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General Method for the Synthesis of 8-Arylsulfanyl Adenine Derivatives

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Abstract: We report a general method for the synthesis of 8-arylsulfanyl adenine derivatives using a mild protocol of coupling 8-mercaptoadenine with a variety of aryl iodides.

The purine skeleton is part of many naturally occurring ligands, and derivatives of purine nucleosides have been extensively studied as biological ligands involved in mediating metabolic processes and signaling pathways in all living organisms.[1] However, the use of the purine moiety as a skeleton for the creation of chemical libraries has been only recently explored. As such, large libraries of 2,6,9-purines have been synthesized by Schultz and co-workers[2] and the activity of these compounds as inhibitors of many biological processes has been demonstrated.[3] On our part, we are interested in creating libraries of 2,6,8,9-purines as selective inhibitors of the molecular chaperone Hsp90.[4] Although there is extensive chemical literature on the purine moiety, substitution at the C8 position has been only minimally explored. Formation of a C−C, C−O, or C−N bond at this position has been previously reported;[5] however, a survey of the existing literature does not offer a straightforward synthetic route to a wide variety of 8-arylsulfanyl purines. Coupling of 8-bromo adenine with thiophenols in the presence of a base has been reported as an alternative method.[6] This strategy is less attractive due to thiophenols' commercial unavailability, stench, and tendency to quickly oxidize. An attractive method would be coupling 8-mercaptopurines with aryl iodides, but to our knowledge there is no literature precedent on the feasibility of this reaction. Literature on formation of aryl−sulfur bonds has usually lagged behind publications reporting formation of aryl−nitrogen and aryl−oxygen bonds. One of the first reactions of aryl halides with thiols was published by Migita using Pd catalyst.[7] Since then, substantial contributions were reported, using Pd(0) and Ni(0) catalysts.[8] Recently, an elegant method using copper catalyst was reported independently by Venkataraman[9] and Buchwald.[10] Venkataraman used CuI in the presence of neocuproine and NaO*t*-Bu to create a variety of aryl sulfides from aryl iodides and aryl/alkylthiols. The method presented by Buchwald utilized CuI, ethylene glycol, and K_2CO_3 to generate aryl sulfides. Unfortunately, these methods were not reported to work with heterocyclic moieties such as purines. Herein, we present the formation of 8-arylsulfanyl adenine derivatives from 8-mercaptoadenine and aryl iodides using copper catalysis.

Our initial exploration into the optimization of the reaction conditions started with studying the cross-coupling of 8-mercaptoadenine with 4-iodo-anisole (Table 1). Due to the poor solubility of 8-mercaptoadenine in most solvents, we were left trying the feasibility of DMSO and DMF as solvents for coupling. Several reactions were performed in the presence of catalyst (CuI and neocuproine), varying the type of base (K_2CO_3, K_3PO_4, or NaO*t*-Bu) in either DMF or DMSO. CuI was chosen as the source of copper catalyst due to its stability in air. As previously reported,[8] the presence of neocuproine was essential for accelerating the reaction. Both DMF and

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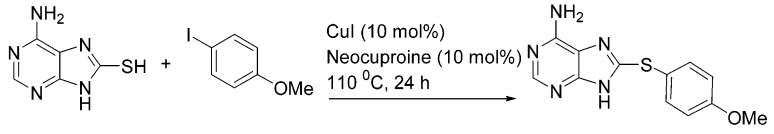
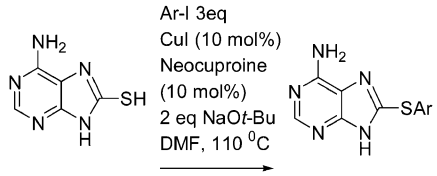
TABLE 1. Reaction Conditions Optimization for the Coupling of 8-Mercaptoadenine with Aryl Iodides

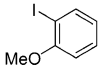
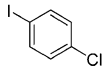
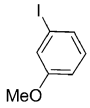
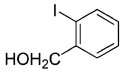
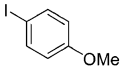
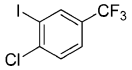
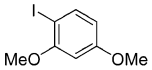


S[a]	DMSO									DMF								
B	K_3PO_4			K_2CO_3			NaO-*t*-Bu			K_3PO_4			K_2CO_3			NaO-*t*-Bu		
I	1.2	2	3	1.2	2	3	1.2	2	3	1.2	2	3	1.2	2	3	1.2	2	3
Y[b]	22.9	57.0	43.5	17.6	30.0	27.9	12.8	32.4	44.2	18.0	25.3	35.9	12.9	21.3	24.2	32.4	58.4	63.4

[a] S = solvent (2 mL); B = base (2 equiv); I = aryl iodide (equiv); Y = yield (%). [b] Yield estimated by HPLC.

TABLE 2. Reactions of 8-Mercaptoadenine with Aryl Iodides



Entry	Aryl Iodide	Yield (%)[a]	Entry	Aryl Iodide	Yield (%)[a]
1		36	6		55
2		54 (80)[b]	7		79
3		62	8		60
4		46	9		62
5		57	10		67

[a] Isolated yield. [b] With 25% neocuproine

DMSO afforded the expected product, suggesting that the polarity of the solvent was not critical for the reaction. Interestingly, higher yields were obtained in DMSO when the base was K_3PO_4, while in DMF, NaO*t*-Bu seemed to perform better. The use of an excess of aryl iodide also improved yields and conversions. Somewhat surprising, the reaction yields reached a plateau value of 60−70%. The TLC and HPLC reaction analyses showed a clean transition from 8-mercaptoadenine to product. However, further analysis of reactant stability under the coupling conditions concluded that decomposition of 8-mercaptoadenine was a cause to reduced yields. An observed increase in the reaction yields when 25% neocuproine was used (entry 2, Table 2) suggests that coordination of copper by the adenine starting material and/or product derivatives may additionally contribute to lowered yields. To reduce the probability of any disulfide byproduct formation, reactions were performed in an inert atmosphere. It is noteworthy that the reaction does not require the use of dry solvents or special handling of the reagents.

On the basis of these observations, we tested the coupling of 8-mercaptoadenine with several aryl iodides using CuI/neocuproine as a catalyst and NaO*t*-Bu/DMF as the base/solvent combination (Table 2).

Our optimized reaction conditions utilize 10 mol % CuI, 10 mol % neocuproine, NaO*t*-Bu (2 equiv), and aryl iodide (3 equiv) in reagent-grade DMF at 110 °C under nitrogen. These conditions resulted in the expected product without noticeable byproducts. It is noteworthy that neither coupling of the C6−NH_2 with the aryl iodides nor disulfide formation has been detected.

The reaction could be used to couple in reasonable yields 8-mercaptoadenine with aryl iodides (Table 2), tolerating diverse substituents at the ortho-, meta-, and para-positions of the aryl moiety. No particular sensitivity to the presence of deactivating functionalities was

seen. As such, electron-rich rings (entries 1−4, 9, and 10, Table 2) allowed for coupling in yields comparable to electron-deficient aromatic moieties (entries 5, 6, and 8, Table 2). Steric hindrance was additionally permitted; the presence of methoxy, methyl, or hydroxymethyl ortho to iodide had minimal to no effect on reaction yields.

In summary, we have developed an efficient Cu-catalyzed formation of 8-arylsulfanyl purines. Considering the ever increasing number of aryl iodides available commercially, the reaction could be used to generate a library of 8-thioarylpurines as potentially useful biological ligands.

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Supporting Information Available: Synthetic procedures and characterization data for products listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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