An Efficient Copper-Catalyzed Microwave-Assisted S-Arylation towards the Synthesis of 8-Arylsulfanyl Adenines

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Received 24 May 2011

Abstract: We report a microwave-assisted synthetic protocol for the C–S cross-coupling reaction of aryl iodides and 8-mercaptoadenine using CuI and *n*-Bu_4NBr with NaO*t*-Bu in DMF. The method is rapid, simple, and cost efficient, and leads in high yields to biologically relevant aryl sulfides.

Key words: microwave, copper-catalyzed S-arylation, phase-transfer catalyst

Cross-coupling reactions of aryl halides with various nucleophilic compounds are among the most widely used synthetic methods for the formation of carbon heteroatom bonds.[1] Amongst them, organosulfur chemistry has received increasing attention since sulfur-containing groups are frequent in organic synthetic sequences.[2] They are also prevalent structural units in numerous natural products and in pharmaceutical compounds with potential clinical applications in diseases such as diabetes, cancer, viral and bacterial infections, and Alzheimer's disease.[3]

To construct these molecules, increasing attention has been given to transition-metal-catalyzed S-arylation.[4] Specifically, palladium with diverse organophosphane ligands has been used in the coupling of aryl halides and thiols.[5] While a versatile reaction, its use is restricted because (for monodentate phosphines) the reactive sulfur functionality may displace the metal-bound phosphines and inactivate the palladium catalyst.[4a] Even though strongly coordinating bidentate ligands resist the displacement of thiolates, the dependence of reaction on environmentally unfriendly PR_3 ligands limits the use of this system. Other transition-metal-catalyst systems, including nickel[6] and cobalt,[7] have also been studied, but the toxicity and high price of these metals have limited their use. An iron-based system has recently been reported to catalyze C–S bond formation.[8]

The copper metal remains the preferred catalyst for S-arylation because of its efficiency, low-cost, and little toxicity. A variety of copper-catalyzed systems have been studied to develop a general and efficient protocol to prepare aryl sulfides. In particular, these efforts aimed to limit the long reaction times, harsh reaction conditions, and often the narrow scope associated with the use of a copper catalyst.[9]

In spite of increasing interest in the development of copper-catalyzed C–S bond-formation reactions, these efforts were rarely applied to biologically relevant heterocycles, potentially because such molecules often contain functionalities that render most catalyst systems impractical and because these compounds tend to be poorly soluble in frequently used organic solvents.

Among the most widely used scaffolds in the synthesis of biologically active compounds is 8-arylsulfanyl adenine, a core structure present in several inhibitors of the heat shock protein 90 (Hsp90).[10] Hsp90 is an attractive target in cancer and neurodegenerative diseases,[11] and there is significant interest over the recent years to develop small-molecule Hsp90 inhibitors. Our laboratory has discovered the purine scaffold as a template in the design and development of Hsp90 inhibitors and has a long-standing interest in these agents as anticancer and antineurodegenerative disease agents.[3a,b,10d,12]

The Hsp90-targeted purine-scaffold molecules may combine a core adenine ring having attached an aromatic moiety through a carbon or sulfur linker at the 8-position of adenine.[10d] In a previous report,[13] we described the utility of microwave in the synthesis of 8-arylmethyl-9*H*-purin-6-amines in one pot from pyrimidine-4,5,6-triamine or pyrimidine-2,4,5,6-tetraamine and aryl acetic acid derivatives. This procedure enabled the efficient synthesis of intermediates containing a carbon linker. Efficient formation of the sulfur-linker compounds, however, remains a challenge. Here we focus on the development of a new and more effective method to create the C–S bond in a variety of biologically relevant 8-arylsulfanyl adenine structures.

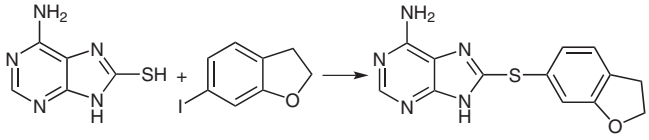
Initially, the CuI and neocuproine with NaO*t*-Bu in DMF system was used in our laboratory for the synthesis of the purine-scaffold S-arylated Hsp90 inhibitors. It coupled 8-mercaptoadenine with 5-iodobenzo[1,3]dioxole in moderate yield (58%).[3a] While this reaction led to the desired product it needed an excess of aryl iodide (3 equiv)[3a] to completely consume the 8-mercaptoadenine. It was also limited by the technical difficulty of separating neocuproine from the product. Further, when 5-iodobenzo-[1,3]dioxole was replaced with 6-iodo-2,3-dihydrobenzofuran, the reaction resulted in only trace amounts of prod-

SYNLETT 2011, No. 20, pp 3008–3012
Advanced online publication: 11.11.2011
DOI: 10.1055/s-0031-1289888; Art ID: S04711ST

uct, as indicated by LC-MS analysis (Table 1, entry 1). These limitations prompted us to explore alternative coupling conditions.

