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Regioselective Intramolecular Arylthiolations by Ligand Free Cu and Pd Catalyzed Reaction

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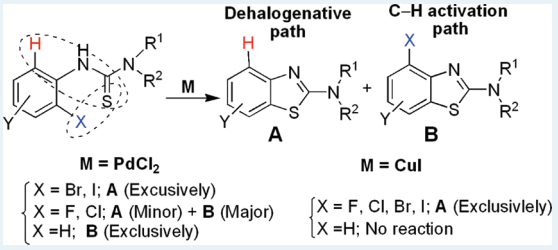
Supporting Information

ABSTRACT: 2-Fluoro and 2-chloro aryl thioureas, which are usually inert toward heteroarylation forms intramolecular C−S linkage by Cu(I) and Pd(II) catalyst. A regioselective intramolecular C−S bond formation is observed during the formation of 2-aminobenzothiazoles from 2-halothioureas using both these transition metal catalysts. While Cu prefers a dehalogenative path, Pd favors predominantly C−H activation strategy during the formation of 2-aminobenzothiazoles. In the absence of 2-halo (−F, −Cl) groups, Pd favors C−H activation, while Cu is unproductive. However, identical selectivities were observed both for Cu- and Pd-catalyzed reactions for 2-bromo and 2-iodo aryl thioureas.



KEYWORDS: *C−H activation, C−S coupling, 2-aminobenzothiazole, Cu-catalysis, Pd-catalysis*

INTRODUCTION

Great progresses have been made in the development of transition metal catalyzed reactions for the construction of C−N and C−O bonds, but until recently selective formation of C−S bonds remained relatively fewer in numbers because of the propensity of sulfur toward oxidative dimerization and their affinity for metals causing catalyst poisoning.[1] These problems have been overcome by the appropriate use of catalyst, ligand and additives through an inter and intra molecular C−H functionalizations. Although, the process of transition metal insertion into C−H bonds are known for several decades, however, this area of research has greatly been explored only after the seminal contributions from Murai et al.[2] and others.[3−11] The C−H bonds can not only be envisioned as dormant synthetic equivalents of active functional groups but also these strategies improve atom economy and overall efficacy of synthetic processes. Among various transition metals, Pd and Cu are most well explored.[4,12−19] Despite of the high cost and difficulties associated with the removal of Pd-residues from polar reaction products, it is still the most preferred transition metal catalyst due to its high turnover number (TN) and selectivity. Relatively inexpensive and easily available Cu has also been used for similar C−H functionalizations.[4] Both Pd and Cu have also been used as efficient catalyst toward carbon-heteroatom bond formations via dehalogenative paths.[5,20−29] Efficient catalytic methods for the formation of C−S bonds are in great demand in synthetic organic chemistry,[30−38] as well as in the material science[39,40] and pharmaceutical industries.[41−45] 2-Aminobenzothiazoles bearing C−S bonds are relevant in agrochemicals and pharmaceuticals.[46,47] Classical synthesis of 2-aminobenzothiazoles involves an intramolecular aromatic electrophilic substitution of thiobenzanilides using various oxidants, including Jacobson's and Hugerschoff methods.[48−53] These compounds have been prepared by intramolecular arylthiolation strategies using Cu or Pd- catalyzed cyclization of *ortho*-halobenzothioureas where the halides are invariably −Br or −I or at best −Cl but rarely with −F substituents.[54−61] All these reactions are carried out in the presence of catalyst, base, ligand and additives or their combinations. Intramolecular oxidative C−H bond activation of *N*-arylthioureas using $Pd(PPh_3)_4/MnO_2/O_2$, Pd−Cu/Bu_4NBr, catalytic system under an oxygen atmosphere[62−64] and alternative strategies involving Pd-catalyzed C−H activation[68−70] are atom economical. No doubt the latter methods (C−H activation) eliminate the need for ortho-halo (Br, I) substituents and a step forward in expanding the C−H activation, and requires 50 mol % of CuI for this methodology[63] and large excess of additives such as Bu_4NBr. Instead of using expensive terminal oxidants such as *para*-benzoquinone, NMO, DMSO, MnO_2, Cu-salts, the cheap molecular oxygen has been employed many a times.[17,71−80] For Cu/Pd catalyzed intramolecular dehalogenative C−Z (Z = O, S, N) cross coupling of 2-halo ureas, guanidines and thioureas follows the order I > Br > Cl[61,81−85] and very few reports using F substituents.[33−38] Herein we made a systematic study to see how Cu or Pd as catalyst behave toward various 2-halo-substituted thioureas. Second, in 2-fluoro- or 2-chloro-substituted thioureas whether a dehalogenative path or a C−H activation path would operate using Cu and Pd catalyst.

