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Silver-Mediated Palladium-Catalyzed Direct C−H Arylation of 3-Bromoisothiazole-4-carbonitrile

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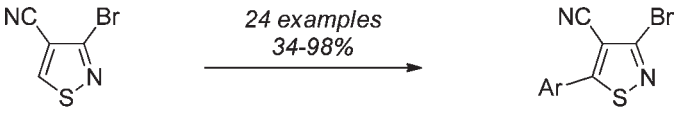
ABSTRACT



Reagents and Conditions: ArI (1.5 equiv), AgF (3 equiv), Ph_3P (10 mol %), $Pd(Ph_3P)_2Cl_2$ (5 mol %), MeCN, 82 °C

Silver(I) fluoride-mediated Pd-catalyzed C−H direct arylation/heteroarylation of 3-bromoisothiazole-4-carbonitrile (1a) gives twenty-four 5-aryl/heteroaryl-3-bromoisothiazole-4-carbonitriles. The reaction was partially optimized with respect to catalyst, ligand, and base. During this study 3,3′-dibromo-5,5′-biisothiazole-4,4′-dicarbonitrile (3a) was isolated as a byproduct and subsequently prepared via the silver-mediated Pd-catalyzed oxidative dimerization of 3-bromoisothiazole-4-carbonitrile in 67% yield. The analogous phenylation and oxidative dimerization of 3-chloroisothiazole-4-carbonitrile (1b) gave 3-chloro-5-phenylisothiazole-4-carbonitrile (4) and 3,3′-dichloro-5,5′-biisothiazole-4,4′-dicarbonitrile (3b) in 96% and 69% yields, respectively.

Isothiazoles display wide-ranging biological activity: Some are potential anticancer agents that inhibit MEK-1 and MEK-2 kinases,[1] while others are prodrugs for the treatment of hyperproliferative disorders,[2] and as active site inhibitors for the hepatitis C virus NS5B polymerase.[3] Commercial isothiazoles include the Kathon preservatives, the artificial sweetener saccharin, and the antibacterial sulfa drug, sulfasomizole. The chemistry of isothiazoles has been reviewed.[4] Most strategies for preparing isothiazoles involve construction of the isothiazole ring with the desired carbon substituents in place, as such the routes are often product specific.[5]

By combining modern transition metal-catalyzed C−C bond forming reactions with readily available halo-substituted isothiazole scaffolds, useful nonproduct specific routes to alkyl-,[6] alkenyl-,[7] alkynyl-,[7a,b,8] aryl-,[6,7b,9] and heteroaryl-substituted[6b,7b,9] isothiazoles can be realized. These reactions, however, require access to organometallic reagents that are often expensive or need to be prepared. Furthermore, a shelf stable isothiazole-5-boronate ester suffered facile protodeboronation under typical Suzuki reaction conditions.[9a]

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Pd-catalyzed direct C−H arylation overcomes the need for expensive organometallic reagents.[10] The reaction has been demonstrated on a wide range of heterarenes by using cheap aryl halides.[11] While many publications appear in the literature about direct C−H arylation of thiazoles,[10,12] to the best of our knowledge, there have been no reported examples of Pd-catalyzed direct arylation of isothiazoles.

During ongoing studies on the versatile 3,5-dibromo- and 3,5-dichloroisothiazole-4-carbonitriles,[13] we developed chromatography free gram scale conditions for the regiospecific C5 hydrodehalogenations that gave 3-bromo- and 3-chloroisothiazole-4-carbonitriles **1a** and **1b**, respectively. Combining the 3-haloisothiazole-4-carbonitriles with Pd-catalyzed C−H direct arylations can be a new route to 5-arylisothiazole-4-carbonitriles that are important due to their cytotoxicity[14] and antiviral activity.[14,15] To date these compounds have been prepared by either treating arylylidenemalononitriles with S_2Cl_2[6b,14,16] or by arylating haloisothiazoles using Suzuki, Stille, or Negishi reactions.[6b,7b,17] However, the former has limitations due to harsh reaction conditions that often lead to chlorination of electron-rich aryls and the latter requires often expensive reagents. Below we demonstrate for the first time the efficient silver-mediated Pd-catalyzed direct C5 arylation of 3-bromoisothiazole-4-carbonitrile (**1a**) using readily available iodoarenes.

