ORGANIC
LETTERS

2009
Vol. 11, No. 19
4254−4257

Intra- and Intermolecular C−S Bond Formation Using a Single Catalytic System: First Direct Access to Arylthiobenzothiazoles

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Received May 21, 2009

ABSTRACT

We have for the first time developed two ligand-assisted Cu(I)-catalyzed sequential intra- and intermolecular *S*-arylations leading to the direct synthesis of arylthiobenzothiazoles in one pot without an inert atmosphere. Low catalyst loading, inexpensive metal catalyst and ligand, lower reaction temperature, and shorter reaction times make this method superior to all reported methods for the synthesis of arylthiobenzothiazole.

In recent years, there has been an ever-increasing interest in the field of metal-catalyzed multistep processes such as tandem, domino, cascade, sequential, and/or concurrent catalysis in which one or more catalysts are employed for two or more transformations in one pot.[1] Great efforts and progress have been made in the development of Pd- and Cu-catalyzed inter- and intramolecular domino reactions involving carbon−heteroatom bond formations for the synthesis of a wide variety of heterocycles.[2] However, the Cu-catalyzed heteroarylation has proved to be much more advantageous over Pd and other metal catalysts in terms of efficiency, selectivity, low costs, and high functional group tolerance.[3]

Although the chemistry of Cu-catalyzed C−C, C−N, and C−O bond formations is well explored,[4] methods available for the C−S bond formation[5] are rather fewer because of

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(1) (a) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (b) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (e) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (f) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (g) de Meijere, A.; Zezschwitz, P. V.; Brase, S. *Acc. Chem. Res.* **2005**, *38*, 413.

(2) (Cu and Pd): (a) Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260(Cu): (b) Zou, B.; Yuan, Q.; Ma, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598. (c) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Org. Lett.* **2003**, *5*, 3843. (d) Cacchi, S.; Fabrizi, G.; Parisi, L. M.; Bernini, R. *Synlett* **2004**, 287.

(3) Cu-catalyzed: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265. (c) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (d) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (e) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev* **2002**, *102*, 1359. Pd-limitations: (f) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (g) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (h) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539.

(4) (a) Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; WILEY-VCH: Weinheim, Germany, 2004; p 699. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Mannier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096.

(5) For a review dealing with the metal-catalyzed formation of carbon−sulfur bonds, see: (a) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. Cu-based C−S intermolecular: (b) Hua-Jian, X.; Xiao-Yang, Z.; Jin Deng, Y. F.; Feng, Y.-S. *Tetrahedron Lett.* **2009**, *50*, 434, and references cited there in. (c) Bhadra, S.; Saha, A.; Ranu, B. C. *Green Chem.* **2008**, *10*, 1224. Intramolecular: (d) Bowman, W. R.; Heaney, H.; Smith, P. H. G. *Tetrahedron Lett.* **1982**, *23*, 5093. (e) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (f) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446. (g) Ma, H. C.; Jiang, X. Z. *Synlett* **2008**, 1335. (h) Wang, J.; Peng, F.; Jiang, J.-l.; Lu, Z.-j.; Wang, L.-y.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467.

10.1021/ol9017535 CCC: $40.75

the propensity of thiols toward oxidative dimerization and their affinity for metals, causing reduced catalytic efficiency. Despite the plethora of C-heteroatom bond formation reported, involving Pd, Cu-catalyzed multicatalytic processes, there is no report on the tandem, domino, cascade, sequential, and/or concurrent catalytic methods involving intramolecular and intermolecular S-arylations. As a part of our ongoing research in developing methods for the synthesis of heterocycles,[6] we were further interested in developing newer protocols for the synthesis of heterocycles via two sequential intra- and intermolecular C−S bond formations using a single catalyst (Cu) in one pot.