RESULTS AND DISCUSSION

We have reported copper catalyzed cascade reactions in the synthesis of various heterocycles involving C−N and C−S heteroarylations.[84−87] In an attempt toward our study the intermediate thiourea (**1**) generated in situ upon mixing phenyl

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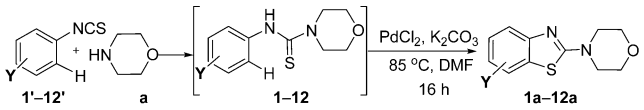
isothiocyanate (**1′**) with morpholine (**a**) when treated with $PdCl_2$ (2 mol %) in DMF at 85 °C under an open atmosphere shows complete disappearance of the thiourea (**1**) with the formation of 2-aminobenzothiazole (**1a**) in excellent yield (91%) (Table 1). It is noteworthy to mention here that similar

Table 1. Synthesis of 2-Aminobenzthiazoles via C−H Functionalization Using $PdCl_2$



Y = H, Me, Bu, F, Br, F, Cl, CN, CF_3, NO_2

substrates	product[a]	yield[b]
(1)	(1a)	91
(2)	(2a)	86
(3)	(3a)	82
(4)	(4a)	93
(5)	(5a)	93
(6)	(6a)	94
(7)	(7a)	91
(8)	(8a)	93
(9)	(9a)	94
(10)	(10a)	91
(11)	(11a)	80
(12)	(12a)	90

[a]Confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. [b]Isolated yield.

transformations have been achieved using $Pd(PPh_3)_4/MnO_2/O_2$.[62] Our results are advantageous as it uses commercially available relatively inexpensive robust catalyst, air (O_2) as the co-oxidant and under a ligand free condition in an air atmosphere. The catalyst $PdCl_2$ was found to be the best among various Pd salts screened in DMF in combination with either K_2CO_3 or Cs_2CO_3 as the base to give the desired product. Thioureas derived from phenyl isothiocyanate (**1′**) and secondary amines such as piperidine (**b**), 4-benzylpiperidine (**c**), 4-thiomorpholine (**d**), pyrrolidine (**e**), 4-cyclohexylpiperizine (**f**), 4-phenylpiperizine (**g**), and diethylamine (**h**) all gave corresponding 2-aminobenzothiazoles (**1b**, 87%), (**1c**, 92%), (**1d**, 88%), (**1e**, 93%), (**1f**, 80%), (**1g**, 90%), (**1h**, 92%) in excellent yields (Table 1).

Under this optimized reaction condition, thioureas (**2**−**7**) were subjected to catalytic combination of $PdCl_2$, K_2CO_3 in DMF at 85 °C under an open atmosphere and all underwent efficient conversion to 2-aminobenzothiazoles (**2a**−**7a**) through a C−H activation strategy. The substituents in the aromatic core ranges from activating −Me (**2**), *n*-Bu (**3**), moderately deactivating −F (**4**), −Br (**5**), and highly deactivating −CN (**6**), $-CF_3$ (**7**), and all gave their corresponding products in good to excellent yields (Table 1). In general, the presence of electron-withdrawing substituents in the aromatic scaffolds gave better yields compared to electron rich ones. *m*-Substituted substrates (**8**−**10**), regioselectively gave 5-substituted products (**8a**−**10a**). The exclusive formation of 5-substituted product is evident from the crystal X-ray crystallography of (**10a**) as shown in Figure 1. The

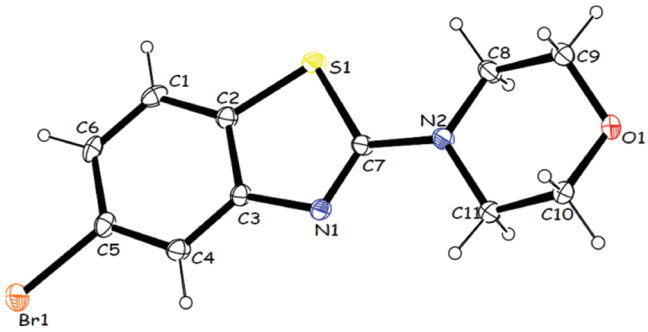


Figure 1. ORTEP Molecular Diagram of **10a**.

disubstituted substrate (**11**) where one of the substituent is *meta* to NH, also regioselectively gave 5-substituted product (**11a**). 1-Naphthylthiourea (**12**) yielded 2-aminobenzothiazole (**12a**) via a C−H activation path.

