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Silver mediated direct C–H arylation of 3-bromoisothiazole-5-carbonitrile

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ABSTRACT

Palladium catalyzed direct C–H arylation of 3-bromoisothiazole-5-carbonitrile with aryl/hetaryl iodides in the presence of AgF gave 13 4-aryl/hetaryl-3-bromoisothiazole-5-carbonitriles. The scope of this arylation was investigated and explanations for the limitations proposed. 3-Bromoisothiazole-5-carboxamide was isolated as a side-product, and its formation was attributed to Ag^+-catalyzed hydration of the C-5 nitrile. The analogous phenylation of 3-chloroisothiazole-5-carbonitrile and 3-bromoisothiazole-4-carboxamide gave 3-chloro-4-phenylisothiazole-5-carbonitrile and 3-bromo-5-phenylisothiazole-4-carboxamide in 83 and 64% yields, respectively.

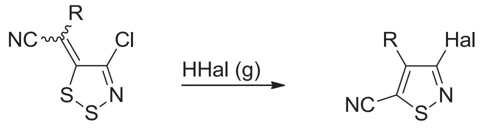
1. Introduction

Isothiazoles are useful compounds owing to their broad biological activity, useful industrial applications, and their use as synthetic intermediates.[1] Examples of biologically useful isothiazoles are the antibacterial drug sulfasomizole, while other isothiazoles have been studied as anticancer agents,[2] or showed insecticidal, fungicidal, and acaricidal activity.[3]

In particular, 4-arylisothiazoles have been investigated as plant antifungals,[4] multiple target non-steroidal anti-inflammatory drugs[5] and NMDA receptor agonists involved in several neurological diseases,[6] while 4-hetarylisothiazoles have been used as herbicides and plant growth inhibitors,[7] HIV inhibitors,[8] analgesic drugs,[9] and mitogen activated protein kinase (MEK1)[10] and checkpoint kinase (CHEK1)[11] inhibitors, which are potentially useful as anticancer agents.

Many useful 4-hetarylisothiazoles have been prepared from 4-haloisothiazoles via a range of transition metal catalyzed C–C bond forming reactions.[6,12] However, most of these transition metal catalyzed reactions such as the Stille, Suzuki, Sonogashira, and Negishi couplings require the preparation of organometallic reagents. Furthermore, the preparation of haloisothiazoles often requires the use of aggressive halogenating agents, such and Cl_2 or Br_2.[3a,13]

Recently, we described the conversion of (4-chloro-5*H*-1,2,3-dithiazolylidene)acetonitriles **1** into 3-chloro-, 3-bromo-, 3,4-dichloro-, and 3,4-dibromoisothiazole-5-carbonitriles **2a**, **2b**, **3a**, and **3b**, respectively, which are potentially useful starting materials for Pd-catalyzed C–C coupling reactions (Scheme 1).[14]



1

2a (R = H, Hal = Cl)
2b (R = H, Hal = Br)
3a (R = Hal = Cl)
3b (R = Hal = Br)

Scheme 1. Route to haloisothiazole-5-carbonitriles **2** and **3** via dithiazoles **1**.[14]

From previous studies,[12d–f] we knew that achieving palladium-catalyzed C–C coupling reactions at the C-3 position was difficult. As such, regioselective C-4 couplings starting from the two 3,4-dihaloisothiazoles **3a** and **3b**, were considered feasible: 5-aryl-3,4-dihaloisothiazoles undergo Suzuki couplings when the 4-halo is bromine, and both Stille and Negishi couplings work when the 4-halo is iodine.[12f] In light of this, we attempted Suzuki, Stille, and Negishi C–C coupling reactions with 3,4-dihaloisothiazole-5-carbonitriles **3a** and **3b**. In our hands, the Suzuki, Stille, and Negishi couplings with 3,4-dichloroisothiazole-5-carbonitrile (**3a**) gave mostly recovered starting materials, while with 3,4-

