General and Selective Synthesis of (Z)-3-Haloacrylates via Palladium-Catalyzed Carbonylation of Terminal Alkynes

Jin-Heng Li,* Shi Tang, and Ye-Xiang Xie

Contribution from the Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, China

jhli@hunnu.edu.cn

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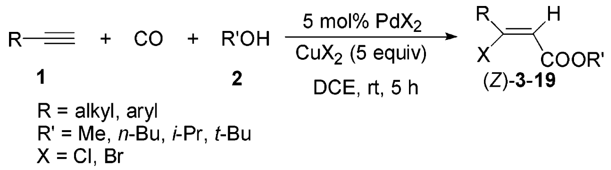

A general and selective palladium-catalyzed carbonylation of terminal alkynes method for the synthesis of (*Z*)-3-haloacrylates is presented. In the presence of a catalytic amount of PdX$_2$ and 5 equiv of CuX$_2$ (X = Cl and Br), terminal alkynes were carbonylated to afford the corresponding (*Z*)-3-haloacrylates exclusively in moderate to good yields. The results showed that the effect of solvent had a fundamental influence on the chemoselectivity and stereoselectivity of the palladium-catalyzed carbonylation reaction.

Introduction

3-Haloacrylates are valuable building blocks in organic synthesis[1,2] and a recurring functional group in many natural products and bioactive compounds.[3] Consequently, a number of efficient and selective methods have been developed for their synthesis.[4–7] Of these transformations, palladium-catalyzed carbonylation is considered to be one of the most effective strategies.[6,7] However, few reports on the palladium-catalyzed carbonylation of an alkyne to a 3-haloacrylate have been described.[7] Furthermore, these reports focused on the PdCl$_2$- and CuCl$_2$-catalyzed carbonylation of alkynes to synthesize 3-chloroacrylates. Thus, the development of an effective palladium-catalyzed carbonylation of alkynes procedure to selectively construct 3-haloacrylate skeletons, including 3-chloroacrylate and 3-bromoacrylate skeletons, would be significant. Here, we report a general and selective palladium-catalyzed carbonylation of alkynes method for the synthesis of (*Z*)-3-haloacrylates.

Results and Discussion

In 1999 we reported the PdCl$_2$- and CuCl$_2$-catalyzed carbonylation of terminal alkynes to form (*Z*)-3-chloroacrylates.[7c] In alcohol (0.6 mL)/benzene (10 mL), various (*Z*)-3-chloroacrylates were obtained exclusively in moderate to good yields using 5 mol % of PdCl$_2$ as catalyst in the presence of 3 equiv of CuCl$_2$ as the catalytic system. Thus, we expected that the use of PdBr$_2$ and CuBr$_2$ instead of PdCl$_2$ and CuCl$_2$ might afford 3-bromoacrylates, but this attempt was unsuccessful (entry 1 in Table

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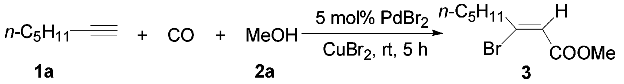
TABLE 1. PdBr$_2$-Catalyzed Carbonylation of 1-Heptyne (1a) with CO and MeOH[a]



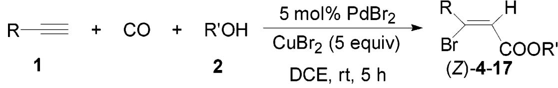
entry	solvent (mL)	CuBr$_2$ (equiv)	yield of **3** (%)[b]
1	benzene/MeOH (10:0.6)	3	–
2	benzene/MeOH (10:0.6)	5	trace
3	benzene/MeOH (10:0.2)	5	16 (*Z*:*E* = 3:2)
4	*n*-hexane/MeOH (10:0.2)	5	40 (*Z*:*E* = 9:1)
5	MeCN/MeOH (10:0.2)	5	–
6	DCE/MeOH (10:0.2)	5	68 (*Z*)
7	DCE/MeOH (10:0.4)	5	53 (*Z*)
8	DCE/MeOH (10:0.1)	5	50 (*Z*)
9	DCE/MeOH (10:0.2)	3	56 (*Z*)
10	DCE/MeOH (10:0.2)	6	67 (*Z*)
11[c]	DCE/MeOH (10:0.2)	–	–

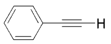
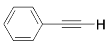
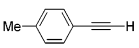
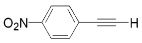
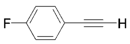
[a] Unless otherwise indicated, the reaction conditions were as follows: **1a** (1 mmol), PdBr$_2$ (5 mol %), CuBr$_2$, and CO (1 atm, bubbled) in the indicated solvent for 5 h at room temperature. [b] Isolated yield. Ratio of (*Z*)-isomer and (*E*)-isomer was determined by GC analysis. [c] KBr (5 equiv) and O$_2$ (1 atm, bubbled) instead of CuBr$_2$. No reaction was observed.

