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Pd-catalyzed thiocarbamoylation of terminal alkynes with sulfenamide and carbon monoxide

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Abstract—Regio- and stereoselective thiocarbamoylation of terminal alkynes successfully took place using 2,4,5-tri-Cl-$C_6H_2SNEt_2$ as a reaction substrate and $PdCl_2(PPh_3)_2/PPh_3/n$-Bu_4NCl as a catalyst system.

Various types of S–X activations (X: element or functional group) with the aid of transition metal complexes have been accomplished in the past decade.[1] On the other hand, sulfenamides ($R^1SNR^2R^3$; **1**), which possess S–N bond with unique $S^{\delta+}$ and $N^{\delta-}$ polarity have been utilized as reagents to introduce an R^1S or an R^2R^3N group in organic synthesis, additives in rubber industry, and insecticides and fungicides in the agrichemical industry.[2] In 1999, we have succeeded in demonstrating that azathiolation of CO by **1** was smoothly catalyzed by Pd-complex to afford thiocarbamate ($R^1SC(O)NR^2R^3$; **2**), showing that **1** had great potential for the substrate of transition metal-catalyzed S–X activation.[3] Since then, Kondo and Mitsudo et al. have reported that Ru-complexes smoothly catalyzed the regio- and stereoselective azathiolation of alkynes by **1**.[4] Furthermore, Meyer and Knapton have reported that Pd-catalyzed regio- and stereoselective selenocarbamoylation of terminal alkynes (**3**) was achieved using **1**, CO, and $(PhSe)_2$.[5] Although this reaction is very fascinating, since PhSe and $R^2R^3NC(O)$ groups were simultaneously introduced into alkynes by a single process, the formation of many by-products remains as a significant drawback with respect to the atom economy. As to the intramolecular Pd-catalyzed thio- and selenocarbamoylation, we have recently found that the desired transformation was facilely realized by $Pd(PPh_3)_4$ as a catalyst using thio- and selenocarbamate.[6]

Herein, we wish to report on the efficient intermolecular Pd-catalyzed thiocarbamoylation of **3** employing **1** and CO as reaction substrates under dichalcogenide-free reaction conditions. First, we have examined the reaction of $PhSNEt_2$ (**1a**, 1.2 mmol) with 1-octyne (**3a**, 1.0 mmol) in pressurized CO (20 kg/cm^2) using $[Pd(SPh)_2(PPh_3)]_2$ (**4a**, 0.01 mmol) and PPh_3 (0.02 mmol) as catalysts in CH_3CN (0.5 mL) at 120 °C for 3 h (entry 1 of Table 1).

Although complex **4a** has been proved to be an active catalyst for the azathiolation of CO,[3] the conversion of **1a** was low (11%) and anticipated thiocarbamoylation product **5a** was produced only in 4% yield with $E/Z = 25/75$ together with 6% of thiocarbamate **2a**.[7] Although intramolecular thiocarbamoylation by thiocarbamate was successfully catalyzed by $Pd(PPh_3)_4$ (**4b**),[6] the yield of **5a** was poor (5%) with low conversion of **1a** (30%) in this reaction system (entry 2). The employment of $PdCl_2(PPh_3)_2$ (**4c**) with an expectation of better carbonylative addition to alkyne also resulted in a miserable result (entry 3).[8] Then the effects of a variety of catalysts, ligands, solvents, and additives were next examined. Among those screened,[9] the reaction performed using **4c** (2 mol %) as a catalyst precursor, PPh_3 (0.04 mmol) and n-Bu_4NCl (0.08 mmol) as additives in CH_3CN (0.5 mL) and CO (20 kg/cm^2) resulted in the best yield of **5a** (57%) (entry 4).

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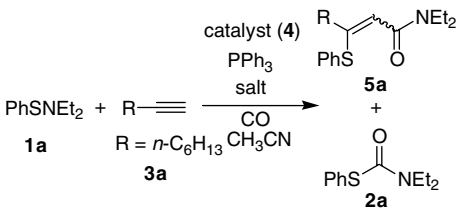
Table 1. Pd-catalyzed thiocarbamoylation of **3a** by **1a**[a]