2-Arylthiobenzothiazoles or 2-arylsulfanylbenzothiazole or substituted 2-mercaptobenzothiazoles (MBTs) are an important class of heterocycles that are found in a broad spectrum of biologically active compounds. Some therapeutic agents containing this core structure include potent heat shock protein-90 inhibitors (**A**)[7a] and an inhibitor of Cathepsin-D (**B**)[7b](Figure 1). They also act as antimicrobial agents especially against Piricularia oryzae and Xanthomonas oryzae.[7c]

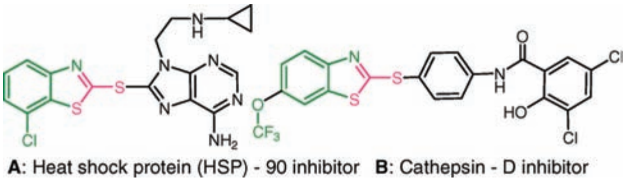
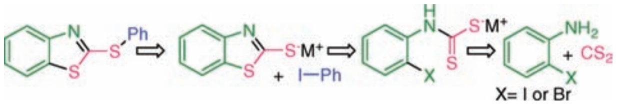


Figure 1. Structures of some biologically important molecules containing the 2-arylthiobenzothiazole moiety.

Classical methods for the synthesis of substituted MBTs involve mainly two types of nucleophilic substitution reactions. One by the nucleophilic attack of arylthiols with a preformed 2-halobenzothiazoles and the second by the nucleophilic attack of mercaptobenzothiazole with haloarenes containing strongly deactivating substituents under a strongly basic condition.[8] Alternatively, several cross-coupling reactions were developed with similar coupling partners to include a wide range of substrates.[9] Pd-catalyzed synthesis of thioethers from aryl iodides and arylthiols[9a,b] as well as the Cu-catalyzed reaction of boronic acids with aryl, hetero aryl, and alkyl *N*-thioimides to yield thioethers has been reported.[9c] Recently, Bolm et al. reported the Fe-catalyzed S-arylation protocol of aromatic and heteroaromatic thiols[9d] but uncertanities exist about the exact catalytic role of Fe.[9f] A Pd-catalyzed, Cu-mediated coupling of heteroaromatic thioethers with aryl, hetero aryl, and alkenyl stannanes has been described.[9e] Alternatively, Wang et al. developed a method for the synthesis of 2-arylthiobenzothiazoles by the S-arylation of benzothiazol-2-thiol with diaryliodonium salts in an ioinic liquid [bmim]BF_4.[10] In addition, methods exist for the syntheses of arylthiobenzothiazoles.[11] However, the preparation of arylthiobenzothiazoles with these methods depends largely on the availability of the requisites, suitably substituted 2-halo benzothiazole or mercapto benzothiazoles.

Previously, Batey and others have developed methods for the synthesis of 2-substituted benzothiazoles from the corresponding 2-halothioanilides and 2-halothioureas via Pd- and Cu-catalyzed intramolecular S-arylation.[5e,12] In continuation of our efforts in the synthesis of substituted 2-mercaptobenzimidazole via Cu-catalyzed intramolecular C−N bond formation[6a] we envisioned that it would be possible to combine both the intra- and the intermolecular S-arylations using a single catalytic system (Cu) in one pot for the synthesis of 2-arylthiobenzothiazoles. Herein, we report our efforts toward this target, resulting in the first direct access to 2-arylthiobenzothiazoles (Scheme 1). In this single catalytic one-pot double arylation strategy, intramolecular S-arylation of dithiocarbamate salt would yield benzothiazol-2-thiol or MBT, which is then followed by an intermolecular C−S coupling giving directly 2-arylthiobenzothiazoles as shown in Scheme 1.

Scheme 1. The Design of Direct Synthesis of Arylthiobenzothiazoles via Two Sequential C−S Bond Formations



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(6) (a) Murru, S.; Patel, B. K.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2009**, *74*, 2217. (b) Murru, S.; Singh, C. B.; Kavala, V.; Patel, B. K. *Tetrahedron* **2008**, *64*, 1931. (c) Yella, R.; Ghosh, H.; Patel, B. K. *Green Chem.* **2008**, *10*, 1307. (d) Singh, C. B.; Murru, S.; Kavala, V.; Patel, B. K. *Org. Lett.* **2006**, *8*, 5397.