1). In our previous results on the palladium-catalyzed carbonylation transformations,[8] both solvent and CuX$_2$ were found to have a fundamental influence on the chemoselectivity and stereoselectivity. Thereby, both solvent and CuX$_2$ were first evaluated, and the results are summarized in Table 1. Indeed, trace amounts of the desired product **3** were observed from treatment of 1-heptyne (**1a**) with CO (1 atm) and MeOH (**2a**, 0.6 mL) in the presence of 5 mol % of PdBr$_2$ and benzene (10 mL) when the loadings of CuBr$_2$ were increased to 5 equiv (entry 2). Interestingly, a 16% yield of **3** as a mixture of (*Z*)- and (*E*)-isomers was obtained by decreasing the amount of MeOH to 0.2 mL (entry 3).[9] Encouraged by the results, we then examined a series of solvents (entries 3–6), and DCE (1,2-dichloroethane) was the most effective (entry 7). In the presence of 5 mol % of PdBr$_2$ and 5 equiv of CuBr$_2$, treatment of **1a** with CO (1 atm) and MeOH (0.2 mL) afforded a 68% yield of (*Z*)-**3** exclusively when DCE was used as the solvent. The results also demonstrated that the amount of MeOH affected the reaction (entries 6–8). The yield of **3** was decreased to some extent in the presence of either 0.4 or 0.1 mL of MeOH. As shown in Table 1, the loading of CuBr$_2$ was observed to influence the reaction too (entries 6, 9, and 10). In the presence of PdBr$_2$, CO, MeOH, and DCE, an identical yield was obtained, even further increasing the loadings of CuBr$_2$ to 6 equiv (entry 10). However, the yield of **3** was decreased to 56% when the loadings of CuBr$_2$ were decreased to 3 equiv (entry 9). The use of KBr and O$_2$ instead of CuBr$_2$ was investigated, and no desired product was observed (entry 11).[10]

As summarized in Table 2, PdBr$_2$/CuBr$_2$ is an effective and selective catalytic system for carbonylation reactions of various terminal alkynes **1b**–**g** with CO and alcohols **2a**–**d** including primary alcohol (**2a** and **2b**), secondary alcohol (**2c**), and tertiary alcohol (**2d**). The results show that the yields of the reaction depend on the structure of alcohols; for example, an additional amount of **2d** was required for carbonylation of alkynes. For example, in the presence of PdBr$_2$ (5 mol %), CuBr$_2$ (5 equiv), CO (1 atm), and DCE (10 mL), treatment of **1b** with **2a**–**c**, respectively, afforded the corresponding (*Z*)-3-bromoacrylates **4**–**6** in 81%, 50%, and 59% yields, respectively (entries 1–3), whereas for carbonylation of **1b** with *t*-BuOH (**2d**, 0.2 mL), only 25% yield of **7** was isolated after 5 h (entry 4). However, a 48% yield of **7** was obtained by increasing the amount of **2d** to 0.4 mL (entry 5). It is noteworthy that for carbonylation of phenylacetylene (**1d**), the reaction was not clean in the presence of 0.2 mL of MeOH, whereas decreasing amount of MeOH to 0.1 mL resulted in a 93% yield of the corresponding (*Z*)-3-bromoacrylate **10** (entries 8 and 9). For the reaction

TABLE 2. PdBr$_2$-Catalyzed Carbonylation of Terminal Alkynes[a]



Entry	Alkyne	Alcohol	Yield (%)[b]
1	n-C$_8$H$_{17}$—≡—H (**1b**)	MeOH (**2a**)	81 (**4**)
2	(**1b**)	*n*-BuOH (**2b**)	50 (**5**)
3	(**1b**)	*i*-PrOH (**2c**)	59 (**6**)
4	(**1b**)	*t*-BuOH (**2d**)	25 (**7**)
5[c]	(**1b**)	*t*-BuOH (**2d**)	48 (**7**)
6	*t*-Bu—≡—H (**1c**)	MeOH (**2a**)	76 (**8**)
7	(**1c**)	*i*-PrOH (**2c**)	51 (**9**)
8[d]	 (**1d**)	MeOH (**2a**)	66 (**10**)
9[e]	 (**1d**)	MeOH (**2a**)	93 (**10**)
10	 (**1e**)	MeOH (**2a**)	82 (**11**)
11[e]	(**1e**)	*n*-BuOH (**2b**)	52 (**12**)
12	(**1e**)	*i*-PrOH (**2c**)	75 (**13**)
13[c]	(**1e**)	*t*-BuOH (**2d**)	46 (**14**)
14	 (**1f**)	MeOH (**2a**)	76 (**15**)
15	(**1f**)	*i*-PrOH (**2c**)	68 (**16**)
16	 (**1g**)	MeOH (**2a**)	71 (**17**)

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (1 mmol), PdBr$_2$ (5 mol %), CuBr$_2$ (5 equiv), CO (1 atm, bubbled), alcohol (0.2 mL), and DCE (10 mL) for 5 h at room temperature. [b] Isolated yield. [c] **2d** (0.4 mL). [d] The reaction was not clean. A mixture of (*Z*)-**10** and (*E*)-**10** was obtained in 66% yield, and the ratio was 1:1 (determined by GC analysis and ^{1}H NMR). [e] Alcohol (0.1 mL).

