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Microwave-assisted palladium-catalyzed regioselective cyanothiolation of alkynes with thiocyanates

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Abstract—Applying microwave irradiation to palladium-catalyzed cyanothiolation of alkynes dramatically shortened the reaction time with good to excellent isolated yields.

Recently, the transition metal-catalyzed introduction of hetero-atoms to carbon–carbon unsaturated compounds has received a great deal of attention,[1] because synthetically useful hetero-functionalized compounds can be easily obtained in one portion. In this respect, silicon, tin, and boron compounds are well developed.[2] However, the use of transition metal catalysts for the synthetic reactions of group 16 heteroatom compounds has only advanced[3] recently, partly because of a widespread belief that sulfur and selenium compounds often tend to bind strongly to the catalyst, thus poisoning them and making catalytic reactions ineffective.

Recently, however, microwave radiation has been widely used as a source of energy.[4] When microwaves are used as a source of energy, the reaction time can be shortened and, in some cases, much higher yields than those obtained in conventional thermal reactions have been achieved. The higher yields and higher purity of products often observed after microwave irradiation can probably be attributed to the superheating effect and the homogeneous and smooth in situ heating.[4c,e,f] The yield of microwave-assisted reactions can be affected by several factors, such as the reaction medium, the rate of heating, and so on.

Our attention was turned toward cyanothiolation since, although the reaction of metal thiocyanates with alkynes represents a valuable synthesis of organic thionitriles, important intermediates for unsaturated nitrile,[5] vinyl sulfide,[6] and mercaptoacrylic acid[7] syntheses, the literature contained only one short communication reporting palladium-catalyzed cyanothiolation of alkynes for syntheses of 3-arylthio-2-alkenenitriles.[8] The reported reaction is quite useful to introduce simultaneously both sulfur and cyano groups into carbon–carbon triple bonds. Moreover, the Letter attracted our attention greatly because of the slow reaction (reaction time: 66 h) and high loading (10 mol %) of the Pd catalyst. Thus, we studied the palladium-catalyzed cyanothiolation of alkynes under microwave irradiation and found that the reaction time could be shortened from 66 h to 1 h with enhanced yields in the presence of a low loading of the catalyst (5 mol %). Herein, we now report the palladium-catalyzed cyanothiolation of alkynes under microwave irradiation to enable a straightforward synthesis of alkenyl cyanothiols with a high degree of selectivity and convenience within 1 h.

Cyanothiolation was studied using 1-octyne as a model substrate, 4-tolyl thiocyanate as a cyanothiolation agent, and $[Pd(PPh_3)_4]$ as a catalyst in 2 mL of a solvent under microwave irradiation. We screened various reaction conditions including the amount of the catalyst, the reaction solvent, the reaction temperature, and the reaction time for the cyanothiolation of 1-octyne. Results are summarized in Table 1. The yield of the reaction in benzene solution (entries 1–4) was highly dependent upon the reaction temperature and the reaction time. The best yield (85%) was obtained when the reaction temperature was 120 °C and the reaction time was 1 h. When the loading of the catalyst was lowered to

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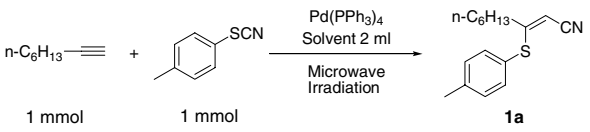
Table 1. Screening the reaction conditions[a]



1 mmol 1 mmol **1a**

Entry	mol %	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	10	Benzene	110	1	53
2	10	Benzene	120	1	85
3	10	Benzene	130	1	50
4	10	Benzene	120	0.5	56
5	5	Benzene	120	1	84
6	2	Benzene	120	1	24
7	5	CH_3CN	120	1	30
8	5	1,4-Dioxane	120	1	62
9	5	Toluene	120	1	68
10	5	Toluene	120	2	65
11	5	Toluene	150	1	71
12	5	Mesitylene	200	1	24

[a] Reaction conditions: 1-octyne (1.0 mmol), 4-tolyl thiocyanate (1.0 mmol), $Pd(PPh_3)_4$.
[b] Isolated yield.

5 mol % (entry 5), the yield (84%) was still high. However, the loading of the catalyst to 2 mol % (entry 6) was detrimental to the yield (24%). Changing the reaction solvent from benzene to another solvent, such as acetonitrile, 1,4-dioxane, toluene, or mesitylene (entries 7–12) was not helpful to the yield even at high temperatures. Thus, the reaction was highly dependent upon the solvent used. The optimum reaction conditions were established as follows: 5 mol % [$Pd(PPh_3)_4$], 2 mL of benzene, at 120 °C, and for 1 h. However, due to the toxicity of benzene, toluene was also used as a reaction solvent. Thus, the reaction time was shortened from 66 h to 1 h with enhanced yields in the presence of a low loading of the catalyst (5 mol %). Initially, other palladium catalysts including [Pd(IPr)(η^3-allyl)] (IPr = *N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidene; allyl = 1,1′-diphenyl-2-methylallyl), [(η^3-PhC_3H_4)-$Pd(C_2H_4)]_2$, and Pd/C were also tested as a catalyst. However, they were all inactive for the cyanothiolation of 1-octyne.