Initially, 3-bromoisothiazole-4-carbonitrile (**1a**) was treated with either chloro-, bromo-, or iodobenzene (PhI) in the presence of a Pd catalyst Pd(dppf)Cl_2·DCM (20 mol %) and base in MeCN at ca. 82 °C. Surprisingly, the use of inorganic bases such as KF, CsF, K_2CO_3, Cs_2CO_3, and Na_2CO_3 and organic bases such as pyridine and *i*-Pr_2-NEt failed to work. In light of this, we investigated the use of silver(I) salts, which are effective additives in both oxidative[18] and nonoxidative arylations.[12d,19]

The addition of $AgNO_3$ assisted the Pd-catalyzed arylation of allyltrimethylsilanes,[20] vinylsilanes,[21] while Ag_2O promoted the Pd-catalyzed cross-coupling reactions of silanols, silanediols, and silanetriols[22] as well the reaction between aryl and alkenyl halides with terminal alkynes.[23] Silver(I) fluoride (AgF) served as both an activator of the electrophilic substitution reaction and as the oxidant of Pd(0),[24] and in combination with Cu(II) salts aided the arylation of acetanilides.[19e] Furthermore, AgF was used as base for the arylation of thiophenes and thiazoles.[12b,25]

In light of the above, we treated 3-bromoisothiazole−4-carbonitrile (**1a**) with PhI (1.2 equiv), AgF (2 equiv), Pd(dppf)Cl_2·DCM (20 mol %), and Ph_3P as ligand (10 mol %) in MeCN at ca. 82 °C for 2 h and obtained the 5-phenylisothiazole (**2a**) in 73% yield. Substituting PhI for PhBr or PhCl gave only traces of product after 2 h. The conditions were subsequently optimized with respect to catalyst, ligand, and base/oxidant (Table 1). Of the catalysts screened, Pd(Ph_3P)$_2Cl_2$ gave the highest yield (88%) in the shortest time (20 min) and was chosen for further optimization. In contrast $Pd_2(dba)_3$ gave a complex reaction mixture, while Pd(OAc)$_2$ and (MeCN)$_2$PdCl$_2$ gave the desired product in only moderate yields and required longer reaction times.

On holding constant the catalyst, Pd(Ph_3P)$_2Cl_2$ (20 mol %), both the reaction time and product yield were affected by varying the equivalents of PhI; the highest yields (88 and 84%) were achieved with 1.2 and 1.5 equiv of PhI over a 20 and 10 min period, respectively. In the absence of additional ligand, the product can still be formed in good yield by increasing the PhI equivalents. Switching the ligand to dppf (10 mol %) led to a longer reaction (7 h) and a 67% product yield, while the use of JohnPhos (10 mol %) gave only traces of product after 4 h. The catalyst loading was then investigated to find the minimum needed for the reaction to succeed. Reducing the catalyst loading to 10 mol % with 1.2 equiv of PhI led to longer reaction times (7 h) and moderate product yields (60%) and gave traces of 3,3′-dibromo-5,5′-biisothiazole-4,4′-dicarbonitrile (**3a**) presumably owing to a competing oxidative C5 dimerization. The formation of the latter can be suppressed by increasing the PhI to 1.5 or 2 equiv, which

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Table 1. Reaction of 3-Bromoisothiazole-4-carbonitrile (**1a**) (0.25 mmol) with PhI, $Pd(Ph_3P)_2Cl_2$, AgF, and Ph_3P in MeCN at ca. 82 °C

1a **2a**

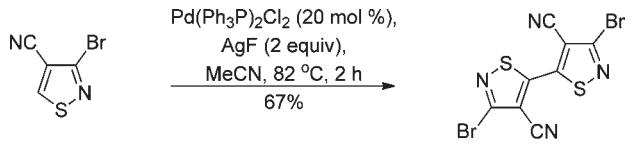
AgF (equiv)	$Pd(Ph_3P)_2Cl_2$ (mol %)	Ph_3P (mol %)	PhI (equiv)	time (h)	yield of **2a** (%)
1	20	10	1.2	24	–[a]
2	20	10	1.2	0.33	88
2	20	10	1	2.50	60
2	20	10	1.5	0.17	84
2	20	0	1.2	1	73
2	20	0	1.5	0.50	86
2	20	0	2	0.17	86
2	10	10	1.2	7	62[b]
2	10	10	1.5	5	80
2	10	10	2	3	73
2	5	10	1.2	12	72[b]
2	5	10	1.5	11	60[c]
3	20	10	1.2	0.17	63[d]
3	20	10	2	0.08	78
3	10	10	2	0.10	83
3	5	10	2	0.13	85
3	1	10	2	0.50	17
3	10	10	1.5	0.12	91[b]
3	5	10	1.5	0.17	93[b]

[a] Incomplete reaction. [b] Traces of dimer **3a** (TLC). [c] Dimer **3a** (15%) was also isolated. [d] Dimer **3a** (14%) was also isolated.

led to shorter reaction times (5 and 3 h, respectively) and the 5-phenylisothiazole (**2a**) in 80% and 73% yields, respectively. Further attempts to reduce the catalyst loading to 5 mol % again led to increased reaction times, lower product yields, and dimer formation.