Interestingly, 2-fluoro-substituted thiourea (**13**) also yielded 2-aminobenzothiazole (**13a**) in good yield under the identical condition but via a C−H functionalization strategy and not by a dehalogenative path (Table 2). Structure of the product (**13a**) with retention of F-group has been confirmed by X-ray crystal structure (Figure 2) as well as from ^{19}F-NMR. Thus, a Pd-catalyzed reaction prefers C−H activation over dehalogenative arylthiolation, possibly because of the inertness of sp^2 C−F bond. Analogous 2-fluorothiourea (**13″**) gave 2-aminobenzothiazole (**13b**) via a C−H activation path. For partially fluorinated phenyl rings there is an intramolecular competition between C−H and C−F bond activation during intramolecular cyclization.[65,66] In the present system electronic effect was observed for disubstituted thioureas during the formation 2-aminobenzothiazole (Table 2). Substrates bearing two fluoro groups in 2,4-positions (**15** and **15″**) gave exclusive/major dehalogenated products **4a** and **4c** which is in sharp contrast to observed nucleophilic C−H activated products for substrates **13** and **13″**. This observation supports the thermodynamic pathway of this intramolecular competitive cyclization.[67] In case of 4-methyl-2-fluoro substrate (**14**) the ring electron density is slightly increased with respect to difluoro substrates (**13**, **13″**, **17**) thus ruling out the possibility of nucleophilic C−H activated product and giving only dehalogenated (C−F bond cleavage) product (**2a**). The propensity of Pd toward C−H activation over defluorinative heteroarylation has been further demonstrated with other 2-fluoro thiourea (**16**) which gave

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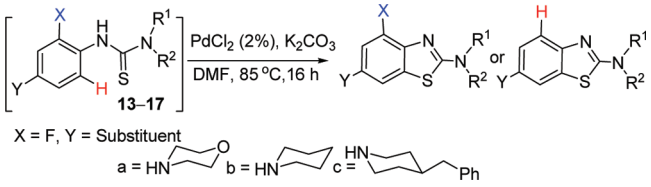
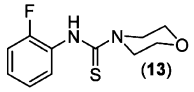
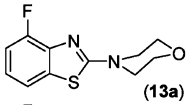
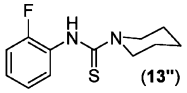
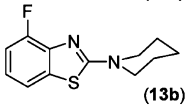
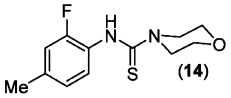
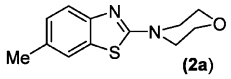
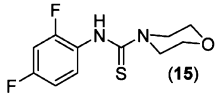
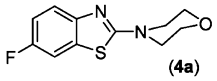
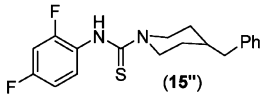
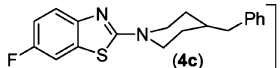
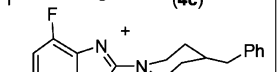
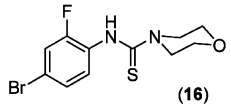
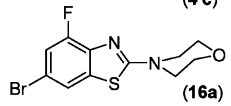
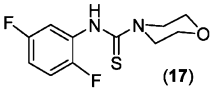
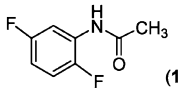
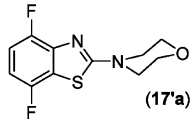
Table 2. Pd-Catalyzed Synthesis of 2-Aminobenzthiazoles via C−H Functionalization



substrates	product[a]	yield%[b]
 (13)	 (13a)	96
 (13")	 (13b)	91
 (14)	 (2a)	93
 (15)	 (4a)	94
 (15")	 (4c)	70
	 (4'c)	20
 (16)	 (16a)	80
 (17)	 (17i)	73
	 (17'a)	87[c]

[a]Confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. [b]Isolated yield. [c]Reaction was performed in DMSO solvent.

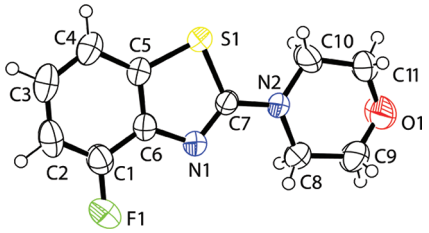


Figure 2. ORTEP Molecular Diagram of **13a**.

benzothiazoles **16a** via C−H functionalization. It may be mentioned here that thiourea (**15**″) gave benzothiazole (**4**′**c**) as the minor product via defluorinative path (Table 2). Instead of thiourea *N*-(2,4-difluorophenyl)morpholine-4-carbothioamide (**15**) when isomeric thiourea *N*-(2,5-difluorophenyl)-morpholine-4-carbothioamide (**17**) was used for the Pd-catalyzed reaction in DMF solvent a completely unexpected product *N*-(2,4-difluorophenyl) acetamide (**17i**) was obtained. The crystal X-ray crystallography of product (**17i**) is shown in Figure 3. The exact mechanism of this reaction is not clear at