We next investigated various alkynes for the cyanothiolation (Table 2).[9] For all the reactions studied, only a

Table 2. $Pd(PPh_3)_4$-catalyzed cyanothiolation of terminal alkynes[a]

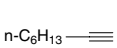
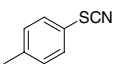
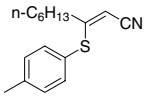
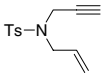
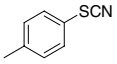
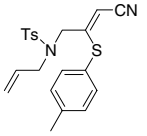
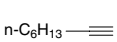
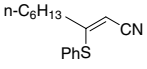
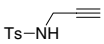
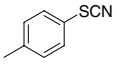
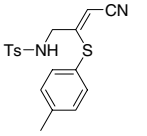
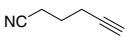
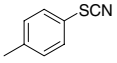
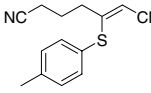
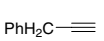
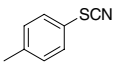
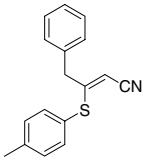
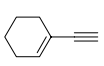
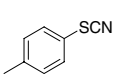
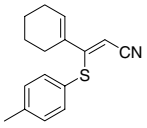
Entry	Alkyne	Thiocyanate	Product	Yield[b] (%)	*E*/*Z*[c]
1			 **1a**	85[d] 71[e]	0/100
2			 **1b**	78[d] 73 58[e]	0/100
3		PhSCN	 **1c**	76[d]	0/100
4			 **1d**	62 53[e]	0/100
5			 **1e**	83 61[e]	0/100
6			 **1f**	72 67[e]	0/100
7			 **1g**	86 69[e]	0/100

Table 2 (*continued*)

Entry	Alkyne	Thiocyanate	Product	Yield[b] (%)	*E*/*Z*[c]
8	Ph—	SCN	CN, S, **1h**	92 72[e]	0/100
9		SCN	CN, S, **1i**	87 57[e]	0/100
10[f]	4-Octyne	SCN		NR[g]	

[a] Reaction conditions: alkyne (1.0 mmol), thiocyanate (1.0 mmol), benzene (2 mL), $Pd(PPh_3)_4$ (5 mol %), 120 °C, 1 h.
[b] Isolated yield.
[c] *E*/*Z* ratios were determined by differential NOE measurements.
[d] 10 mol % catalyst used.
[e] Toluene (2 mL), 150 °C.
[f] Mesitylene (2 mL), 200 °C.
[g] No reaction.

Z-isomer was obtained. Thus, the reaction was highly regioselective. In order to compare with the published results, we also examined the reactions using 10 mol % of the catalyst. Treatment of 1-octyne with 4-tolyl thiocyanate in the presence of 10 mol % of the catalyst in benzene for 1 h gave (*Z*)-3-(4-tolylthio)-2-nonenenitrile (**1a**) in 85% yield in benzene (treated with 5 mol % of the catalyst, 71% yield in toluene) as the sole product (entry 1). When a 1,6-enyne with an N-Ts tether was treated with 10 mol % or 5 mol % of the catalyst (entry 2), the yield was 78% and 73% (58% in toluene), respectively. Thus, the loading of the catalyst can be lowered to 5 mol % without losing the yield of the reaction. Functionalities such as secondary amine, cyano, and olefinic groups also tolerated the reaction conditions (entries 4, 5, and 7). For the cyanothiolation of 1-octyne with phenyl thiocyanate (entry 3), the expected cyanothiolated compound (**1c**) was obtained in 76% yield compared to 61% under the thermal reaction conditions.

For cyanothiolation of 5-hexynenitrile, 2-propyn-1-ylbenzene, 1-ethynyl-cyclohexene, and phenylacetylene, 1-ethynyl-4-methylbenzene (entries 5–9), the use of 5 mol % catalyst gave high yields (72–92% in benzene and 57–69% in toluene) of the corresponding cyanothiolated products. Unfortunately, an internal alkyne, 4-octyene, was inert under our reaction conditions (entry 10). Single crystals for the cyanothiolated products in entries 2 (**1b**) and 4 (**1d**) suitable for an X-ray diffraction study were grown in dichloromethane and their structures were solved (Figs. 1 and 2).[10] However, unfortunately, reactions with *n*-butyl thiocyanate gave poor yields of cyanothiolation products.