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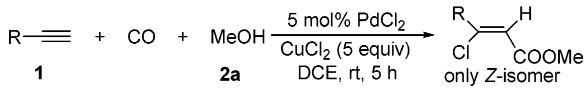
(9) The stereochemistry of the products **3**–**19** was determined on the basis of the chemical shift of the olefinic proton of the corresponding products.[5,7]

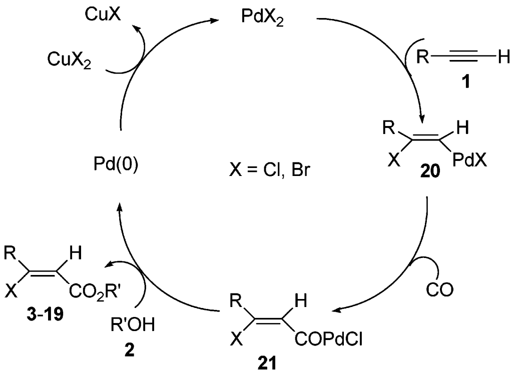
(10) For a review on the use of PdI$_2$–KI–O$_2$ as the catalytic system for carbonylation of alkynes, see: Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219.

SCHEME 1. $PdCl_2$-Catalyzed Carbonylation of Terminal Alkynes 1a and 1d



Entry	R	Isolated yield (%)
1	*n*-C_5H_{11} (**1a**)	57 (**18**)
2	C_6H_5 (**1d**)	80 (**19**)

SCHEME 2



of **1e** with **2b** and CO, the use of 0.1 mL of **2b** gave the best results (entry 11).

As expected, carbonylation of 1-alkynes **1a** and **1d**, carried out under conditions analogous to those reported above but in the presence of $PdCl_2$ (5 mol %) and $CuCl_2$ (5 equiv), selectively led to (*Z*)-3-chloroacrylates (Scheme 1). In the presence of $PdCl_2$ (5 mol %), $CuCl_2$ (5 equiv), CO (1 atm), **2a** (0.2 mL), and DCE (10 mL), carbonylation of **1a** and **1d** reacted smoothly to afford the corresponding (*Z*)-3-chloroacrylates **18** and **19** exclusively in 57% and 80% yields, respectively.

A working mechanism for the palladium-catalyzed carbonylation of alkynes based on the reported mechanism was proposed as outlined in Scheme 2.[6,11] First, the *cis*-addition of alkyne with PdX_2 occurred to form *cis*-halopalladation intermediate **20**.[6c,11] Then migratory insertion of CO to intermediate **20** resulted in the formation of intermediate **21**, followed by alcoholysis of intermediate **21** to afford the desired products **3**−**19**. Finally, the active Pd(II) species were regenerated by the oxidation reaction of Pd(0) with CuX_2 to start a new catalytic cycle.

In summary, PdX_2 catalyzed carbonylation of terminal alkynes with CO and various alcohols including the bulky tertiary alcohol in the presence of CuX_2 to form (*Z*)-3-haloacrylates (halo = Cl and Br) in moderate to good yields with excellent regioselectivity and stereoselectivity. Currently, further applications of this reaction and these products in organic synthesis are underway in our laboratory.

Experimental Section

Typical experimental procedure for the palladium-catalyzed carbonylation of terminal alkynes (entry 6 in Table 1).

A mixture of heptyne, **1a** (1.0 mmol), $PdBr_2$ (5 mol %), $CuBr_2$ (5 equiv), DCE (10 mL), and MeOH (0.2 mL) was stirred under an atmospheric pressure of CO at room temperature for 5 h until complete consumption of starting material as judged by TLC and GC analysis. Then the mixture was filtered and evaporated; the residue was purified by flash column chromatography to afford (*Z*)-Methyl 3-bromooct-2-enoate (**3**) in 68% isolated yield (hexane/ethyl acetate).

(Z)-Methyl 3-Bromooct-2-enoate (**3**)**.** Colorless oil. ^1H NMR (400 MHz) δ: 6.29 (s, 1H), 3.75 (s, 3H), 2.57 (t, $J = 7.6$ Hz, 2H), 1.65−1.61 (m, 2H), 1.34−1.31 (m, 4H), 0.90 (t, $J = 6.8$ Hz, 3H). ^{13}C NMR (100 MHz) δ: 164.7, 142.7, 118.9, 51.5, 43.6, 30.6, 27.0, 22.3, 13.9. IR (CH_2Cl_2, cm^{-1}): 1731, 1633. LRMS (EI, 20 eV) *m/z* (%): 236 ($M^+ + 2$, 3), 234 (M^+, 4), 205 (18), 203 (22), 155 ($M^+ - Br$, 100). HRMS (EI) for $C_9H_{15}{}^{79}BrO_2$ (M^+): calcd 234.0255, found 234.0254.

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Supporting Information Available: Experimental procedure and spectra (^1H and ^{13}C NMR) for all the products **3**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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