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Microwave-assisted Sonogashira-type cross couplings of various heterocyclic methylthioethers

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ABSTRACT

A novel, microwave-assisted, palladium-catalyzed Sonogashira-type coupling of terminal alkynes with a variety of heteroaryl thiomethylethers is reported. The developed protocol allows for further utility and diversification of a number of chemically and biologically interesting scaffolds.

Palladium-catalyzed cross-coupling reactions are one of the most versatile procedures used in organic synthesis.[1] Typical reactions of this sort generally involve the coupling of organometallic reagents or boronic acids with vinyl or aryl halides and triflates. There are numerous reports describing the Stille,[2] Suzuki–Miyaura,[3] Negishi,[4] and Sonogashira[5] reactions with vinyl or aryl halides and triflates. Unfortunately, the availability of many heteroaryl halides and triflates is limited and requires alternative coupling partners to access a wider variety of molecules. Recently, a new class of coupling partners was developed to extend the scope of these versatile reactions.

Liebeskind reported palladium-catalyzed, Cu(I)-mediated couplings of boronic acids with a variety of thioorganics, including heteroaryl methylthioethers, under neutral conditions to form carbon–carbon bonds.[6] The methodology was also extended to couple organotin reagents with heteroaryl thioethers under similar conditions.[7] There are a few examples of carbon–carbon cross couplings involving Ni-catalyzed Kumada-type couplings of heteroaromatic thioethers with Grignard reagents, but reaction conditions are harsh and not compatible with most functionalities.[8] The copper-mediated couplings, however, are quite facile and allow most functionalities to be present. Heteroaryl thioethers have also been successfully coupled with organozinc reagents in the absence of the Cu(I) additive.[9] Surprisingly, there are limited reports using thioethers as coupling partners despite their inherent reactivity and compatibility with numerous transformations. It is our intent to expand the scope of Sonogashira reactions using methylthioethers as coupling partners. The methodology reported herein will investigate the reactivity of heterocyclic methylthioethers with alkynes using both conventional Sonogashira reaction protocols as well as the effect of microwaves on the reaction.

Medicinal chemistry is a practice that is challenging and requires the ability to diversify particular structural scaffolds to develop structure–activity relationships (SARs) and to optimize for biological activity.[10] The propensity of drugs to have substituted aryl and heteroaryl moieties is unrivaled and the development of new methods to diversify structural scaffolds is particularly appealing. Recently, it was reported that boronic acids could be successfully coupled to cyclic thioamides using the Liebeskind protocol under microwave irradiation.[11] Microwaves provide a powerful way to do synthetic chemistry, and the ability of microwaves to shorten reaction times, increase reaction yields, and to facilitate reactions that are otherwise unsuccessful under conventional hood conditions is the property that medicinal chemists are looking for to optimize their everyday procedures.[12]

The afore-mentioned palladium-catalyzed reactions using various thiol derivatives compelled us to explore the scope and reactivity of a variety of heteroaryl methylthioethers using microwaves. Because palladium insertion into the carbon-sulfur bond is quite facile,[6] it should be possible to access other types of reactions in addition to the Suzuki- and Stille-type of protocols mentioned above. There has been only one report, which has recently published, of Sonogashira-type couplings using terminal alkynes and thiophenyl-substituted pyrazinones.[13] We wish to report herein Sonogashira-type couplings of terminal alkynes to a variety of heteroaromatic methylthioethers using microwave irradiation.

Commercially available 2-(methylthio)pyridine was chosen to investigate the coupling of alkynes and heteroaromatic thioethers. Phenylacetylene was used initially as the coupling partner as a number of reaction conditions were tried. Various Cu(I) salts such as CuI, CuOTf, and CuTC (copper(I) 2-thiophene carboxylate) were used in combination with a palladium(II) catalyst to carry out the reaction. CuI proved to be the copper salt of choice, which is also true for typical Sonogashira reactions. Initially, reactions were run in refluxing THF using conventional heating conditions in the hood. Unfortunately, only starting materials were recovered from the reactions as no desired coupling products were formed after 16 h (Table 1, entries 1 and 2), suggesting that more vigorous conditions were required to facilitate the reaction. We then tried running the reactions in the microwave at 100 °C for 0.5 h (Table 1, entry 3) and the coupling product was formed in 24% yield.