In conclusion, we have demonstrated the usefulness of microwave irradiation in the palladium-catalyzed cyanothiolation of terminal alkynes. Compared to thermal reactions, the reaction yielded much higher yields with a high regioselectivity and the reaction time was dramatically shortened from 66 h to 1 h with a slightly low loading of the catalyst.

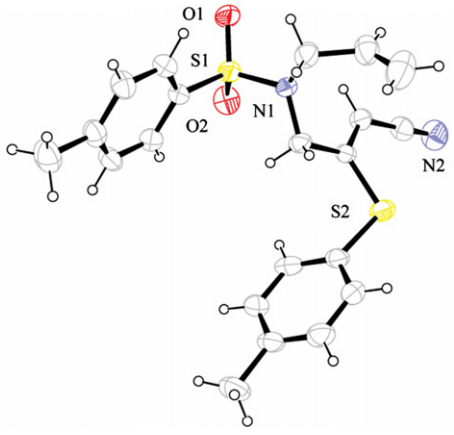


Figure 1. X-ray structure of **1b**.

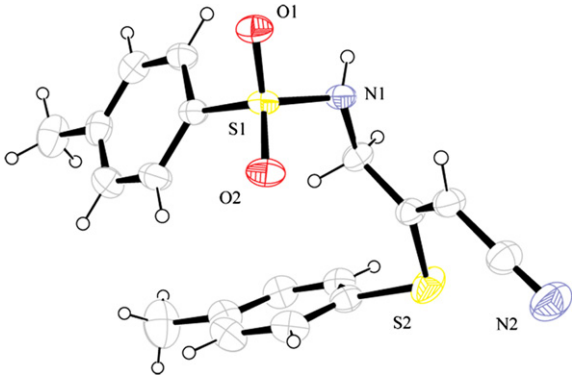


Figure 2. X-ray structure of **1d**.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.041.

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9. General procedure: microwave-assisted reactions were carried out on a CEM Discover microwave reactor with a circular (1.3 cm (d) × 8 cm (l), volume: 10 mL), single mode, self-tuning microwave applicator operation at 2450 MHz (300 W). Into a 10 mL glass tube of a microwave reactor, $Pd(PPh_3)_4$ (5 mol %), benzene (2 mL), alkyne (1.0 mmol), and thiocyanate (1.0 mmol) were added in one portion and the tube was sealed. After microwave irradiation for 1 h at 120 °C, the tube was cooled to room temperature. A column chromatography (eluted with hexane/ethylacetate) gave the cyanothiolation products.
Compound **1a**: ^{1}H NMR ($CDCl_3$): δ 0.83 (t, $J = 7.2$ Hz, 3H), 1.13 (m, 4H), 1.21 (m, 2H), 1.39 (m, 2H), 2.12 (m, 2H), 2.38 (s, 3H), 5.25 (s, 1H), 7.19 (d, $J = 7.9$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.2, 21.5, 22.6, 28.4, 28.5, 31.4, 36.2, 92.8, 116.4, 125.8, 130.3, 135.2, 140.2, 166.5; Exact mass for ($C_{16}H_{21}N_1S_1$, FAB): Calcd 259.1395. Found: 259.1391.
Compound **1b**: ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 2.43 (s, 3H), 3.68 (d, $J = 6.8$ Hz, 2H), 3.70 (d, $J = 1.6$ Hz, 2H), 5.00 (dd, $J = 1.1$, 17.0 Hz, 1H), 5.09 (d, $J = 10.1$ Hz, 1H), 5.45 (tdd, $J = 6.8$, 10.1, 16.9 Hz, 1H), 5.70 (t, $J = 1.5$ Hz, 1H), 7.19 (d, $J = 8.2$ Hz 2H), 7.28 (d, $J = 7.8$ Hz, 2H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.57 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.7, 50.6, 51.8, 96.2, 115.9, 120.9, 124.7, 127.4, 130.1, 130.6, 131.5, 134.8, 136.1, 140.5, 144.3, 158.7; Exact mass for ($C_{21}H_{22}N_2O_2S_2$, FAB): Calcd 398.1123. Found: 398.1120.
Compound **1d**: ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 2.44 (s, 3H), 3.58 (d, $J = 6.5$ Hz, 2H), 4.89 (t, $J = 6.1$ Hz, 1H), 5.52 (s, 1H), 7.18 (d, $J = 7.8$ Hz, 2H), 7.30 (m, 4H), 7.61 (d, $J = 7.6$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 21.8, 46.6, 96.0, 115.6, 124.3, 127.2, 130.1, 130.8, 134.9, 136.7, 140.8, 144.4, 159.0; Exact mass for ($C_{18}H_{18}N_2O_2S_2$, FAB): Calcd 358.0810. Found: 358.0810.
Compound **1e**: ^{1}H NMR ($CDCl_3$): δ 1.75 (m, 2H), 2.25 (t, $J = 7.0$ Hz, 2H), 2.33 (t, $J = 7.4$ Hz, 2H), 2.39 (s, 3H), 5.36 (s, 1H), 7.22 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 16.3, 21.5, 24.0, 34.6, 95.1, 115.8, 118.7, 125.1, 130.7, 135.0, 140.8, 163.2; Exact mass for ($C_{14}H_{14}N_2S_1$, FAB): Calcd 242.0878. Found: 242.0876.
Compound **1f**: ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.39 (s, 2H), 5.04 (s, 1H), 6.96 (d, $J = 6.6$ Hz, 2H), 7.18 (d, $J = 7.9$ Hz, 2H), 7.26 (m, 3H), 7.35 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 42.4, 94.6, 116.3, 125.3, 127.5, 128.9, 129.3, 130.4, 135.6, 135.9, 140.5, 165.1; Exact mass

