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# The First Palladium-Catalyzed Desulfitative Sonogashira-Type Cross-Coupling of (Hetero)aryl Thioethers with Terminal Alkynes

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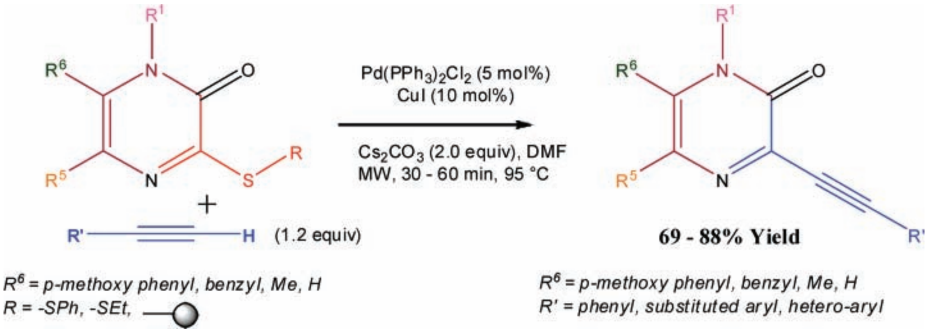
## ABSTRACT



**An unprecedented desulfitative Sonogashira-type cross-coupling protocol is exemplified by the synthesis of substituted 5-chloro-3-alkynylpyrazinones from the corresponding 5-chloro-3-(phenylsulfanyl) pyrazin-2(1*H*)-ones. The applicability of the method is extended to solid-phase linked pyrazin-2(1*H*)-ones as well as to some oxazinones, pyrazines, and phenyl thioesters.**

Palladium-catalyzed C−C and C-heteroatom bond forming reactions are among the most powerful methods in organic synthesis.[1] The Sonogashira cross-coupling reaction is an illustrative example representing an important tool for the coupling of a terminal alkyne with an aromatic halide in the presence of a copper cocatalyst and a base.[2] The past few years have witnessed a fierce search for convenient conditions, better yields, and shorter reaction times for this protocol.[3] Notwithstanding the continued interest in the transition-metal-catalyzed cross-coupling reactions during the past years, organometallic cross-coupling reactions involving the desulfitative removal of the C−S bond of aryl and alkyl thioethers, sulfones, and sulfonyls as electrophilic partners have gained attention rather recently.[4] Seminal work by Liebeskind and co-workers described the application of

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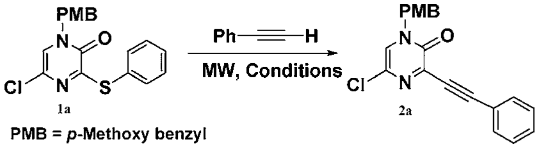
**Table 1.** Optimization Study for the Desulfitative Alkynylation of **1a**[a]



| entry | substrate | Pd catalyst (mol %) | Cu source | base | solvent | time (min) | yield of **2a**[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | $Pd(OAc)_2$ (5) | CuI | $Et_3N^c$ | DMF | 40 | 54 |
| 2 | **1a** | $PdCl_2(5)/PPh_3(10)$ | CuI | $Et_3N^c$ | DMF | 40 | 45 |
| 3 | **1a** | $Pd(PPh_3)_4$ (5) | CuI | $Et_3N^c$ | DMF | 40 | 65 |
| 4 | **1a** | $Pd_2(dba)_3$ (5) | CuI | $Et_3N^c$ | DMF | 60 | $0^d$ |
| 5 | **1a** | $Pd(dppf)Cl_2$ (5) | CuI | $Et_3N^c$ | DMF | 60 | $0^d$ |
| 6 | **1a** | $Pd(PPh_3)Cl_2$ (5) | CuI | $Et_3N^c$ | DMF | 40 | 74 |
| 7 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) |  | $Et_3N^c$ | DMF | 60 | 28 |
| 8 | **1a** |  |  | $Et_3N^c$ | DMF | 60 | $0^d$ |
| 9 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuBr | $Et_3N^c$ | DMF | 60 | 57 |
| 10 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuTC | $Et_3N^c$ | DMF | 60 | $0^d$ |
| 11 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuI | $K_2CO_3$ | DMF | 60 | 58 |
| **12** | **1a** | **$Pd(PPh_3)_2Cl_2$ (5)** | **CuI** | **$Cs_2CO_3$** | **DMF** | **45** | **79** |
| 13 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuI | $Cs_2CO_3$ | DMF | 60 | 75 |
| 14 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuI | $Cs_2CO_3$ | THF | 60 | 62 |
| 15 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuI | $Cs_2CO_3$ | MeCN | 60 | 49 |
| 16 | **1a** | $Pd(PPh_3)_2Cl_2$ (5) | CuI | $Cs_2CO_3$ | 1,4-Dioxane | 60 | 55 |