(7) (a) Zhang, L.; Fan, J.; Vu, K.; Hong, K.; Le Brazidec, J.-Y.; Shi, J.; Biamonte, M.; Busch, D. J.; Lough, R. E.; Grecko, R.; Ran, Y.; Sensintaffar, J. L.; Kamal, A.; Lundgren, K.; Burrows, F. J.; Mansfield, R.; Timony, G. A.; Ulm, E. H.; Kasibhatla, S. R.; Boehm, M. F. *J. Med. Chem.* **2006**, *40*, 5352. (b) Dumas, J.; Brittelli, D.; Chen, J.; Dixon, B.; Hatoum-Mokdad, H.; Konig, G.; Sibley, R.; Witowsky, J.; Wong, S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531. (c) Kiyoshi, T.; Gozaburo, D.; Kozo, S.; Shoichi, O. *Patent no. JP 4907114219740710*, 1974.

(8) (a) Xu, Y.-G.; Hua, W.-Y.; Liu, X.-Y.; Zhu, D.-Y. *Youji Huaxue* **2004**, *24*, 1217. (b) Katritzky, A. R.; Aurrecoechea, J. M.; de Vazquez, M.; Luis, M. *Heterocycles* **1987**, *26*, 427. (c) Rakowitz, D.; Hennig, B.; Nagano, M.; Steger, S.; Costantino, L.; Matuszczak, B. *Arch. Pharm.* **2005**, *338*, 411. (d) Nagarajan, K.; Goud, A. N.; Rao, V. R.; Shah, R. K.; Sen, H. G.; Deb, B. N. *Indian J. Pharm. Sci.* **1986**, *48*, 53.

(9) (a) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069. (b) Barbieri, R. S.; Bellato, C. R.; Dias, A. K. C.; Massabni, A. C. *Catal. Lett.* **2006**, *109*, 171. (c) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309. (d) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (e) Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801. (f) Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.

(10) (a) Wang, F.-Y.; Chen, Z.-C.; Zheng, Q.-G. *J. Chem. Res.* **2004**, *2*, 127. (b) Kotali, E.; Varvoglis, A. *J. Chem. Res.* **1989**, 142.

(11) (a) Lohmann, S.; Andrews, S. P.; Burke, B. J.; Smith, M. D.; Attfield, J. P.; Tanaka, H.; Kaneko, K.; Ley, S. V. *Synlett* **2005**, 1291. (b) Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Heterocycles* **1996**, *43*, 471. (c) Amatore, C.; Beugelmans, R.; Bois-Choussy, M.; Combellas, C.; Thiebault, A. *J. Org. Chem.* **1989**, *54*, 5688. (d) Thomas, H. N.; Howlett, E. C. *J. Am. Chem. Soc.* **1951**, *73*, 4720.

(12) (a) Bowman, W. R.; Heaney, H.; Smith, P. H. G. *Tetrahedron Lett.* **1982**, *23*, 5093. (b) Benedi, C.; Bravo, F.; Uriz, P.; Fernandez, E.; Claverb, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073. (c) Bernardi, D.; Ba, L. A.; Kirsch, G. *Synlett* **2007**, 2121. (d) Ma, H. C.; Jiang, X. Z. *Synlett* **2008**, 1335. (e) Wang, J.; Peng, F.; Jiang, J.-l.; Lu, Z.-j.; Wang, L.-y.; Bai, J.; Pan, Y. *Tetrahedron Lett.* **2008**, *49*, 467. (f) Vera, M. D.; Pelletier, J. C. *J. Comb. Chem.* **2007**, *9*, 569.

The dithiocarbamate salt of 2-iodoaniline **1** was prepared by treating it with CS_2 and triethylamine following the literature procedure,[13] which was then used as a model substrate for reaction optimization. Initially, the coupling of dithiocarbamate **1** and iodobenzene (**a**) was selected to optimize the reaction conditions taking CuI as the precatalyst and K_2CO_3 as the base. In the absence of suitable ligand, the first step (intramolecular) of the reaction was slow and the second step (intermolecular) was not at all effective, while phenanthroline ligand (L1) (Figure 2) was found to be most effective (81%), an observation consistent with our previous report on intramolecular C−N bond formation.[6a] Surprisingly, the less expensive cyclohexyl-1,2-diamine ligand (L5) was found to be even better in terms of superior yield (86%) in a short reaction time (4 h) for this sequential reaction.