Entry	4	PPh_3 (mmol)	Salt[b]	5a (%)[c] E/Z	2a (%)[c]
1	$[Pd(SPh)_2(PPh_3)]_2$] **4a**	0.02	—	4 (25/75)	6
2	$Pd(PPh_3)_4$ **4b**	—	—	5 (20/80)	7
3	$PdCl_2(PPh_3)_2$ **4c**	—	—	11 (18/82)	50
4	**4c**	0.04	*n*-Bu_4NCl	57[d] (41/59)	37
5	**4c**	0.04	—	34 (34/66)	25
6	**4c**	—	*n*-Bu_4NCl	27 (44/56)	45
7	**4c**	0.04	NaCl	31 (24/76)	31
8	**4c**	0.04	Et_4NCl	7 (29/71)	80
9	**4c**	0.04	$CaCl_2$	17 (29/71)	80

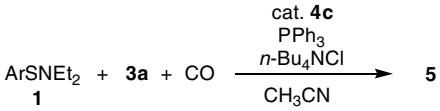
[a] Conditions: **1a** (1.2 mmol), **3a** (1.0 mmol), **4** (0.02 mmol of Pd), CO (20 kg/cm^2), and CH_3CN (0.5 mL) at 120 °C for 3 h.
[b] 0.08 mmol.
[c] NMR yield.
[d] Isolated yield.

Elimination of either *n*-Bu_4NCl or PPh_3 decreased the yields of **5a** (entries 5 and 6). On the other hand, the employment of NaCl, Et_4NCl, and $CaCl_2$ instead of *n*-Bu_4NCl also brought about lower yield of **5a** (entries 7–9). Although the yield of **5a** was increased, unlike the case of selenocarbamoylation,[5] a mixture of stereoisomers ($E/Z = 41/59$) was generated and the yield of **5a** was still unsatisfactory.

To anticipate improvement of the efficiency of the intermolecular thiocarbamoylation, the effects of substituents in Ar of **1** were next examined (Table 2). Clearly, electron-donating groups significantly suppressed the thiocarbamoylation, while electron-withdrawing groups hardly improved the yield of **5** (entries 2, 4, and 6). It is worth noting that the introduction of substituents at the *ortho* position showed a more remarkable effect. Although 2-Me (**1c**) hampered the formation of desired **5c**, the substrate with 2-Cl (**1e**) afforded **5e** in 73% yield with $E/Z = 18/82$ (entries 3 and 5). Moreover, it was found that the reaction using 2,4,5-tri-Cl-$C_6H_2SNEt_2$ (**1g**) produced the desired **5g** in 86% isolated yield with high *Z*-selectivity ($E/Z = 2/98$) (entry 7).[10] On the other hand, di-Cl substituents such as 2,4, 2,5, 2,6-di-Cl were less effective than **1g** for the formation of **5** (entries 8–10). The results of Pd-catalyzed thiocarbamoylation of some terminal alkynes with **1g** and CO under the present optimized conditions were summarized in Table 3.

While the Pd-catalyzed selenocarbamoylation was not applicable to phenyl acetylene (**3b**) or the alkyne with a hydroxyl group,[5] **3b**, 4-MeC_6H_4CCH (**3c**), and

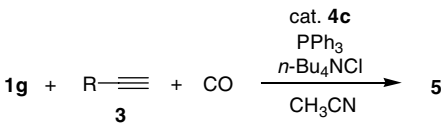
Table 2. Effect of substituents in **1** on the thiocarbamoylation of **3a**[a]

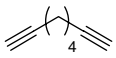
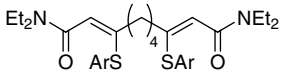
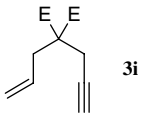
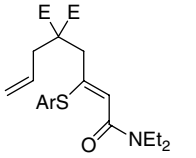


Entry	Ar	1	Yield of 5 (%)[b]		(E/Z)
1	Ph	**1a**	**5a**	57	(41/59)
2	4-MeC_6H_4	**1b**	**5b**	20	(15/85)
3	2-MeC_6H_4	**1c**	**5c**	8	(50/50)
4	4-ClC_6H_4	**1d**	**5d**	59	(31/69)
5	2-ClC_6H_4	**1e**	**5e**	73	(18/82)
6	4-$CF_3C_6H_4$	**1f**	**5f**	64	(20/80)
7	2,4,5-Tri-Cl-C_6H_2	**1g**	**5g**	86[c]	(2/98)
8	2,4,Di-Cl-C_6H_3	**1h**	**5h**	68	(9/91)
9	2,5-Di-Cl-C_6H_3	**1i**	**5i**	61	(10/90)
10	2,6-Di-Cl-C_6H_3	**1j**	**5j**	37	(4/96)

[a] Conditions: **1** (1.2 mmol), **3a** (1.0 mmol), CO (20 kg/cm^2), **4c** (0.02 mmol), PPh_3 (0.04 mmol), *n*-Bu_4NCl (0.08 mmol), and CH_3CN (0.5 mL) at 120 °C for 3 h.
[b] NMR yield.
[c] Isolated yield.