[a] Reactions were run on a 0.1mmol scale of **1a**, applying phenylacetylene (1.2 equiv), Pd catalyst (5 mol %), Cu source (10 mol %), base (2.0 equiv), and solvent (3.0 mL). The reaction was irradiated (monomode microwave instrument) for the stipulated time at 95 °C ceiling temperature using a maximum power of 75 W. [b] Isolated yields of the products (single runs). [c] $Et_3N$ was used as a mixture with DMF (1:1). [d] Only unreacted starting material was recovered.

CuTC as an effective cocatalyst for the coupling of aryl heteroaryl thioethers with organoboron, organotin, or organoindium compounds.[5] The same authors also reported the coupling of electrophilic thioalkynes with arylboronic acids.[6] Desulfitative Stille-, Suzuki−Miyaura-, and Sonogashira−Hagihara cross-couplings as well as Mizoroki−Heck couplings of sulfonyl chlorides have been described by Vogel and co-workers.[7] However, to the best of our knowledge, to date, no report has appeared regarding the coupling of an electrophilic aryl or heteroaryl thioether with a terminal alkyne applying a transition-metal-catalyzed cross-coupling protocol. We here disclose the unprecedented desulfitative Sonogashira-type cross-coupling reaction of an aromatic thioether applying 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones and variously substituted terminal alkynes. The applicability of the method was extended to solid-phase linked pyrazin-2(1*H*)-ones as well as to some oxazinones, pyrazines, and phenyl thioester.

Pursuant to our longstanding interest in the synthesis and microwave-assisted decoration of the pyrazin-2(1*H*)-one scaffold[8] and to our recently described protocol for the transition-metal-catalyzed orthogonal solid-phase decoration of the 2(1*H*)-pyrazinone scaffold using a sulfur linker,[9] we were keen to investigate whether a desulfitative Sonogashira-type reaction at the C3-position of 5-chloro-3-(phenylsulfanyl) pyrazin-2(1*H*)-ones should be possible. The test reactions were performed with 5-chloro-1-(4-methoxybenzyl)-3-(phenylsulfanyl)pyrazin-2(1*H*)-one (**1a**) and phenylacetylene as a model system. Different palladium catalysts, cocatalysts, bases, and solvents were screened to derive an optimized protocol (Table 1).

Six different palladium catalysts were investigated (Table 1, entries 1−6). All of these reactions were performed, as per the standard Sonogashira protocol,[2] by applying 10 mol % of CuI as the cocatalyst and $Et_3N$ as the base in dry DMF under microwave irradiation at 95 °C ceiling temperature for the stipulated time. Among these different palladium catalysts, $Pd(PPh_3)_2Cl_2$ provided the best yield of 74% (Table 1, entry 6). Reaction with $Pd(PPh_3)_4$ resulted in a moderate yield of 65% (Table 1, entry 3), while the reaction did not proceed at all when $Pd_2(dba)_3$ or $Pd(dppf)Cl_2$ were used even

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(7) (a) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (b) Dubbaka, S. R.; Vogel, P. *Adv. Syn. Catal.* **2004**, *346*, 1793. (c) Dubbaka S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95. (d) Dubbaka, S. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 7674 and references cited therein. (e) Vogel P. Pierre; Turks M. S.; Bouchez L. Laure; Marković D. Dean; Varela-Álvarez A. Adrián; Sordo J. A. *Acc. Chem. Res.* **2007**, *40*, 931.