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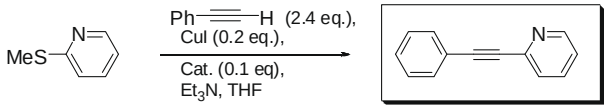
Table 1
Optimization of coupling protocol[a]



Entry	Catalyst	Heat source	Temperature (°C)	Time (h)	Yield (%)
1	$Pd(dppf)Cl_2$	Hood	66	16	0
2	$Pd(PPh_3)_2Cl_2$	Hood	66	16	0
3	$Pd(dppf)Cl_2$	μw	100	0.5	24
4	$Pd(dppf)Cl_2$	μw	100	1	35
5	$Pd(dppf)Cl_2$	μw	66	1	6
6	$Pd(PPh_3)_2Cl_2$	μw	100	1	20
7	$Pd(dppf)Cl_2$[b]	μw	100	1	40
8	$Pd(dppf)Cl_2$[c]	μw	100	2 × 0.5 h	53
9	$Pd(dppf)Cl_2$[d]	μw	100	2 × 1 h	65

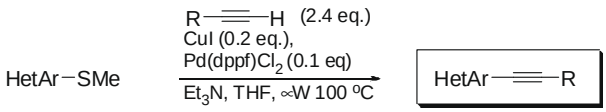
[a] Typical reaction uses CuI (0.2 equiv), Pd (0.1 equiv), and Et_3N (2 equiv).
[b] Used CuI (0.4 equiv), Pd (0.2 equiv), and Et_3N (4 equiv).
[c] Typical reaction for 0.5 h then add additional CuI (0.2 equiv), Pd (0.1 equiv), and Et_3N (2 equiv).
[d] Typical reaction for 1 h then add additional CuI (0.2 equiv), Pd (0.1 equiv), and Et_3N (2 equiv).

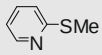
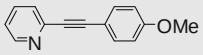
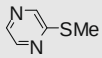
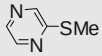
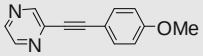
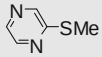
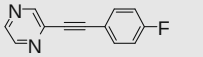
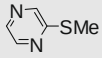
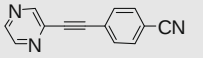
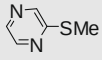
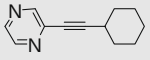
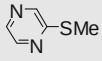
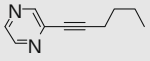
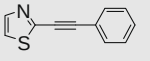
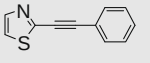
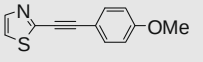
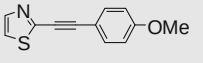
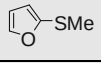
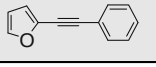
Increasing reaction time to 1 h resulted in only a slight increase in yield (Table 1, entry 4). It was unclear at this point if the microwaves were facilitating the reaction or if product was being formed simply from increased reaction temperature. Running the reaction in the microwave at 66 °C, the boiling point of THF (Table 1, entry 5), gave only traces of product, suggesting that increased temperature is essential for the reaction to take place, but does not explain what effect the microwaves have on the reaction. One major advantage of using the microwave to run reactions is the ability to superheat solvent without using pressure tubes. Using a more common palladium catalyst, $Pd(PPh_3)Cl_2$, for Sonogashira reactions gave lower yield of the desired product (Table 1, entry 6).