3,3′-Dibromo-5,5′-biisothiazole-4,4′-dicarbonitrile (**3a**) was isolated as colorless plates, mp 286 °C (PhCl). Elemental analysis and mass spectrometry supported a molecular formula of $C_8Br_2N_4S_2$. Infrared spectroscopy supported the presence of nitrile functionality ν(C≡N) 2230 cm^{-1} and ^{13}C NMR spectroscopy gave only 4 carbon resonances indicating a symmetrical molecule. Treating 3-bromoisothiazole-4-carbonitrile (**1a**) with AgF (2 equiv) and $Pd(Ph_3P)Cl_2$ (20 mol %) in the absence of PhI gave the 5,5′-biisothiazole (**3a**) in 67% yield (Scheme 1).

Scheme 1. Oxidative Dimerization



1a **3a**

The formation of a dimer **3a** in the absence of ArI implied that direct palladation of isothiazole **1a** by a palladium(II) species was possible and as such the silver salt served as an oxidant to support a Pd(II)/Pd(IV) catalytic cycle. This hypothesis also agreed with the observation that Br remained intact during the catalysis.

Control reactions revealed that the presence of both the Pd catalyst and the AgF was needed for the reaction to work, while the use of Ph_3P was not. Attempts to decrease the catalyst loading to 5 mol % led to longer reaction time (12 h) and a drop in yield (51%).

With these partially optimized arylation conditions, the need for AgF was further investigated. In our hands, the use of other silver(I) reagents such as AgBr, $AgNO_3$, Ag_2O, Ag_2SO_4, $AgBF_4$, $AgSbF_6$, AgOTf, and AgOAc proved to be ineffective in the arylation reaction of 3-bromoisothiazole-4-carbonitrile (**1a**) with PhI. Nevertheless, Ag_2CO_3 was effective with 20 mol % of catalyst giving the desired 3-bromo-5-phenylisothiazole-4-carbonitrile (**2a**) in good yields (68−73%) together with some amount of dimer (**3a**). However, attempts to decrease the catalyst loading to 10 or 5 mol % by using 2 or 3 equiv of Ag_2CO_3 led to only traces of phenylated product. As such, further optimizations were restricted to the use of AgF.

Screening the AgF equivalents needed for the reaction revealed that 1 equiv was insufficient to drive the reaction to completion within 24 h, while the use of 3 equiv led to fast reaction times (10 min), a reduced yield of the desired 3-bromo-5-phenylisothiazole-4-carbonitrile (**2a**) (63%), and an increased yield of dimer (**3a**) (14%). Fortunately, the formation of the dimer could be suppressed by increasing the amount of PhI. As such, when PhI (2 equiv) and AgF (3 equiv) were used the reaction finished in 5 min affording the desired product in 78% yield with no dimer byproduct. This last result was promising and under these conditions the Pd catalyst loading was reduced from 10 to 5 mol %. Successfully, the desired product was isolated in high yield (85%) in very short reaction time (8 min). Reducing the catalyst loading to 1 mol % gave low yields of the desired product, while decreasing the PhI to 1.5 equiv with 10 and 5 mol % catalyst loading led to fast reactions and very high yields of the desired product but traces of the dimer were also present.

The best conditions were applied to a variety of iodoarenes providing a range of 5-aryl- and 5-heteroarylisothiazole-4-carbonitriles (Table 2).

The reactions worked well with aryl derivatives bearing both electron-releasing (e.g., entries 2−6) and electron-withdrawing (e.g., entries 7−9) groups. Furthermore, the existence of a second halide (Cl or Br) on the iodoarenes did not affect the reaction and showed that the reaction was haloselective (entries 19−23). In most cases iodoheteroarenes worked equally well (entries 11−13 and 17−22), but in some cases dimer was formed (entries 14−16). Comparatively poor yields were obtained for 4-amino-3-nitroiodobenzene (entries 10) and the 7-iodoindoles (entries 16 and 23) and presumably these reactions would

Table 2. Reaction of the 3-Bromoisothiazole **1a** (0.25 mmol) with ArI (2 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol %), AgF (3 equiv), and Ph_3P (10 mol %) in MeCN at ca. 82 °C