In an initial screening effort, we investigated several conditions for the coupling of 8-mercaptoadenine and 6-iodo-2,3-dihydrobenzofuran (Table 1). When the $PdCl_2$(dppf)-catalyzed coupling conditions were used, the reaction could not be completed even with considerable amounts of catalyst (30 mol%) and extended reaction times of up to 48 hours (Table 1, entry 2). We next attempted the Bolm's iron-catalyzed S-arylation. This method – coupling thiols with aryl iodides – was reported to work with heterocyclic thiols such as imidazoles and benzothiazoles.[8] It uses the $FeCl_3$ and DMEDA with NaO*t*-Bu catalyst system and toluene as a solvent. Because 8-mercaptoadenine is poorly soluble in toluene, we attempted to replace it with DMF. No product was observed under either set of conditions in our hands (Table 1, entry 3 and 4).

Table 1 Screening Conditions for the Coupling of 8-Mercaptoadenine and 6-Iodo-2,3-dihydrobenzofuran



Entry	Reagents[a]	Temp (°C)	Time (h)	P/SM[b]
1	CuI, neocuproine, NaO*t*-Bu[3a]	110	12	2:98
2	$PdCl_2$(dppf), Cs_2CO_3	120	48	40:60
3	$FeCl_3$, DMEDA, NaO*t*-Bu, PhMe[8]	135	24	0:100
4	$FeCl_3$, DMEDA, NaO*t*-Bu	135	24	0:100
5	CuI, NMP, K_2CO_3[9]	100	12	0:100
6	CuI, EG, K_2CO_3, *i*-PrOH[14a]	80	24	0:100
7	CuI, *n*-Bu_4NBr (20 mol%), K_3PO_4[14c]	130	24	10:90
8	CuI, *n*-Bu_4NBr (20 mol%), K_3PO_4, MW	190	1.5	70:30
9	CuI, n-Bu_4NBr (20 mol%), Cs_2CO_3, MW	190	1.5	20:80
10	CuI, *n*-Bu_4NBr (20 mol%), NaO*t*-Bu, MW	190	1.5	100:0
11	CuI, *n*-Bu_4NBr (10 mol%), NaO*t*-Bu, MW	190	1.5	50:50
12	CuI, *n*-Bu_4NBr (5 mol%), NaO*t*-Bu, MW	190	1.5	10:90

[a] DMF was used as solvent unless indicated otherwise.
[b] P/SM is the ratio of the sulfide product (P) to starting material (SM) aryl iodide according to LC analysis; dppf = 1,1′-bis(diphenylphosphino)ferrocene, EG = ethylene glycol.

No product was observed when the reaction was performed using a ligand-free copper catalyst[9] (Table 1, entry 5) or when ethylene glycol was used as a ligand[14a] (Table 1, entry 6). The CuI–PEG system[14b] led to low yields (data not shown). This limitation, added to the difficulty of removing PEG in the workup procedure, suggested that we should move to another system. The phase-transfer catalyst *n*-Bu_4NBr, proposed to keep the CuI species in solution, has been used for the S-arylation of thiols with aryl iodides.[14c] When the CuI, *n*-Bu_4NBr and K_3PO_4 system was heated at 110 °C for 12 hours, it gave the desired product but in low yield. Increasing the temperature to 130 °C and extending the reaction time to 24 hours failed to improve the yield (Table 1, entry 7). In addition, we observed that the benzofuran side product appeared and accumulated as the reaction time increased. We therefore concluded that shorter reaction times were desired in order to prevent side-product formation.