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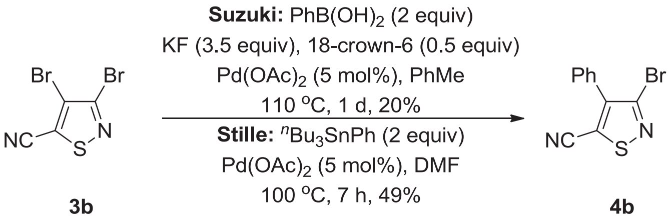
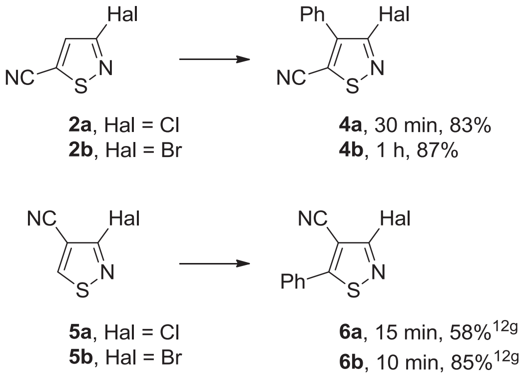
dibromoisothiazole-5-carbonitrile (**3b**) only the Suzuki and Stille couplings gave the 4 phenyl derivative **4** in low (20%) to moderate (49%) yields, respectively (Scheme 2).



Scheme 2. Suzuki and Stille couplings of 3,4-dibromoisothiazole-5-carbonitrile (**3b**).

Compared to the 5-aryl analogues, the isothiazole-5-carbonitriles reacted poorly, presumably owing to the electron withdrawing nitrile that deactivates the ring system by making it more electron deficient. Similar results were observed for thiophenes; e.g., Suzuki couplings of both 3,4-dibromothiophene-2-carbonitrile[15] and 3,4-dibromothiophene-2-carbaldehyde,[16] bearing an electron withdrawing group at C-2, gave generally lower yields (17–36%), than those with 2-unsubstituted 3,4-dibromothiophene (31–96%).[16,17]

The poor reactivity of 3,4-dihaloisothiazoles **3a** and **3b** toward C-4 arylation was overcome by looking at the direct C–H arylation of 4-unsubstituted analogues **2a** and **2b** (Scheme 1). As reported first by Miura,[18] direct C–H arylation avoids the need for difficult-to-access organometallic reagents, as it requires only activated C–H bonds and suitable organohalides. The usefulness and versatility of this reaction has been demonstrated over the last decade, with a wide range of heteroarenes and aryl halides.[19] While the C–H arylation of thiazoles has been extensively investigated[19c,20] to the best of our knowledge only the Ag-mediated Pd-catalyzed direct C-5 arylation of 3-chloro- and 3-bromoisothiazole-4-carbonitriles (**5a** and **5b**) using iodoarenes has been reported for isothiazoles (Scheme 3).[12g] In these examples the C-5 position of isothiazoles was very reactive owing to the neighboring ring sulfur.



Reagents and conditions: PhI (2 equiv), AgF (3 equiv), Pd(Ph$_3$P)$_2$Cl$_2$ (5 mol%), MeCN, 82 °C.

Scheme 3. Direct C–H arylation of 3-haloisothiazoles **2a**, **2b**, **5a**, and **5b** with phenyl iodide.