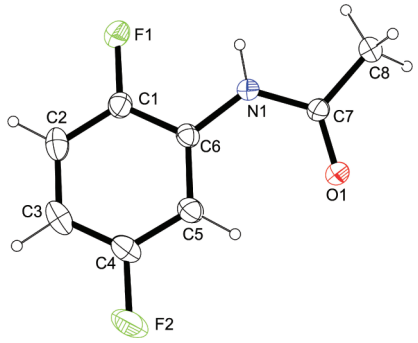


Figure 3. ORTEP molecular diagram of **17i**.

the moment but it seems the acetyl group is originating from solvent DMF. This is a very very substrate specific reaction and no other substrates examined (Table 1, 2 and 3) gave similar product. Switching the solvent from DMF to DMSO gave the expected product (**17a**′) thus further supporting our assumption. Whereas regioisomeric substrate having two fluoro groups in 2,5-positions (**17**) exclusively gave nucleophilic C−H activation product (**17a**′) over dehalogenated (C−F bond cleavage) product which supports the kinetic pathway over thermodynamic pathway.[67]

During Cu/Pd-catalyzed intramolecular dehalogenative cross coupling reaction of 2-halo ureas, guanidines, and thioureas follows the order I > Br > Cl > F. We wanted to see if −Cl a relatively more reactive halogen than −F prefer dehalogenation or C−H activation when subjected to Pd-catalyzed reaction. A Pd-catalyzed reaction of 2-chloro-substituted thioureas (**18**, **18**″, **19**, **19**″, and **20**) gave two types of benzothiazoles one via a dehalogenative process and the other follows a C−H activation path. Barring the case of (**18**″and **19**″) (Table 2), the major product is obtained via a C−H activation path with the retention of Cl group (**18a**, **19**′**a**, and **20a**), while the minor products (**1a**, **19a**, and **5a**) are obtained via a dehalogenative path. Not only the aryl ring but also the nature of the secondary amines present in thioureas also dictates the outcome of the regioselectivity. All other parameters remaining the same morpholino containing thioureas (**18**, **19**, and **20**) gave C−H activation as the major product while the analogous piperidine (**18**″) and 4-benzylpiperidine (**19**″) preferred dahalogenation over C−H activation giving (**1b**) and (**19c**) as the major product (Table 3).

In general both Cu and Pd catalyst exhibits comparable selectivity and reactivity toward sp^2 C−H's activation and arylthiolation involving C−halogen bonds. In the study of thiourea (**13**) with CuI (2 mol %) as catalyst under an identical condition to that of Pd-catalyzed reaction showed exclusive formation of dehalogenated product, benzothiazole (**1a**) sluggishly in moderate yield (50%). Using DMSO as the solvent and 5 mol % of catalyst gave benzothiazole (**1a**) in excellent yield (83%). These show preference for Cu toward dehalogenative path over C−H activation even with fluoro substituents. This assumption has been supported with the help of six other 2-fluoro substituted thioureas (**13**″, **14**, **15**, **15**″, **16**, and **17**) and all underwent defluorinative path giving products (**1b**, **2a**, **4a**, **4c**, **5a**, and **17a**) respectively (Table 4). Although *N*/*O*-arylation of fluoro substituted substrates with Cu and Fe

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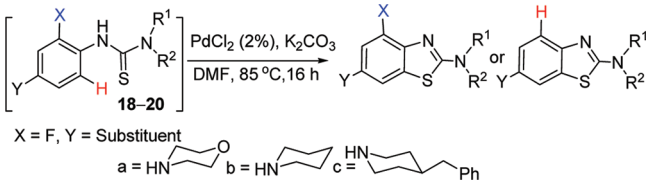
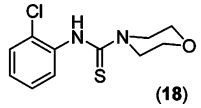
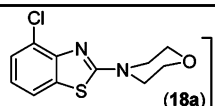
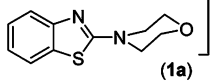
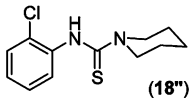
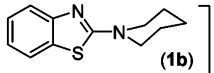
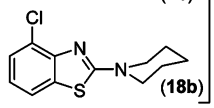
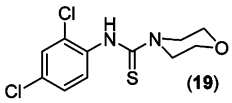
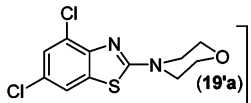
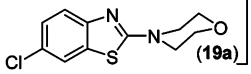
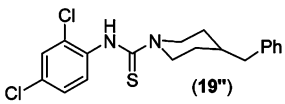
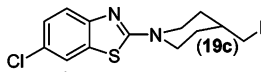
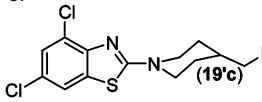
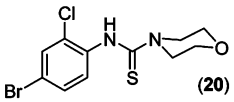
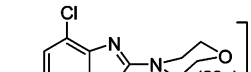
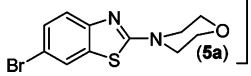
Table 3. Pd-Catalyzed Synthesis of 2-Aminobenzthiazoles via C−H Functionalization