Keeping $Pd(dppf)Cl_2$ as the palladium source, we tried increasing the reaction time to 2 h, but it did not increase the conversion. We then decided to change the amounts of reagents, while keeping the same reaction time. Doubling the reagents, CuI (0.4 equiv), $Pd(dppf)Cl_2$ (0.2 equiv), and Et_3N (4 equiv), at the beginning of the reaction followed by irradiation for 1 h gave a slightly higher yield (40%, Table 1, entry 7). Interestingly, when additional fresh CuI (0.2 equiv), $Pd(dppf)Cl_2$ (0.1 equiv), and Et_3N (2 equiv) were added to the original reaction mixture after 0.5 h followed by irradiation for an additional 0.5 h the product was formed in 53% (Table 1, entry 8). This represents a significant increase in yield when comparing entries 7 and 8 which have the same reaction time and reagents equivalents, but the addition of reagents at the beginning and halfway through the reaction resulted in higher yield of product (entry 8) than that obtained from adding all the reagents at the beginning of the reaction (entry 7). This suggests that the catalyst decomposes under the reaction conditions, and that it is somewhat overcome when the reagents are added portionwise. Increasing the reaction time from 0.5 h to 1 h for the portionwise protocol gave a reasonable 65% yield (Table 1, entry 9), and it was this procedure that was used to determine generality and scope of the reaction.[14]

With a better understanding of the reaction conditions and which protocol that should be followed, we explored the scope of the reaction using various heteroaromatic thiomethylethers and substituted alkynes. 4-Methoxyphenyl acetylene reacted with 2-(methylthio)pyridine to give yield (71%) comparable to that obtained with phenylacetylene (compare Table 1, entry 9, with Table 2, entry 1) indicating that the electron-donating group did not increase reactivity for this particular example. Attention then turned to different heterocyclic thiomethyl ethers to determine

Table 2[16]
Scope of Sonogashira couplings[a]



Entry	HetAr	Product	Yield (%)	# of 1 h Runs
1[b]			71	2
2			74	1
3			70	1
4[c]			48	1
5[c]			24	1
6			68	1
7			60	1
8			31	1
9[b]			72	2
10			35	1
11[b]			68	2
12[b]			17	2

[a] Typical reaction uses CuI (0.2 equiv), Pd (0.1 equiv), and Et_3N (2 equiv).
[b] Typical reaction for 1 h then add additional CuI (0.2 equiv), Pd (0.1 equiv), and Et_3N (2 equiv).
[c] An additional run yielded 65% and 31% of the F and CN analogs, respectively.

their reactivity with respect to 2-(methylthio)pyridine. 2-(Methylthio)pyrazine proved to be more reactive than the 2-(methylthio)pyridine as just one 1 h run using phenylacetylene gave 74% (Table 2, entry 2) of the coupled product and only 35% for the pyridine analog (Table 1, entry 4). The 4-methoxyphenyl acetylene works well with 2-(methylthio)pyrazine and again showed no difference when compared to phenylacetylene (Table 2, entry 3). Interestingly, when entry 3 (Table 2) was run in the hood, not shown, in refluxing THF for 16 h, only 32% of the desired product was formed. This result suggests that higher temperature and microwaves, or both are required to form product in appreciable yields. Using phenylacetylenes that contain electron-withdrawing groups, like the 4-fluoro and 4-cyano analogs, gave lower yields, 48% and 24%, respectively (Table 2, entries 4 and 5). An additional run with the fluoro analog gave a good 65% yield of product, but the yield of cyano derivative only increased slightly to 31%. The

2-(methylthio)pyrazine was generally more reactive as it also reacts with non-aromatic and acyclic alkynes (Table 2, entries 6 and 7) to give good yields of the coupled products after a single 1 h run.

There are a large number of drugs that contain five-membered heterocycles, so application of this methodology to those systems would be essential.[15] 2-Methylthio-1,3-thiazole reacts with phenylacetylene giving a surprisingly low (31%) yield of the coupled product as we expected more robust reactivity of this methylthioether (Table 2, entry 8). A second run, however, afforded a good 72% yield of the desired product (Table 2, entry 9). 4-Methoxyphenyl acetylene gives yields comparable to those given by phenylacetylene after both one and two runs (Table 2, entries 10 and 11). To our delight, the very unreactive 2-methylthiofuran gave desired product albeit in low yield even after two runs (Table 2, entry 12).