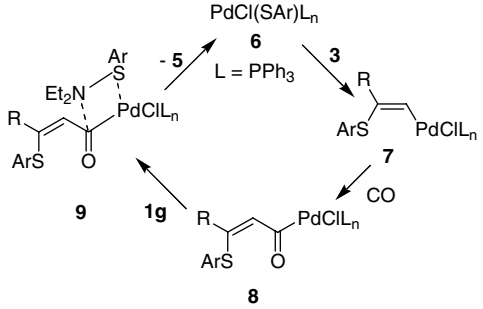
Table 3. Pd-catalyzed thiocarbamoylation of **3** by **1g**[a]



Entry	R	(**3**)	Isolated yield (%) of **5**		(*E*/*Z*)
1	Ph	**3b**	**5k**	72	(3/97)
2	4-MeC_6H_4	**3c**	**5l**	81	(6/94)
3	$HO(CH_2)_3$	**3d**	**5m**	86	(0/100)
4	$NC(CH_2)_3$	**3e**	**5n**	70	(17/83)
5	$PhCH_2$	**3f**	**5o**	62	(8/92)
6	$(Me)_2NCH_2$	**3g**	**5p**	64	(0/100)
7[b]	 **3h**	 **5q**	49	(0/100)	
8	 **3i** E = CO_2Me	 **5r**	56	(0/100)	

[a] Unless otherwise noted, 1.2 mmol of **1g**, 1.0 mmol of **3**, **4c** (0.02 mmol), PPh_3 (0.04 mmol), *n*-Bu_4NCl (0.08 mmol), and CO (20 kg/cm^2) in CH_3CN (0.5 mL) at 120 °C for 3 h.
[b] 2.0 mmol of **1g**.

$HO(CH_2)_3CCH$ (**3d**) smoothly underwent the thiocarbamoylation to give the corresponding β-sulfenyl acrylamide derivatives **5k**, **5l**, and **5m** in good yields with high *Z*-selectivity (entries 1–3). Other functional groups such as –CN, $–CH_2Ph$, and $–NMe_2$ were also tolerant toward the present thiocarbamoylation and double thiocarbamoylation occurred when 1,7-octadiene (**3h**) was employed (entries 4–7). The acetylene (**3i**) bearing a tethered ene unit underwent chemoselective reaction at the triple bond (entry 8). A possible reaction pathway of the present Pd-catalyzed thiocarbamoylation is depicted in Scheme 1. We wish to propose that the complex with the formula $PdCl(SAr)(PPh_3)_n$ (**6**) be an active catalyst for intermolecular thiocarbamoylation of terminal alkynes **3**.[11,12] The cis-insertion of **3** into the S–Pd bond would produce vinylpalladium **7**,[13] which would resist the C–Cl bond-forming reductive elimination due to the thermodynamic disadvantage. The insertion of CO into the resultant C–Pd bond would follow to afford acylpalladium **8** and subsequent σ-bond metathesis between Pd–C of **8** and N–S bond of **1** through transition state **9** to furnish the thiocarbamoylation product **5** with the regeneration of **6**. The roles of addition of *n*-Bu_4NCl and PPh_3 are not clear at the moment but one possibility is that these additives suppress the formation of catalytically less active $Pd(SAr)_2(PPh_3)_2$ and more polymeric $Pd(SAr)_2(PPh_3)_n$.



Scheme 1. A proposed reaction pathway of thiocarbamoylation of **3**.

In summary, this letter demonstrated that the intermolecular Pd-catalyzed thiocarbamoylation of terminal alkynes by sulfenamide and CO was successfully realized using 2,4,5-tri-Cl-$C_6H_2SNEt_2$ as the reaction substrate and $PdCl_2(PPh_3)_2/PPh_3$/*n*-Bu_4NCl as the catalyst system. The scope and limitations of the present reaction system as well as the details about the reaction mechanism are now in progress.