substrates	product[a]	yield%[b]
 (18)	 (18a)	71
	 (1a)	15
 (18")	 (1b)	42
	 (18b)	33
 (19)	 (19'a)	51
	 (19a)	32
 (19")	 (19c)	70
	 (19'c)	15
 (20)	 (20a)	72
	 (5a)	17

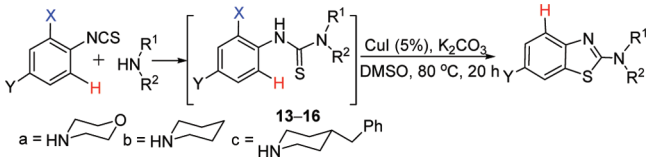
[a]Confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. [b]Isolated yield.

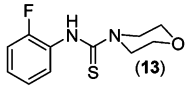
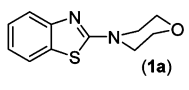
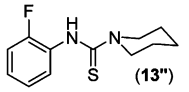
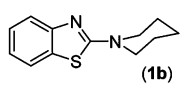
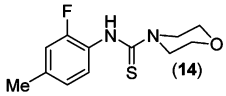
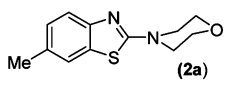
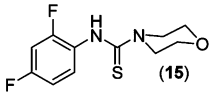
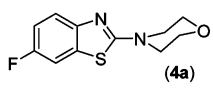
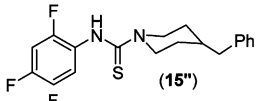
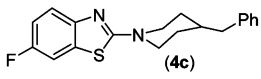
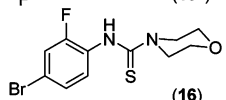
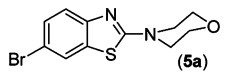
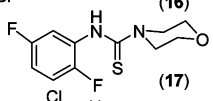
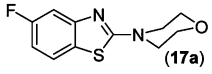
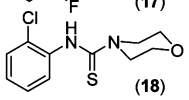
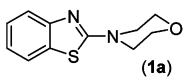
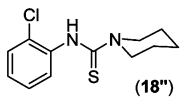
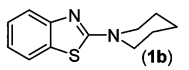
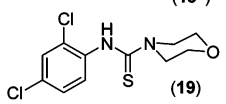
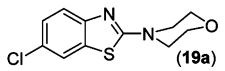
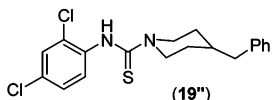
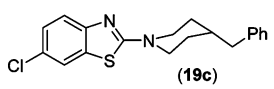
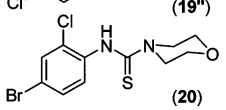
salts have been reported.[88−91] However, an intramolecular *S*-arylation involving defluorinative path is yet to be explored. 2-Chloro substituted thioureas (**18**), (**18″**), (**19**), (**19″**), and (**20**) gave benzothiazoles (**1a**), (**1b**), (**19a**), (**19c**), and (**5a**) (Table 4) via a dehalogenative path; an observation, in sharp contrast to the Pd-catalyzed reactions (Table 2 and 3).

Copper- and palladium-catalyzed synthesis of 2-amino-benzthiazoles are reported for 2-Br and 2-I thioureas in the presence of ligand.[54−61] The same has been achieved under ligand and catalyst free condition[92] and in the presence of additives.[60] But these procedure requires longer reaction times or high temperature.