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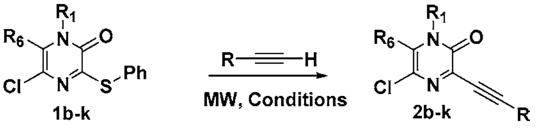
upon an extended reaction time (Table 1, entries 4 and 5). Having established $Pd(PPh_3)_2Cl_2$ as the optimal catalyst, we investigated the influence of the cocatalyst. However, replacement of CuI for CuBr or CuTC resulted in a low yield or no conversion at all (Table 1, entries 9 and 10). Moreover, it was observed that both the catalyst and the cocatalyst were mandatory for successfully performing the reaction, as very little or even no product was formed in the absence of one or both of them (Table 1, entries 7 and 8). Having found the optimum catalyst/cocatalyst combination, further investigations were made for the choice of the base (Table 1, entries 11 and 12), the solvent (Table 1, entries 14−16), and reaction time (Table 1, entries 12 and 13). Interestingly, we found that when $Et_3N$ was replaced by $Cs_2CO_3$ an increased yield of 79% was obtained (Table 1, entry 12). Finally, optimum reaction conditions were achieved when a mixture of 1.2 equiv of phenyl acetylene, 5 mol % of $Pd(PPh_3)_2Cl_2$, 10 mol % of CuI, and 2.0 equiv of $Cs_2CO_3$ in 3.0 mL of DMF was irradiated for 45 min at a ceiling temperature of 95 °C applying a maximum power of 75 W, affording the desired compound **2a** in 79% yield (Table 1, entry 12). The protocol was checked with conventional heating conditions providing lower yield of 35% of **2a** after 6 h.

Having found the optimal conditions for the desulfitative alkynylation reaction, we next investigated the scope and limitations of the protocol. A series of differently substituted 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones (**1b**−**k**) was subjected to the optimized conditions (Table 2). The reaction progressed excellently in case of either alkyl or aryl acetylenes and irrespective the substitution pattern of the pyrazinone. Also the 3-thiophenyl acetylene worked well yielding compound **2k** in 69% yield (Table 2, entry 10).

**Table 2.** Investigation of the Scope and Limitations of the Optimized Desulfitative Alkynylation Protocol[a]

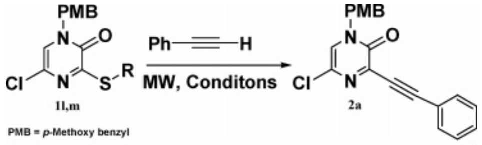


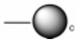
| entry | $R^1$ | $R^6$ | R | product | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | PMB | H | 4-$^t$Bu-Ph | **2b** | 85 |
| 2 | PMB | H | hexyl | **2c** | 78 |
| 3 | PMB | H | 2-Me-Ph | **2d** | 79 |
| 4 | PMB | 4-OMe-Ph | 4-F-Ph | **2e** | 88 |
| 5 | PMB | 4-OMe-Ph | 4-Et-Ph | **2f** | 84 |
| 6 | PMB | Bn | Ph | **2g** | 72 |
| 7 | PMB | Bn | 4-$CH_3$-Ph | **2h** | 80 |
| 8 | PMB | Me | cyclohexyl | **2i** | 81 |
| 9 | $CH_2$-cyclohexyl | H | 4-OMe-Ph | **2j** | 82 |
| 10 | $(CH_2)_3$-Ph | H | 3-thiophenyl | **2k** | 69 |

[a] Reactions were run on a 0.3 mmol scale of **1b**−**k** using the optimized protocol. The mixture was irradiated for 45 min in a sealed tube (monomode microwave instrument) at a ceiling temperature of 95 °C and 75 W maximum power. [b] Isolated yields of the products (single runs).

Next, we were interested to see if an alkylthio substituent in C3-position, instead of a phenylthio substituent, would also allow the same Sonogashira-type transformation. Therefore the ethylthio-substituted pyrazinone **1l** was subjected to the newly developed protocol. Gratifyingly the reaction proceeded smoothly upon irradiation for 60 min, yielding the desired compound **2a** in 65% (Table 3, entry 1).