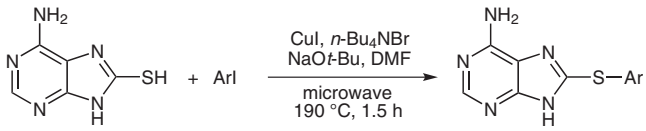
Microwave irradiation is reported[15] to accelerate transformation of reactants to products with great synthetic versatility compared to conductive heating experiments. When microwave irradiation was applied in conjunction with the CuI, *n*-Bu_4NBr and K_3PO_4 system, we obtained improved yields in a shorter reaction time (Table 1, entry 8). To improve the synthesis, we next screened several bases and found that NaO*t*-Bu gave the highest conversion and yield (Table 1, entries 8–10). In addition to being efficient, this optimized protocol (CuI, *n*-Bu_4NBr, NaO*t*-Bu, MW)[16] is also cost effective as it uses only one equivalent of aryl iodide to entirely consume the 8-mercaptoadenine. Attempts to reduce the amount of *n*-Bu_4NBr from 20% to 5% resulted in the incomplete conversion of the starting material (Table 1, entries 10–12). We next demonstrated that the procedure is scalable; when attempted on 0.58 g of aryl iodide, the reaction resulted in the desired product in 53% recovered yield, somewhat lower than the yield obtained on the 16 mg scale (92%, Table 2, entry 1).

To evaluate the scope of the optimized coupling conditions,[16] a variety of aryl iodides with electron-donating, electron-neutral, and electron-withdrawing groups were synthesized and coupled with 8-mercaptoadenine (Table 2). Both electron-rich and electron-neutral aryl iodides coupled efficiently. For example, iodides with saturated benzofused heterocyclic rings (Table 2, entries 1–5,) and indole (Table 2, entry 6) gave good to excellent yields. Other heterocyclic iodides (Table 2, entries 7, 8, 10, and 11,) gave C–S coupled products in moderate yields. We were able to successfully couple sterically hindered iodides that contained functionalities in the *ortho* position, such as amino (Table 2, entries 3 and 4,), chloro (Table 2, entry 12), and ethyl (Table 2, entry 13). Electron-withdrawing groups at this position, such as nitro, limited the product formation (Table 2, entry 14), potentially by decreasing the reactivity of the aryl iodide towards S-arylation.

When the aryl iodide contained multiple electron-withdrawing halogens, the reaction resulted in several side products, as determined by LC-MS analysis. Milder conditions (150 °C for 1 h), however, overcame this limitation and offered the desired product in moderate to good yields (Table 2, entries 15–18). Dichloro-substituted aryl iodide (Table 2, entry 15) gave the highest yield when compared to bromo- and iodo-substituted aryl iodide

(Table 2, entries 16–18), potentially due to competition of the several halides for coupling with the thiol.

Table 2 Microwave-Assisted C–S Cross-Coupling of Aryl Iodides and 8-Mercaptoadenine



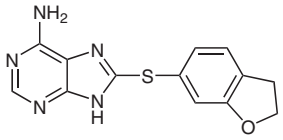
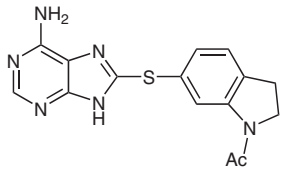
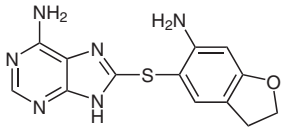
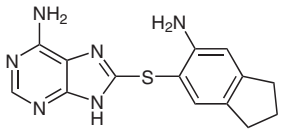
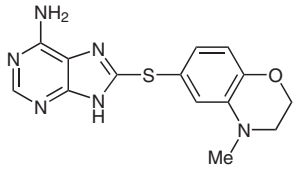
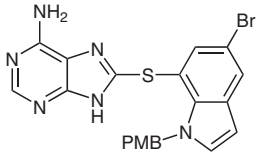
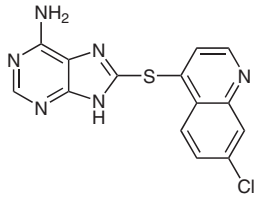
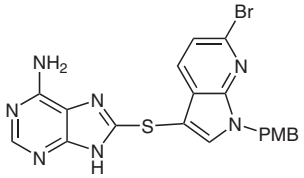
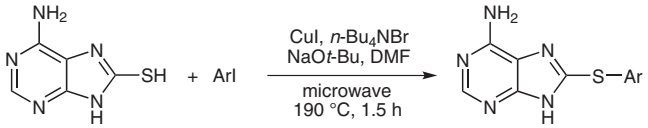
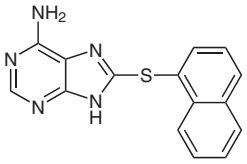
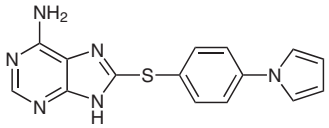
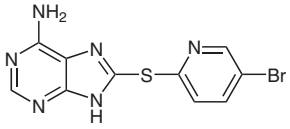
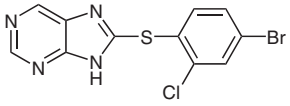
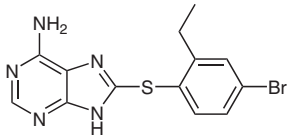
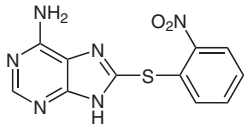
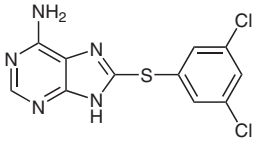
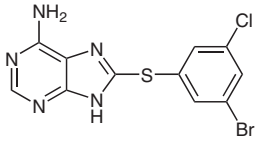
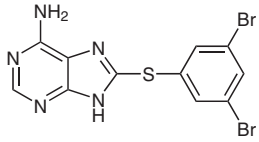
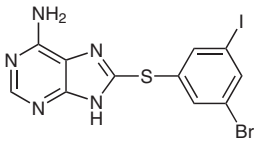
Entry	Product	Yield (%)[b]
1		92
2		65
3		80
4		84
5		70
6		53
7		48
8		47