2. Results and discussion

2.1. C–H arylation chemistry of 3-bromoisothiazole-5-carbonitrile 2b

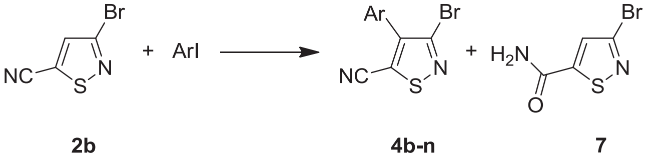
As such, we investigated the Ag-mediated Pd-catalyzed C–H arylation of the C-4 unsubstituted 3-haloisothiazole-5-carbonitriles **2** and to enable comparison used the same protocol as that described for the isomeric 3-haloisothiazole-4-carbonitriles **5** (Scheme 3).[12g] Gratifyingly, treating 3-chloro- or 3-bromoisothiazole-5-carbonitrile (**2a** and **2b**) with PhI under these conditions, gave 3-bromo-4-phenylisothiazole-5-carbonitrile (**4a**) in 83 and 87% yields, respectively. The yields for these couplings were similar (83/87 vs 85%) to the analogous arylation of 3-bromoisothiazole-4-carbonitrile (**5b**), however, the reaction times were longer (0.5–1 h vs 10 min). This indicated that the arylation at C-5 occurred faster than that at C-4, presumably owing to steric factors since the C-4 position is flanked by both the C-3 halide and the C-5 nitrile. Furthermore, unlike the reaction of 3-chloro-isothiazole-4-carbonitrile (**5a**), which gave only a moderate yield (58%) owing to a competing oxidative coupling leading to formation of a 5,5′-biisothiazole, we saw no similar 4,4′-biisothiazole formation with either 3-chloro- or 3-bromoisothiazole-5-carbonitriles.

3-Bromoisothiazole-5-carbonitrile (**2b**) was chosen as the substrate for further investigation since the bromine at C-3 was more labile than the chlorine to further functionalization and also because more data existed[12g] for the isomer 3-bromoisothiazole-4-carbonitrile (**5b**), which facilitated a direct comparison of their reactivity.

A brief optimization of the reaction conditions for the C–H arylation of 3-bromoisothiazole-5-carbonitrile (**2b**) was attempted. The parameters investigated were: equivalents of iodide and AgF, the use of DMF as solvent, pivalic acid as an additive, and also MW irradiation. However, no significant improvement was observed to the previously published conditions.[12g] Increasing the equivalents of iodide was the only change that appeared marginally beneficial; as such, we chose to use 2 equiv of iodide for our general reaction conditions and restricted the use of more equivalents for problematic analogues (Table 1).

Table 1

Reaction of 3-bromoisothiazole-5-carbonitrile (**2b**) (0.25 mmol) with ArI (2 equiv), Pd(Ph$_3$P)$_2$Cl$_2$ (5 mol %), AgF (3 equiv), and Ph$_3$P (10 mol %) in MeCN at ca. 82 °C



Entry	Ar	Time (h)	4	Yields (%) 7	2b[a]
1	Ph	1	**4b** (87)	—	—
2	2-Tol	24	—	29	32
3	4-Tol	3	**4c** (79)	Traces	—
4	2-MeOC$_6$H$_4$	3	**4d** (71)[b]	Traces	—
5	3-MeOC$_6$H$_4$	2	**4e** (81)	—	—
6	4-MeOC$_6$H$_4$	48	**4f** (47)[c]	39	—
7	2,4-(MeO)$_2$C$_6$H$_3$	20	**4g** (28)	52	—
8	2-O$_2$NC$_6$H$_4$	24	—	24	37
9	3-O$_2$NC$_6$H$_4$	1	**4h** (67)	Traces	—
10	4-O$_2$NC$_6$H$_4$	4	**4i** (83)	—	—
11	3-BrC$_6$H$_4$	1	**4j** (95)[d]	—	—
12	Pyrid-2-yl	24	—	39	42
13	Pyrid-3-yl	24	—	14	(16)
14	Pyrid-4-yl	24	—	34	(31)
15	2-F-Pyrid-4-yl	1	**4k** (55)	Traces	—
16	2-Cl-Pyrid-4-yl	1	**4l** (43)	Traces	—
17	2-Br-Pyrid-4-yl	1	**4m** (84)	—	—
18	6-F-Pyrid-3-yl	4	**4n** (61)	Traces	—
19	2-Cl-Pyrid-3-yl	24	—	34	(26)
20	Thien-2-yl	24	—	15	(52)
21	Thien-3-yl	24	Complex	14	—

[a] Starting material recovered.

[b] ArI (10 equiv), with ArI (5 equiv) yield of **4d** (43%) after 2 d.

[c] ArI (5 equiv), at ca. 70 °C.

[d] ArI (5 equiv): with 2 equiv the reaction after 24 h was incomplete giving **2b** (53%)+**4j** (12%).