**Table 3.** Extension of the Procedure to Alkylthio-Substituted and Resin-Linked Pyrazinones[a]



| entry | R | product | time (min) | yield (%)[b] |
|---|---|---|---|---|
| 1 | ethyl | **2a** | 60 | 65 |
| 2 |  [c] | **2a** | 90 | 54 |

[a] Reactions were run on a 0.3 mmol scale of **1l**,**m** using the optimized protocol. The mixture was irradiated for 60 min in a sealed tube (monomode microwave instrument) at a ceiling temperature of 95 °C and 75 W maximum power. [b] Isolated yields of the products (single runs). [c] A commercially available mercapto phenylpropionyl AM resin (loading 0.88 mmol/g) was used; 3.0 equiv of acetylene was applied.

Moreover, to broaden the scope of our protocol, a resin-linked pyrazinone **1m**, was subjected to the same procedure. This resulted in the formation of the desired alkynylated pyrazinone **2a** in 54% yield, after an irradiation time of 90 min (Table 3, entry 2). The resin used was a commercially available mercaptophenylpropionyl AM resin (loading 0.88 mmol/g) while the pyrazinone was linked via a thioether bond at its C3-position. This interesting extension of our methodology opens the way for the fast generation of a small combinatorial library of valuable C3-alkynylated pyrazinones, using our previously described transition-metal-atalyzed orthogonal solid-phase protocol using a sulfur linker.[9]

**Table 4.** Desulfitative Alkynylation of Compounds **3a**−**e**[a]

| entry | substrate | acetylene | product | yield[b] (%) |
|---|---|---|---|---|
| 1 | **3a** | phenylacetylene | **4a** | 79 |
| 2 | **3b** | *p*-tolylacetylene | **4b** | 65 |
| 3 | **3c** | phenylacetylene | **4c** | 45 |
| 4 | **3d** | phenylacetylene | **4d** | 72 |
| 5[c] | **3d** | *p*-tolylacetylene | **4e** | 52 |
| 6 | **3e** | phenylacetylene | **4f** | 58 |
| 7[d] | **3e** | 1-hexyne | **4g** | 42 |

[a] Reactions were run on a 0.3 mmol scale of **3a**−**e** using the optimized protocol. The mixture was irradiated for 45 min in a sealed tube (monomode microwave instrument) at a ceiling temperature of 95 °C and 75W maximum power. [b] Isolated yields of the products (single runs). [c] Reaction was run for 60 min. [d] Reaction was run for 60 min with 3.0 equiv of acetylene.

The scope of the protocol was also investigated for systems other than pyrazinones (Table 4).[10] A mixture of oxazinone **3a**, phenyl acetylene (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and $Cs_2CO_3$ (2 equiv) in DMF (3.0 mL) was irradiated for 45 min at 95 °C and 75 W maximum power (Table 4, entry 1). Much to our delight, the reaction proceeded regioselectively at the C3-position of the oxazinone affording the desired compound **2a** in 79% yield without any trace of the dialkynylated product.

Finally, the newly developed protocol was applied for trisubstituted pyrazines bearing a thio methyl functionality. The reaction proceeded smoothly yielding the desired compounds in moderate to good yields (Table 4, entries 2 and 3). The application of the methodology was also extended to the heteroaromatics and thiol esters yielding the desired compound in good yields (Table 4, entires 4−7).

In conclusion, we have developed a hitherto unknown desulfitative Sonogashira-type cross-coupling reaction exemplified by the synthesis of substituted 5-chloro-3-alkynylpyrazinones from the corresponding 5-chloro-3-(phenylsulfanyl)pyrazin-2(1*H*)-ones. Excellent yields and tolerance of various functional groups toward the reaction conditions are the merits of this protocol. The possible extension of the protocol toward solid-phase linked pyrazinones as well as to other systems as oxazinones, pyrazines, and phenyl thioester was demonstrated.

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**Supporting Information Available:** Spectroscopic data for all new compounds prepared, as well as detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) See the Supporting Information for the structures of starting substrates and products.