From our present studies it is evident that Cu prefers a dehalogenative path even with less reactive halogens such as −F

Table 4. Cu-Catalyzed Synthesis of 2-Aminobenzthiazoles via Dehalogenative Path



substrates	product[a]	yield[b]
 (13)	 (1a)	83
 (13")	 (1b)	79
 (14)	 (2a)	79
 (15)	 (4a)	73
 (15")	 (4c)	76
 (16)	 (5a)	81
 (17)	 (17a)	76
 (18)	 (1a)	91
 (18")	 (1b)	83
 (19)	 (19a)	81
 (19")	 (19c)	83
 (20)	(5a)	71

[a]Confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. [b]Isolated yield.

and −Cl. In contrary Pd gave exclusively C−H activated product with fluoro and a mixture of C−H activated and dehalogenated product in the case of −Cl substrates (Table 4 and 5). Thus it is expected with reactive halogens such as −Br and −I both Pd and Cu should behave identically giving only dehalogenated products. To prove this assumption 2-bromo substituted thioureas (**21**−**24**) were reacted with $PdCl_2$ (2 mol %) and all gave corresponding benzothiazoles as shown in Table 5 via a dehalogenative path. It may be mentioned here that with a similar substrate (**21**) using ligand assisted Pd salt only traces of dehalogenated product is reported along with the

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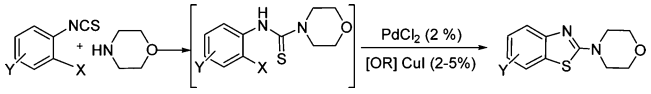
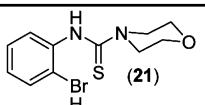
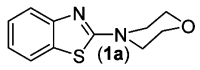
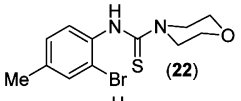
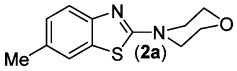
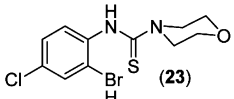
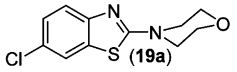
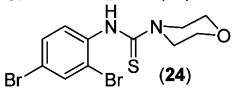
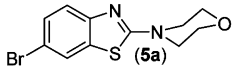
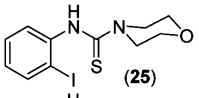
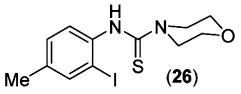
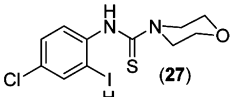
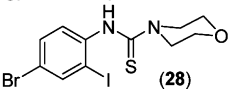
Table 5. Pd/Cu-Catalyzed Synthesis of Benzothiazoles[a]



substrates	product	yield[b] Cu / Pd
 (21)	 (1a)	91 / 96
 (22)	 (2a)	93 / 95
 (23)	 (19a)	94 / 97
 (24)	 (5a)	90 / 95
 (25)	(1a)	99 / 97
 (26)	(2a)	96 / 91
 (27)	(19a)	93 / 89
 (28)	(5a)	94 / 96

[a]Confirmed by IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. [b]Isolated yield. [c]CuI (5 mol %), room temperature, 2 h. $PdCl_2$ (2 mol %), 85 °C, 1 h. [d]CuI (2 mol %), $PdCl_2$ (2 mol %), room temperature, 0.5 h.

recovery of starting material. Identical results were also obtained using 2-iodo substituted thioureas (**25**−**28**). For 2-bromo substrates the reaction works best using 2 mol % of the catalyst at 85 °C and iodo substrates goes at room temperature with 2 mol % of the catalyst. Identical results were obtained with Cu also but interestingly for 2-Br and 2-I thioureas the reaction goes at room temperature. The reaction works best with 5 mol % of the catalyst for −Br substrates whereas for −I substrates 2 mol % of catalyst was sufficient giving excellent yields of products (Table 4).

In path-I Pd(II) in the presence of base gets reduced to Pd(0).[98,99] This upon oxidative insertion to halogroup of thiourea followed by co-ordination with sulfur generates intermediate (I). Subsequent reductive elimination provides benzothiazoles with concomitant generation of Pd(0) which maintains the catalytic cycle (path I, Scheme-1).[54,98,99] In an alternative path (path II) substrates containing 2-F, Cl substituents, precoordination of sulfur to Pd occur and the palladacycle is formed *via* σ bond metathesis giving intermediate (II) or via a base-assisted deprotonative metalation giving intermediate (III).[62,64,93−97] Thus, benzothiazole is obtained via C−H activation path with the retention of 2-halo (Cl, F) substituents. The in situ generated Pd(0) in this path (Path II) gets oxidized to Pd(II) in air to take part in the next cycle.[62,64] Depending on the nature of the substituents present they prefer to go either via path I or path II and in some cases two paths compete with each other giving both types of product. While, the Cu catalyzed reaction involves an intramolecular C−S cross-coupling of *ortho*-halothioureas for the entire range of halogens (F, Cl, Br, and I) and is believed to proceed via an oxidative insertion/reductive elimination path through a Cu(I)/Cu(III) manifold.[61]

