 8, column A). The corresponding propiolic acid product was obtained in 76% yield while the solid ferrocenylacetylene that is almost insoluble in liquid DBU was used as substrate (entry 9, column A). However, only a trace amount of the product was isolated below the critical point of pressure (entry 10, column A). The results show that ScCO₂ acts as a solvent rather than a liquid DBU in the reaction system. Terminal alkynes with ester group cannot be carboxylated by CO₂ under same conditions (entry 11, column A). It might be caused by the Michael-type addition occurring predominantly between the reaction of alkynyl esters and DBU.

The carboxylation reactions of various terminal alkynes with $ScCO_2$ were also investigated in the absence of CuI under same conditions to explore the role of DBU in the reaction (entries 1–9, column B). The results indicate that DBU-mediated

Table 3

Direct carboxylation of terminal alkynes with CO2^a



Entry	R	Product	Yield ^b (%)	
			A	В
1	C ₆ H ₅ (1a)	1b	92	90
2	$p-CH_3OC_6H_4(2a)$	2b	81	73
3	$p-FC_6H_4(3a)$	3b	96	92
4 ^c	$p-ClC_6H_4(4a)$	4b	84	78
5 ^c	p-BrC ₆ H ₄ (5a)	5b	86	82
6	<i>n</i> -C ₆ H ₁₃ (6a)	6b	90	76
7	2-Thienyl(7a)	7b	83	68
8 ^d	Cyclopropyl(8a)	8b	70	56
9 ^c	Ferrocenyl(9a)	9b	76	78
10 ^e	Ferrocenyl(9a)	9b	Trace	_
11	EtOOC(10a)	-	-	-

Reaction conditions: method A: terminal alkynes (2 mmol), CuI (2 mol %), DBU (200 mol %), CO2 (8 MPa), 50 °C, 12 h; method B: terminal alkynes (2 mmol), DBU (200 mol %), CO2 (12 MPa), 80 °C,16 h.

^b Isolated yield.

Method A was proceeded at 60 °C.

Method B was proceeded for 24 h.

Method A was proceeded at 6 MPa, 60 °C.

carboxylation reactions are suitable for the alkynes with electronwithdrawing groups as shown in column B of entries 1, 3, 5, and 9. Compared to the copper(I) catalyzed reactions, DBU-mediated carboxylation reaction requires higher temperatures and pressure, and affords the corresponding products in slightly lower yields. These results indicate DBU acted as co-catalyst of copper(I) salt in method A and dual roles of activating C-H and capturing CO₂ in method B.

Based on the results obtained above and previous reports,¹⁸ the reaction mechanism for copper(I)-catalyzed carboxylation process of terminal alkynes with CO₂ in the presence of DBU might be similar to the previous reports.^{10,19} It can be concluded that DBU functions as a ligand of copper(I) catalyst and base in the reaction. The DBU-mediated direct carboxylation reaction involves the formation of DBU-CO₂ adduct followed by the nucleophilic addition of terminal alkyne to afford a propiolate-DBU salt.^{15,20} Thus, DBU acts as both nucleophile and base in the DBU-mediated direct carboxylation process.

In summary, a new DBU triggered, Cu-catalyzed, and organic solvent free carboxylation reaction of terminal alkynes with ScCO₂ was developed.²¹ The ScCO₂ acts as both reactant and reaction solvent for the carboxylation of terminal alkynes. DBU alone can also mediate the carboxylation of terminal alkynes with CO₂ in the absence of transit metal catalyst.²² These two reaction pathways of functionalized propiolic acid formation from the carboxylation of terminal alkynes with CO₂ are environment-friendly, simple, and economic.

Acknowledgments

We are grateful to the Natural Science Foundation of China (NSFC 21266019, NSFC 21062011 and NSFC21362019), and the Program for New Century Excellent Talents in University (NCET-08-858) for financial support.

Supplementary data

Supplementary data (experimental details and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.024.

