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Copper- and palladium-catalyzed intramolecular C–S bond formation: a convenient synthesis of 2-aminobenzothiazoles†

Laurie L. Joyce, Ghotas Evindar and Robert A. Batey*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, Canada M5S 3H6. E-mail: rbatey@chem.utoronto.ca

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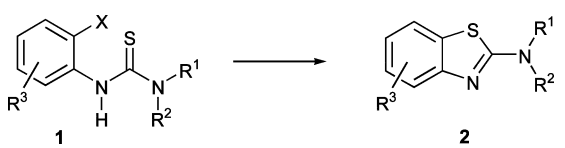
Copper- and palladium-catalyzed intramolecular C–S bond formation by cross-coupling between an aryl halide and thiourea functionality is demonstrated for the synthesis of 2-aminobenzothiazoles, wherein the Cu-catalyzed protocol is generally superior and more cost effective than the Pd-catalyzed protocol; the Cu-catalyzed reaction also further expands recent studies exploring the utility of Cu salts as replacements for Pd in carbon–heteroatom bond-forming reactions. A one-pot variant combining the synthesis of the thiourea and the cyclization was also demonstrated.

Aryl–heteroatom bond formation *via* transition metal-catalyzed cross-coupling has been a subject of particular interest in recent years. While a considerable body of work has been amassed in the new C–N and C–O bond-forming technologies, there are few protocols for the corresponding reactions involving C–S bond formation, despite the importance of sulfur-containing aromatic and heteroaromatic biologically-active compounds. One such class of compounds are 2-aminobenzothiazoles which have both pharmaceutical and agrochemical relevance.[1] As an extension of our recent interest in 2-aminobenzimidazole synthesis through copper- and palladium-catalyzed intramolecular aryl guanidinylation, we now report the synthesis of 2-aminobenzothiazoles through analogous C–S bond-forming methodologies.[2]

Palladium catalysis has been demonstrated for cross-coupling reactions of thiols with aryl halides to achieve aryl C–S bond formation.[3] Disadvantages of Pd-catalyzed methods include the high cost of the catalysts and the well-known problems associated with the removal of palladium-residues from polar reaction products during the late stages of pharmaceutical compound synthesis. Copper salts have also been used to mediate C–S bond formation, although the traditional methods suffer from the use of high reaction temperatures, functional group sensitivity, the requirement for substrates with *ortho*-carbonyl groups that are both electron-withdrawing and capable of chelating copper, and the use of stoichiometric amounts of copper.[4–5] Recently, new catalytic copper-based processes for the intermolecular cross-coupling of aryl iodides with thiols have been reported by Palomo *et al.*,[6] Venkataraman and co-workers,[7] and Buchwald and Kwong.[8]

Based on the success of these intermolecular aryl thiolation processes, we considered that either Cu- or Pd-catalyzed cyclization of *ortho*-halobenzothioureas **1** would represent a viable method for the formation of substituted 2-aminobenzothiazoles **2** (Scheme 1). This route would provide significant benefits over traditional methods for the formation of **2**, which employ multi-step routes using harsher reaction conditions not compatible with certain group functionalities.[9] We were also particularly interested to make a direct comparison between the use of Pd *versus* Cu catalysts for the cyclization of **1**.[10]

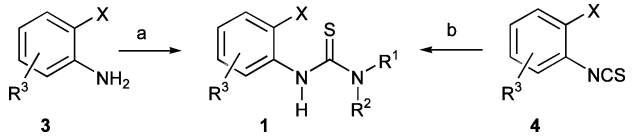


Scheme 1

The precursors **1** were readily synthesized using isothiocyanate methodology, using commercially available *ortho*-haloanilines **3** or *ortho*-haloaryl isothiocyanates **4** (Scheme 2). Reaction of **3** with isothiocyanate in dimethylformamide (DMF) gave thiourea **1** in 12–48 h, whereas reaction of **4** with either primary or secondary amines in acetonitrile gave **1** in less than 10 min, in quantitative yield, without any requirement for work-up. The intramolecular cyclization of **1** was investigated using either $Pd(PPh_3)_4$ (5 mol%) or CuI (5 mol%) and 1,10-phenanthroline (10 mol%), in the presence of a mild base (Cs_2CO_3, 2 equiv.), in dimethoxyethane (DME) at 80 °C. These conditions were modified from those previously optimized for intramolecular aryl guanidinylation.[2,11] Initial studies focussed upon the reaction of *N*,*N*′-disubstituted thioureas **1** containing an *ortho*-bromoaryl group (Table 1, entries 1–5). In general, good to excellent yields of **2** were obtained with both Pd and Cu catalysis, although poorer conversions were apparent in the case of the Pd-catalyzed reactions. In these cases, only products **2** resulting from cyclization through S were observed, with no evidence for the formation of *N*-substituted 1,3-dihydrobenzoimidazole-2-thione products that would form from cyclization through the N atom.[12] In the case of *N*,*N*,*N*′-trisubstituted thioureas **1**, excellent conversion (> 98%) and yields were obtained for both Pd and Cu catalysis (Table 1, entries 6–11). These results reflect the presumably more nucleophilic nature of the trisubstituted thioureas as compared with their disubstituted analogs, which results in greater conversions in the case of the Pd-catalyzed reactions, as well as the much greater solubility of the products **2** when R^1 and $R^2 \neq H$. The reaction is compatible with both electron-withdrawing and electron-donating substituents on the aromatic ring (Table 1, entries 12–15). The reaction also works with *ortho*-iodoaryl precursors **1**, giving comparable or somewhat higher yields than the corresponding reactions from the *ortho*-bromoaryl precursors (Table 1, bracketed entries 1, 4, 6, 7 and 11).