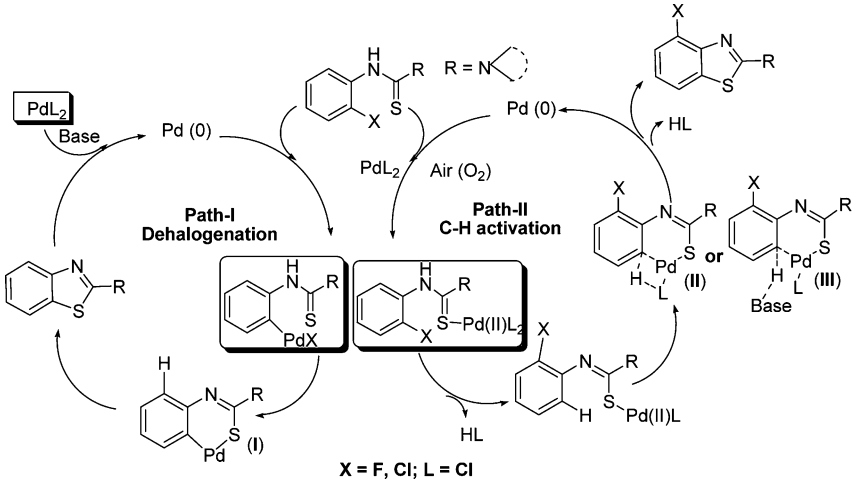
CONCLUSIONS

In summary, we have demonstrated the regioselective intramolecular C−S bond formation during the formation of 2-aminobenzothiazole from 2-halo substituted thioureas using Cu and Pd catalyst. With few exceptions palladium prefers a C−H activation path over dehalogenative for less reactive halogens, such as fluoro. However, no satisfactory explanation on selectivity has emerged from the present study. For bromo and iodo a dehalogenative path is favored while chloro substituted thioureas undergoes either of the paths giving both types of benzothiazoles. However, Cu prefers dehalogenative path only for the entire range of halogens. These ligand free regioselective synthesis of 2-amino benzothiazole are advantageous over other reported methods in literature.

EXPERIMENTAL SECTION

The aryl isothiocyanatres are synthesized by following our Green synthetic protocol.[100,101]

Scheme 1. Plausible Mechanism for the Differential Selectivity Using Pd(II) Catalyst



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2-Morpholinobenzo[*d*]thiazole (1a): White solid; R_f = 0.55 (EtOAc/hexane (2:8); mp 120−122 °C (Lit.[62,64] 119−120 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59 (t, 4H, J = 4.4 Hz), 3.80 (t, 4H., J = 4.4 Hz), 7.07 (t, 1H, J = 7.6 Hz), 7.28 (t, 1H, J = 8.0 Hz), 7.57 (dd, 1H, J_1 = 6.4 Hz, J_2 = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.5, 66.2, 119.4,120.8, 121.7, 126.1, 130.6, 152.5, 169.0 IR (KBr): 2918, 2854, 1591, 1537, 1441, 1377, 1289, 1229, 1113, 1067, 1032, 945, 859, 756 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_2OS$ C 59.97, H 5.49, N 12.72, S 14.56; Found C 60.07, H 5.55, N 12.62, S 14.48.

2-(4-Benzylpiperidin-1-yl)benzo[*d*]thiazole (1c): White solid; R_f = 0.5 (EtOAc/hexane (2:8); mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 1H), 1.77 (d, 4H, J = 10.8 Hz), 2.59 (d, 2H, J = 7.2 Hz), 3.06 (t, 2H, J = 12.8 Hz), 4.15 (d, 2H, J = 13.2 Hz), 7.08 (t, 1H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.0 Hz), 7.26 (d, 1H, J = 7.2 Hz), 7.32 (m, 3H), 7.60 (t, 2H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 38.0, 43.0, 49.0, 118.9, 120.7, 121.2, 126.0, 126.2, 128.4, 129.2, 130.8, 139.9, 153.0, 168.7; IR (KBr) 3061, 3024,2937, 2920, 2851, 1595, 1539, 1492, 1444, 1388, 1324, 1278, 1258, 1172, 922, 752, 727 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}N_2S$ (M + H$^+$) 309.0955; found 309.0959.

6-Butyl-2-morpholinobenzo[*d*]thiazole (3a): White solid; R_f = 0.5 (EtOAc/hexane (2:8); mp 61−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.6 Hz), 1.33 (m, 2H), 1.58 (m, 2H), 2.61 (t, 2H, J = 8.0 Hz), 3.52 (t, 4H, J = 4.4 Hz), 3.74 (t, 4H, J = 4.4 Hz), 7.09 (d, 1H, J = 8.0 Hz), 7.38 (s, 1H), 7.47 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.2, 33.9, 35.4, 48.4, 66.1, 118.9, 120.1, 126.6, 130.6, 136.5, 150.5, 168.4; IR (KBr) 2953, 2920, 2856, 1538, 1462, 1375, 1340, 1290, 1231, 1110, 1072, 1032, 944, 877, 822, 658 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}N_2SO$ (M + H)$^+$ 277.0684; found 277.0687.