Table 2 Microwave-Assisted C–S Cross-Coupling of Aryl Iodides and 8-Mercaptoadenine (continued)



Entry	Product	Yield (%)[b]
9		25
10		58
11		40
12		42[a]
13		49
14		5
15		54[a]
16		40[a]
17		34[a]
18		16[a]

[a] Reaction conditions: MW, 150 °C, 1 h.
[b] Isolated yields.

In summary, we have developed facile microwave-irradiated C–S cross-coupling conditions to prepare several 8-arylsulfanyl adenines. Given that C–S bond formation is of great significance to medicinal chemistry, this microwave-assisted catalytic system offers a rapid, simple, and efficient procedure to prepare a wide range of biologically relevant heterocyclic aryl sulfides.

Acknowledgment

This work was supported in part by the National Institute of Allergy and Infectious Diseases (1R21AI090501), the National Cancer Institute (1R01CA155226-01), and the National Institute on Aging (1U01AG032969).

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(16) **General Procedure for the Microwave Coupling Reaction**

In a conical-bottomed Biotage microwave vial, the mixture of 8-mercaptoadenine (16 mg, 0.1 mmol), 6-iodo-2,3-benzofuran (24 mg, 0.1 mmol), CuI (3.6 mg, 0.02 mmol), NaO*t*-Bu (28 mg, 0.3 mmol) and TBAB (6.4 mg, 0.02 mmol) in DMF (2 mL) was charged. The sealed vial was irradiated in the microwave for 1.5 h at 190 °C. After cooling, the reaction mixture was condensed in vacuo and purified by flash chromatography (CH_2Cl_2–MeOH = 10:1) to yield compound 8-(2,3-dihydrobenzofuran-6-ylthio)-9*H*-purin-6-amine (25 mg, 92%, Table 2, entry 1) as a yellow solid.

Analytical Data

^{1}H NMR (500 MHz, MeOH-d_4): δ = 8.14 (s, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.07 (d, *J* = 7.3 Hz, 1 H), 6.97 (s, 1 H), 4.62 (t, *J* = 8.7 Hz, 2 H), 3.25 (t, *J* = 8.7 Hz, 2 H). ESI-MS: *m/z* = 285.9 $[M + H]^+$. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{13}H_{12}N_5OS$: 286.0763; found: 286.0768. HPLC analyses were performed on a Waters Autopurification system with PDA, MicroMass ZQ and ELSD detector and a reversed-phase column (Waters X-Bridge C18, 4.6 × 150 mm, 5 μm). The mobile phase was the mixture of 5–95% MeCN–H_2O with 0.1% TFA having a flow rate at 1.2 mL/min for 12 min; t_R = 7.47 min; purity, 99%; HRMS data were collected using Waters LCT Premier XE.