Finally, a convenient one-pot Pd- and Cu-catalyzed variant of the reaction was developed for the formation of **2a** from **4a** (Scheme 3). Treatment of *ortho*-bromophenylisothiocyanate with benzylamine in acetonitrile could be accomplished at room temperature within 1 h. Addition of the appropriate catalyst/ligand [*i.e.* CuI and 1,10-phenanthroline, or $Pd(PPh_3)_4$] and Cs_2CO_3, then achieved the essentially quantitative formation of **2a** after refluxing in acetonitrile for 24 h.

In summary, we have demonstrated an efficient intramolecular aryl thiolation using catalytic amounts of $Pd(PPh_3)_4$ and CuI. In general, the copper-catalayzed protocol leads to greater yields and conversions than the palladium-catalyzed protocol. Cu and Pd one-pot protocols were also demonstrated, combining the thiourea



Scheme 2 *Reagents and conditions*: (a) R^1NCS, DMF, 12–48 h; (b) R^1R^2NH, MeCN, 10 min.

† Electronic supplementary information (ESI) available: general experimental details, general procedure for the preparation of 2-aminobenzothiazoles, and analytical data for 2-aminobenzothiazole products. See http://www.rsc.org/suppdata/cc/b3/b311591g/

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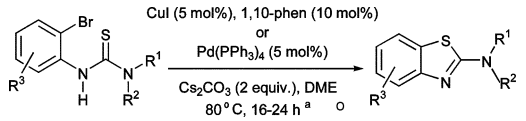
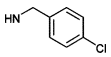
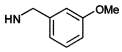
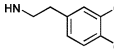
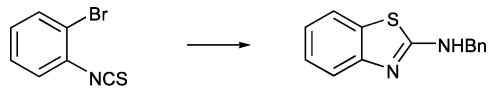
Table 1 Intramolecular 2-aminobenzothiazole **2** synthesis from *ortho*-bromo- and -iodo-arylthioureas **1**



			Pd catalyst		Cu catalyst	
Entry	R^1R^2N	R^3	Conv. (%)[b]	Yield (%)[c]	Conv. (%)[b]	Yield (%)[c]
1	BnNH	H	84 (>98)	95 (quant.)	>98 (>98)	quant. (quant.)
2		H	90	86	95	70
3		H	85	59	>98	85
4		H	90 (95)	80 (94)	>98 (>98)	90 (quant.)
5		H	>98	52	>98	86
6		H	>98 (>98)	94 (quant.)	>98 (>98)	98 (quant.)
7		H	>98 (>98)	87 (quant.)	>98 (>98)	94 (quant.)
8		H	>98	94	>98	87
9		H	>98	89	>98	quant.
10		H	>98	86	>98	93
11	$MeN(CH_2)_2CN$	H	>98 (>98)	84 (93)	>98 (>98)	84 (quant.)
12	BnNH	4-F	90	93	90	69
13	BnNH	4-Me	80	71	>98	97
14	BnNH	4-Me-6-Br	>98	88	>98	89
15	BnNH	5-CF_3	>98	90	>98	78

[a] Reaction times not optimized.[b] Conversion determined by ^{1}H NMR. Conversions shown in brackets are those derived from the corresponding iodide substrate. [c] Yields after silica gel column chromatography. Yields shown in brackets are those derived from the corresponding iodide substrate.



4a **2a**

Scheme 3 *Reagents and conditions*: $BnNH_2$, MeCN, rt, 1 h; then Cs_2CO_3 with CuI (5 mol%) and 1,10-phenanthroline (10 mol%), or $Pd(PPh_3)_4$ (5 mol%), reflux, 24 h.

formation with the cyclization reaction. These results further underscore the recent trend of replacing Pd-mediated carbon–heteroatom formation reactions by the more cost effective Cu-catalyzed processes.

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12 Confirmation that cyclization occurred through S, rather than N, was established by comparison of the isolated product **2a** (R^1 = Bn, R^2, R^3 = H) with a sample independently synthesized by the nucleophilic displacement reaction of benzylamine with 2-chlorobenzothiazole.