6-Bromo-2-morpholinobenzo[*d*]thiazole (5a): White solid; R_f = 0.43 (EtOAc/hexane (2:8); mp 165−167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (t, 4H, J = 4.8 Hz), 3.80 (t, 4H, J = 4.8 Hz), 7.37 (s, 2H), 7.68 (s, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 48.5, 66.3, 114.0, 120.5, 123.3, 129.4, 132.4, 151.6, 169.1; IR (KBr) 2918, 2857, 1591, 1535, 1443, 1372, 1280, 1258, 1229, 1110, 1026, 940, 863, 813 cm^{-1}; Anal. Calcd for $C_{11}H_{11}N_2OSBr$ C 44.16, H 3.71, N 9.36, S 10.72; found C 44.23, H 3.76, N 9.28, S 10.64.

5-Bromo-2-morpholinobenzo[*d*]thiazole (10a): White solid; R_f = 0.45 (EtOAc/hexane (2:8); mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (t, 4H, J = 4.8 Hz), 3.78 (t, 4H, J = 4.8 Hz), 7.01 (d, 1H, J = 8.4 Hz), 7.44 (d, 1H, J = 8.4 Hz), 7.50 (s 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.6, 66.3, 120.9, 121.9, 122.3, 124.6, 129.5, 154.1, 169.9; IR (KBr) 2924, 2853, 1526, 1443, 1338, 1230, 1110, 1068, 1030, 876, 800 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OSBr$ (M + H)$^+$ 300.9868; found 300.9870.

2-Morpholinonaptho[1,2-*d*]thiazole (12a): Pinkish solid; R_f = 0.5 (EtOAc/hexane (2:8); mp 183−184 °C (Lit.[97] 183−184 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (t, 4H, J = 4.8 Hz), 3.86.(t, 4H, J = 4.8 Hz), 7.58 (m, 3H), 7.98 (s, 1H), 8.23 (m, 1H), 8.57 (m, 1H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 48.7, 66.4, 114.9, 122.4, 124.6, 125.5, 126.8, 126.7, 127.5, 127.9, 130.5, 148.5, 169; IR (KBr): 2961, 2844, 1568, 1531, 1496, 1451, 1393, 1351, 1278, 1226, 1156, 1112, 1080, 1035, 910, 758 cm^{-1}; Anal. Calcd for $C_{15}H_{14}N_2OS$ C 66.64, H 5.22, N 10.36, S 11.86; found C 66.70, H 5.24, N 10.27, S 11.79.

4-Fluoro-2-morpholinobenzo[*d*]thiazole (13a): White solid; R_f = 0.45 (EtOAc/hexane (2:8); mp 122−123 °C (Lit.[62] 122−122.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (t, 4H, J = 4.8 Hz), 3.80 (t, 4H, J = 4.8 Hz), 6.98−7.04 (m, 2H), 7.34−7.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.5, 66.2, 112.3($^2J_{CF}$ = 73.2 Hz), 116.5, 122.1 ($^2J_{CF}$ = 23.6 Hz), 133.1, 152.2, 154.7, 169.0; ^{19}F NMR ($CDCl_3$ + Hexafluoro Benzene) δ 35.6; IR (KBr) 2931, 2917, 2865, 1610, 1542, 1474, 1375, 1336, 1282, 12, 1121, 949, 927, 780 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{11}N_2OSF$ (M + H$^+$) 239.0616; found 239.0619.

4,6-Dichloro-2-morpholinobenzo[*d*]thiazole (19′a): White solid; R_f = 0.42 (EtOAc/hexane (2:8); mp 141−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (t, 4H, J = 4.4 Hz), 3.74 (t, 4H, J = 4.8 Hz), 7.30 (d, 1H, J = 2.0 Hz), 7.43 (d, 1H, J = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.4, 66.2, 119.1, 123.9, 126.4, 126.5, 132.4, 148.4, 168.9; IR (KBr) 3060, 2856, 1587, 1536, 1431, 1380, 1336, 1275, 1231, 1115, 1070, 1026, 942 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}Cl_2N_2OS$ (M + H)$^+$ 289.0002; found 289.0002.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectroscopic data, copies of ^{1}H, ^{13}C NMR, all compounds, selected mass spectra, and crystallographic information of compounds (**10a**) and (**13a**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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