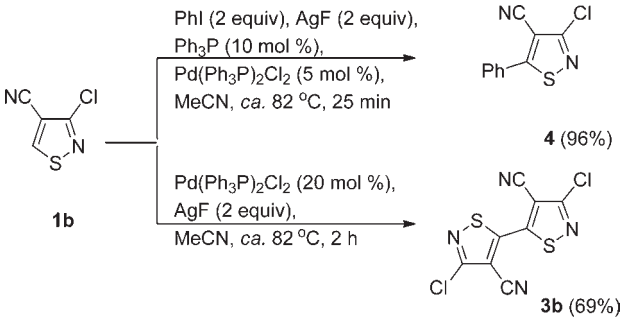
entry	Ar	time (h)	yield of **2b**−**x** (%)	yield of **3a** (%)
1	4-Tol	3.50	**2b** (82)	
2	2-$MeOC_6H_4$	7	**2c** (89)	
3	3-$MeOC_6H_4$	3	**2d** (91)	
4	4-$MeOC_6H_4$	2.50	**2e** (81)	
5	2,4-$(MeO)_2C_6H_3$	4	**2f** (73)	
6	4-HOC_6H_4	4	**2g** (79)	
7	2-$O_2NC_6H_4$	0.67	**2h** (89)	
8	3-$O_2NC_6H_4$	0.67	**2i** (83)	
9	4-$O_2NC_6H_4$	0.50	**2j** (98)	
10	4-H_2N-3-$O_2NC_6H_3$	0.17	**2k** (41)[a]	
11	Pyrid-2-yl	20	**2l** (74)	
12	Pyrid-3-yl	5	**2m** (92)	
13	Pyrid-4-yl	20	**2n** (95)	
14	Pyrazinyl	2	**2o** (72)	16
15	Indol-5-yl	3	**2p** (66)	20
16	Indol-7-yl	2	**2q** (52)	28
17	Thien-2-yl	0.33	**2r** (93)	
18	Thien-3-yl	0.67	**2s** (92)	
19	3-BrC_6H_4	1.50	**2t** (97)	
20	2-Cl-Pyrid-4-yl	6	**2u** (78)	
21	2-Br-Pyrid-4-yl	4	**2v** (87)	
22	7-Cl-Quinolin-4-yl	1.50	**2w** (94)	
23	5-Br-Indol-7-yl	20	**2x** (34)[b]	

[a] Reaction finished immediately but 24% of ArI was recovered. [b] Yield based on 43% recovered starting isothiazole **1a**.

require additional optimization to maximize the product yields.

The best conditions for the direct arylation of 3-bromoisothiazole-4-carbonitrile (**1a**) were also used with the 3-chloroisothiazole (**1b**). The chemistry was subtly different. Treating 3-chloroisothiazole-4-carbonitrile (**1b**) with PhI (2 equiv) in the presence of AgF (3 equiv), Ph_3P (10 mol %), and $Pd(Ph_3P)_2Cl_2$ (5 mol %) in MeCN at ca. 82 °C gave after 15 min 3-chloro-5-phenylisothiazole-4-carbonitrile (**4**) in moderate yield (58%) and traces of 3,3′-dichloro-5,5′-biisothiazole-4,4′-dicarbonitrile (**3b**). In light of the above study we rationalized that decreasing the AgF to 2 equiv could help avoid the competing oxidative dimerization and indeed obtained in 25 min the desired product (**4**) in excellent yield (96%) with no traces of dimer. The influence of the 3-halogen was surprising since it was not near the reaction site, but presumably chlorine being more electronegative than bromine would make the C5 hydrogen marginally more acidic and this may play a role. This is now under further study. Finally, by applying the conditions used for the dimerization of the bromo

Scheme 2. Arylation and Dimerization of 3-Chloroisothiazole-4-carbonitrile (**1b**)



analogue [$Pd(Ph_3P)_2Cl_2$ (20 mol %), AgF (2 equiv)] onto 3-chloroisothiazole-4-carbonitrile (**1b**), the 3,3′-dichloro-5,5′-biisothiazole-4,4′-dicarbonitrile (**3b**) was isolated in 69% yield after 2 h (Scheme 2).

In conclusion, 3-bromoisothiazole-4-carbonitrile (**1a**) readily undergoes Pd-catalyzed direct CH arylation at C5 with a range of iodoarenes in the presence of AgF to give twenty-four 5-aryl- and heteroarylisothiazole-4-carbonitriles in good yields. Furthermore, treating 3-bromoisothiazole-4-carbonitrile (**1a**) with AgF and Pd catalyst led to oxidative dimerization affording 3,3′-dibromo-5,5′-biisothiazole-4,4′-dicarbonitrile (**3a**). Similarly, phenylation at C5 and oxidative C5 dimerization were demonstrated for 3-chloroisothiazole-4-carbonitrile (**1b**) affording the chloro-phenylated and dimerized analogues **4** and **3b** in 96% and 69% yields, respectively. The method is simple and effective, uses cheap commercially available iodoarenes, and is suitable for obtaining otherwise difficult to access 5-aryl-/ heteroarylisothiazole-4-carbonitriles.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new com-pounds are available free of charge *via* the Internet at http://pubs.acs.org.