In conclusion, we report novel Sonogashira-type couplings using microwave irradiation with a variety of heterocyclic methylthioethers as coupling partners. The standard protocol is general across a number of heterocyclic methylthioethers and terminal alkynes. The generality of these reactions will continue to be explored as they can offer unique utility and diversification to a variety of biological systems.

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14. *Representative procedure for coupling heteroaromatic thiomethylethers*: Solid CuI (30 mg, 0.16 mmol) and Pd(dppf)Cl_2 (65 mg, 0.08 mmol) were added to a THF solution (3 mL) of 2-(methylthio)pyridine (89 μL, 0.80 mmol), phenylacetylene (0.17 mL, 1.60 mmol), and Et_3N (0.22 mL, 1.60 mmol) and the mixture was heated in the microwave at 100 °C for 1 h. Additional solid CuI (30 mg, 0.16 mmol), Pd(dppf)Cl_2 (65 mg, 0.08 mmol), and Et_3N (0.22 mL, 1.60 mmol) were added and the mixture was heated in the microwave at 100 °C for 1 h . The mixture was diluted with EtOAc and the organic layer was washed with 10% aq NH_4OH, water, and then with brine; dried (Na_2SO_4); concentrated; and purified via column chromatography (20–80% EtOAc/heptane) to give 93 mg (65%) of 2-phenylethynyl-pyridine.
Representative procedure for coupling to 2-(methylthio)pyrazine: Solid CuI (30 mg, 0.16 mmol) and Pd(dppf)Cl_2 (65 mg, 0.08 mmol) were added to a THF solution (3 mL) of 2-(methylthio)pyrazine (100 mg, 0.79 mmol), phenylacetylene (0.17 mL, 1.58 mmol), and Et_3N (0.22 mL, 1.58 mmol), and the mixture was heated in the microwave at 100 °C for 1 h. The mixture was diluted with EtOAc and the organic layer was washed with 10% aq NH_4OH, water, and then with brine; dried (Na_2SO_4); concentrated; and purified via column chromatography (0–50% EtOAc/heptane) to give 105 mg (74%) of 2-phenylethynyl-pyrazine.All experiments were carried out on a CEM Explorer microwave system using a 10 mL vial that contained a stir bar and snap-on cap. The reaction settings were as follows: temperature = 100 °C; power = 300 W; ramp = 3 min; hold time = 60 min; pressure = 250 psi; stirring on.
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16. *Spectroscopic data for new compounds in* Table 2: *Entry 3*: ^{1}H NMR (chloroform-*d*, 300 MHz): δ 8.74 (s, 1H), 8.56 (s, 1H), 8.46 (d, J = 2.6 Hz, 1H), 7.52–7.61 (m, J = 8.7 Hz, 2H), 6.86–6.96 (m, J = 8.7 Hz, 2H), 3.85 ppm (s, 3H); MS m/z 211 (M+H); *Entry 4*: ^{1}H NMR (chloroform-*d*, 300 MHz): δ 8.76 (d, J = 1.5 Hz, 1H), 8.59 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 7.55–7.69 (m, 2H), 7.05–7.15 ppm (m, 2H), MS m/z 199 (M+H); *Entry 5*: ^{1}H NMR (chloroform-*d*, 300 MHz): δ 8.80 (s, 1H), 8.63 (s, 1H), 8.56 (d, J = 2.3 Hz, 1H), 7.70 ppm (s, 4H), MS m/z 206 (M+H); *Entry 6*: ^{1}H NMR (chloroform-*d*, 300 MHz): δ 8.61 (d, J = 1.5 Hz, 1H), 8.48–8.53 (m, 1H), 8.42 (d, J = 2.3 Hz, 1H), 2.58–2.75 (m, 1H), 1.86–1.99 (m, 2H), 1.70–1.84 (m, 2H), 1.49–1.66 (m, 3H), 1.29–1.45 ppm (m, 3H), MS m/z 187 (M+H).