References and notes

- 1. (a) Sakakura, T.; Choi, J.-C.; Yasuda, H. Chem. Rev. 2007, 107, 2365; (b) Izumi, Y. Coord. Chem. Rev. 2013, 257, 171.
- (a) Manjolinho, F.; Arndt, M.; Gooßen, K.; Gooßen, L. J. ACS Catal. 2012, 2, 2014; 2 (b) Yu, D.; Tan, M. X.; Zhang, Y. Adv. Synth. Catal. 2012, 354, 969.
- (a) Lehmann, F.; Lake, L.; Currier, E. A.; Olsson, R.; Hacksell, U.; Luthman, K. Eur. J. Med. Chem. 2007, 42, 276; (b) Dong, Y.; Guo, X.; Yu, Y.; Liu, G. Mol Divers. **2013**, 17, 1,
- (a) Li, Y.; Jardine, K. J.; Tan, R.; Song, D.; Dong, V. M. Angew. Chem., Int. Ed. 2009, 121, 9870; (b) Bararjanian, M.; Balalaie, S.; Rominger, F.; Movassagh, B.; 4. Bijanzadeh, H. R. J. Org. Chem. 2010, 75, 2806; (c) Feng, H.; Ermolat'ev, D. S.; Song, G.; Van der Eycken, E. V. Adv. Synth. Catal. 2012, 354, 505.
- (a) Yeung, C. S.; Dong, V. M. J. Am. Chem. Soc. 2008, 130, 7826; (b) Correa, A.; 5. Martín, R. Angew. Chem., Int. Ed. 2009, 48, 6201.
- (a) Ohishi, T.; Nishiura, M.; Hou, Z. Angew. Chem., Int. Ed. 2008, 47, 5792; (b) 6 Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. Org. Lett. 2008, 10, 2697.
- 7. (a) Shi, M.; Nicholas, K. M. J. Am. Chem. Soc. 1997, 119, 5057; (b) Wu, J.; Hazari, N. Chem. Commun. 2011, 47, 1069.
- (a) Sasano, K.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2013**, *135*, 10954; (b) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842; (c) Boogaerts, I. I. F.; Nolan, 8. S. P. J. Am. Chem. Soc. **2010**, 132, 8858; (d) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R.; Cazin, C. S.; Nolan, S. P. Angew. Chem., Int. Ed. **2010**, 49, 8674; (e) Inomata, H.; Ogata, K.; Fukuzawa, S.-I.; Hou, Z. Org. Lett. 2012, 14, 3986.
- 9. Gooßen, L. J.; Rodrguez, N.; Manjolinho, F.; Lange, P. P. Adv. Synth. Catal. 2010, 352 2913
- 10. Yu, D.; Zhang, Y. Proc. Natl. Acad. Sci. 2010, 107, 20184.
- Zhang, X.; Zhang, W.-Z.; Ren, X.; Zhang, L.-L.; Lu, X.-B. Org. Lett. 2011, 13, 2402.
 Arndt, M.; Risto, E.; Krause, T.; Gooßen, L. J. ChemCatChem 2012, 4, 484.
- 13 Yu, D.; Zhang, Y. Green Chem. 2011, 13, 1275.
- 14. Saito, S.; Nakagawa, S.; Koizumi, T.; Hirayama, K.; Yamamoto, Y. J. Org. Chem. **1999**, 64, 3975.
- 15. Wang, X.; Lim, Y. N.; Lee, C.; Jang, H.-Y.; Lee, B. Y. Eur. J. Org. Chem. 2013, 1867.
- 16. (a) Yu, B.; Diao, Z.-F.; Guo, C.-X.; Zhong, C.-L.; He, L.-N.; Zhao, Y.-N.; Song, Q.-W.; Liu, A.-H.; Wang, J.-Q. Green Chem. 2013, 15, 2401; (b) Inamoto, K.; Asano, N.; Kobayashi, K.; Yonemoto, M.; Kondo, Y. Org. Biomol. Chem. 2012, 10, 1514.
- 17. Ma, L.; Dolphin, D. J. Chem. Soc., Chem. Commun. 1995, 2251.
- (a) Feng, E.; Huang, H.; Zhou, Y.; Ye, D.; Jiang, H.; Liu, H. J. Org. Chem. 2009, 74, 18. 2846; (b) Thaku, K. G.; Sekar, G. Synthesis 2009, 16, 2785; (c) Sekar, G.; Gupta, A. D.; Singh, V. K. Tetrahedron Lett. 1996, 37, 8435; (d) Wei, W.; Hu, X.-Y.; Yan, X.-W.; Zhang, Q.; Cheng, M.; Ji, J.-X. Chem. Commun. 2012, 48, 305.
- 19. Zhang, L.; Cheng, J.; Ohishi, T.; Hou, Z. Angew. Chem., Int. Ed. 2010, 49, 8670.
- (a) Wang, Y.; Han, Q.; Wen, H. Mol. Simulat. 2013, 39, 822; (b) Heldebrant, D. J.; 20 Yonker, C. R.; Jessop, P. G.; Phan, L. Energy Environ. Sci. 2008, 1, 487; (c) Heldebrant, D. J.; Jessop, P. G.; Thomas, C. A.; Eckert, C. A.; Liotta, C. L. J. Org. Chem. 2005, 70, 5335.
- 21. General procedure for CuI and DBU mediated carboxylation of terminal alkynes with CO2: CuI (7.6 mg, 0.04 mmol), Alkyne (2.0 mmol), DBU (609 mg, 4.0 mmol) were added to a 50 mL autoclave with a stir bar after the air was evacuated, respectively. The autoclave was pressurized to 8 MPa by CO2 at 50 °C. The reaction mixture was stirred for 12 h. After the reaction was finished, the system was cooled to room temperature and CO₂ was carefully released from the autoclave. The residue was diluted with water and then acidified with aqueous HCl (2 N) at a low temperature. The mixture was extracted with diethyl ether (4 \times 30 mL). The combined organic layers were washed with water and brine, respectively, dried over anhydrous Na₂SO₄, and filtered. The solvent was removed under vacuum and the products (1b-9b) were obtained.
- 22. General procedure for DBU-mediated direct carboxylation of terminal alkynes with CO2: alkyne (2.0 mmol) and DBU (609 mg, 4.0 mmol) were added to a 50 mL autoclave with a stir bar after the air was evacuated, respectively. The autoclave was pressurized to 12 MPa by CO2 at 80 °C. The reaction mixture was stirred for 16 h. To isolate propiolic acids, the follow-up experimental procedures are similar to Ref. 21.