Acknowledgment

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7. The stereo- and regiochemistry of **5a** were determined by the NOE experiment and the synthesis of a mixture of stereoisomers of **5a** by the reaction of (*Z*)-1,3-bis(phenylthio)-2-nonen-1-one with Et_2NH.
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9. Catalyst: $PdBr_2(PPh_3)_2$, $PdI_2(PPh_3)_2$, $PdCl_2(AsPh_3)_2$, $PdCl_2(SbPh_3)_2$, $PdCl_2[P(o\text{-tolyl})_3]_2$, $PdCl_2$(dppf), $PdCl_2$(dppe), $PdCl_2(PCy_3)_2$, and $PdCl[P(OPh)_3]_2$ in CH_3CN; ligand: $P(OMe)_3$, $P(OEt)_3$, P(2-furyl)$_3$, and P(*o*-tolyl)$_3$ with the combined use of $Pd(dba)_2$; solvent: C_6H_6, xylene, THF, dioxane, pyridine, CH_3CN, and N-methylmorpholine in the presence of **4c**; additive: *n*-Bu_4NCl, NaCl, $CaCl_2$, and CaH_2 in the presence of **4c**.
10. Spectral data of **5g**: *Z*-isomer. Yellow oil; ^1H NMR (400 M Hz, $CDCl_3$) δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.08–1.26 (m, 12H), 1.36–1.46 (m, 2H), 2.12 (t, $J = 7.6$ Hz, 2H), 3.38 (q, $J = 7.2$ Hz, 2H), 3.45 (q, $J = 7.1$ Hz, 2H), 6.28 (s, 1H), 7.67 (s, 1H), 7.70 (s, 1H). NOE study: Irradiation of vinyl singlet at δ 6.28 resulted in 2.1% increase at δ 2.12 (methylene triplet); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 13.3, 14.1, 14.7, 22.5, 28.6, 28.8, 31.4, 36.8, 40.1, 42.6, 118.0, 130.9, 132.6, 133.0, 136.2, 136.8, 149.8, 165.4; IR (NaCl) 2958, 2930, 2857, 1633, 1574, 1434, 1379, 1361, 1315, 1260, 1221, 1151, 1114, 1059, 889, 868, 818 cm^{-1}; mass spectrum (EI) *m*/*e* 423 (M^+, 13%), 351 (12%), 210 (100%), 100 (8%); Anal. Calcd for $C_{19}H_{26}Cl_3NOS$: C, 53.97; H, 6.20; N, 3.31. Found: C, 54.01; H, 6.35; N, 3.35. *E*-Isomer. Yellow oil; 8.4 mg, 2%, ^1H NMR (400 M Hz, $CDCl_3$) δ 0.80 (t, $J = 6.8$ Hz, 3H), 0.96 (t, $J = 7.2$ Hz, 3H), 1.05 (t, $J = 7.2$ Hz, 3H), 1.08–1.28 (m, 8H), 2.55 (t, $J = 7.6$ Hz, 2H) 3.13 (q, $J = 7.1$ Hz, 2H), 3.30 (q, $J = 6.9$ Hz, 2H), 5.52 (s, 1H), 7.54 (s, 1H), 7.57 (s, 1H); ^{13}C NMR (100 M Hz,$CDCl_3$) δ 13.3, 14.2, 14.4, 22.7, 29.10, 29.13, 31.7, 32.9, 40.0, 42.6, 118.4, 131.1, 131.2, 131.6, 133.8, 136.6, 149.8, 164.8, IR (NaCl) 2930, 2857, 1634, 1435, 1379, 1321, 1259, 1221, 1150, 1116, 1060, 874 cm^{-1}; mass spectrum (EI) *m*/*e* 421 (M^+, 10%), 351 (9%), 320 (9%), 210 (100%), 100 (17%); exact mass (M^+) calcd for $C_{19}H_{26}Cl_3NOS$; 421.0801 Found; 421.0796.
11. The oxidative addition of **1g** to Pd(0) did not take place in CD_3CN.
12. One possible explanation for giving **5** efficiently by employing **1g** is the stability of **6g** against disproportionation. Actually, the reaction of $PdCl_2(PPh_3)_2$ with $Pd(SAr)_2(PPh_3)_2$ (Ar = 2,4,5-tri-Cl-C_6H_2) in C_6D_6 afforded suspected **6g** in 89% yield after 2.5 h at 25 °C.
13. We have already reported that the insertion of DMAD into the S–Pd bond of $Pd(SAr)_2$(DPPE) furnished vinylpalladium, see: Sugoh, K.; Kuniyasu, H.; Kurosawa, H. *Chem. Lett.* **2002**, 106.