for ($C_{17}H_{15}N_1S_1$, FAB): Calcd 265.0925. Found: 265.0923.

Compound **1g**: ^{1}H NMR ($CDCl_3$): δ 1.39 (m, 4H), 1.97 (m, 4H), 2.24 (s, 3H), 5.42 (s, 1H), 6.34 (s, 1H), 7.02 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.3, 21.5, 22.3, 26.1, 27.2, 96.0, 117.1, 129.4, 129.9, 131.8, 134.7, 136.1, 138.1, 162.2; Exact mass for ($C_{16}H_{17}N_1S_1$, FAB): Calcd 255.1082. Found: 255.1081.

Compound **1h**: ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H), 5.61 (s, 1H), 6.99 (m, 2H), 7.17 (m, 2H), 7.29 (m, 3H), 7.43 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 21.3, 96.7, 116.6, 127.7, 128.5, 128.7, 130.0, 130.6, 132.9, 136.4, 138.7, 162.1; Exact mass for ($C_{16}H_{13}N_1S_1$, FAB): Calcd 251.0769. Found: 251.0771.

Compound **1i**: ^{1}H NMR ($CDCl_3$): δ 2.24 (s, 3H), 2.29 (s, 3H), 5.59 (s, 1H), 6.99 (d, $J = 7.8$ Hz, 2H), 7.06 (d, $J = 7.8$ Hz, 2H), 7.16 (d, $J = 7.9$ Hz, 2H), 7.33 (d, $J = 7.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.3, 21.5, 96.3, 116.8, 128.1, 128.5, 129.5, 130.1, 132.7, 133.6, 138.5, 141.1, 161.8; Exact mass for ($C_{17}H_{15}N_1S_1$, FAB): Calcd 265.0925. Found: 265.0923.

10. Single crystals were grown by slow evaporation of CH_2Cl_2 solution. Crystal data for **1b**: $C_{21}H_{22}N_2O_2S_2$ (295 K). $M = 398.53$, triclinic, space group $P\bar{1}$, $a = 8.9886(4)$ Å, $b = 15.8861(6)$ Å, $c = 16.8435(5)$ Å, $\alpha = 64.748(2)°$, $\beta = 88.721(2)°$, $\gamma = 80.136(2)°$, $V = 2139.68(14)$ Å^3, $Z = 4$, $\rho_{calc.} = 1.237$ g/cm^{-3}, absorption coefficient = 0.266 mm^{-1}, total reflections collected 14,217, unique 9732 ($R_{int} = 0.0455$), GOF = 1.022, $R_1 = 0.0789$, $R_w = 0.1979$ ($I > 2\sigma(I)$). Crystal data for **1d**: $C_{18}H_{18}N_2O_2S_2$ (295 K). $M = 358.46$, monoclinic, space group $P2_1/c$, $a = 10.0840(2)$ Å, $b = 19.8786(8)$ Å, $c = 10.2642(3)$ Å, $\beta = 116.207(2)$, $V = 1846.01(10)$ Å^3, $Z = 4$, $\rho_{calc.} = 1.290$ g/cm^{-3}, absorption coefficient = 0.300 mm^{-1}, total reflections collected 6894, unique 4042 ($R_{int} = 0.0208$), GOF = 1.099, $R_1 = 0.0436$, $R_w = 0.1274$ ($I > 2\sigma(I)$). CCDC reference numbers 647,483 (**1b**) and 646,092 (**1d**) contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.