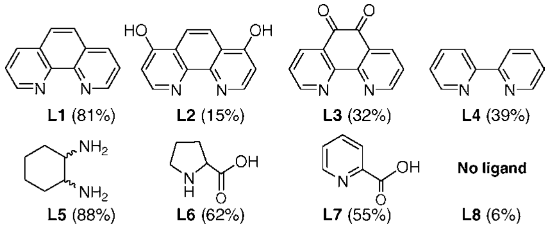
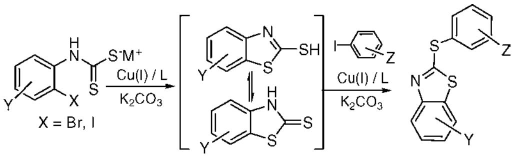


Figure 2. Effects of ligands on the Cu(I)-catalyzed reaction.

Thus from a series of experiments (Figure 2) the optimum ratios of dithiocarbamate:aryl iodide:CuI:ligand (L5):base were found to be 1:1:0.05:0.1:3. Further experimentation revealed the significance of the solvent dependence for both steps. Among the various solvents (DMF, 1,4-dioxane, DMSO, DMA, and toluene) tested, the reaction was found to be fastest in DMSO, and K_2CO_3 was found to be the ideal base. Although the reaction works faster at higher temperature we maintained a uniform temperature of 90 °C for both steps for all the reactions. Further, the reactions are much faster (4−8 h) compared to several similar intermolecular C−S bond forming reactions reported to be taking place above 100 °C for several hours.[5]

It is reasonable to assume that the initial reaction proceeds by an intramolecular S-arylation to give 2-mercaptobenzothiazole (MBT), the intermediacy of which has been confirmed by its isolation. Since MBTs have found a wide range of applications in different fields and their synthesis involves arduous reaction conditions, in the absence of iodoarenes the reaction can be stopped to isolate MBT in quantitative yields.[14] In the absence of any ligand or with less efficient ligands (Figure 2), 2-mercaptobenzothiazole (MBT) was obtained as the major product confirming the faster intramolecular over the intermolecular S-arylation (Scheme 2). For aryldithiocarbamates having *o*-halo (I or Br) substituents, no initial intermolecular S-arylation was observed. In the absence of 2-halo substituents Cu−nanoparticle catalyzed intermolecular S-arylation has been reported.[5c] The intramolecular S-arylation is then followed by an intermolecular S-arylation giving the arylthiobenzothiazole in excellent yield as shown in Scheme 2 and Table 1.

Scheme 2. Synthesis of 2-Arylthiobenzothiazoles via Sequential Cu-Catalyzed Intra- and Intermolecular *S*-Arylations



Even though the reaction is carried out in an air atmosphere, no disulfide formation of any kind was observed, thus ruling out the possibility of an oxidative path involving dithiocarbamate disulfide as intermediate (Scheme 2), an observation consistent with recent Fe-catalyzed C−S bond formation.[9d]

Next, the scope of the reaction with various dithiocarbamates of 2-halo anilines and substituted anilines such as 2-iodoaniline **1**, 2-bromoaniline **1′**, 2-iodo-4-methylaniline **2**, 2-bromo-4-methylaniline **2′**, 4-chloro-2-iodoaniline **3**, 4-bromo-2-iodoaniline **4**, 2,4-dibromoaniline **4′**, 2-bromo-4-methoxyaniline **5′**, 2-iodo-4,5-dimethylaniline **6**, 2-bromo-4,5-dimethylaniline **6′**, and 2-bromo-4-(2-methyl[1,3]dithiolan-2-yl-aniline **7′** was evaluated with various iodoarenes (**a**−**h**) as their intermolecular coupling partners. In general, all the reactions were very clean, and the 2-arylthiobenzothiazole derivatives were obtained in high yields under the optimized reaction conditions (Table 1). In these reactions, the most crucial aspect is the formation of dithiocarbamate salts,[13] and once the dithiocarbamate salts are obtained, the intramolecular S-arylation is very effective. So far as the intramolecular S-arylation is concerned both dithiocarbamate salts of substituted 2-iodoanilines **1**, **2**, **3**, **4**, and **6** and 2-bromoanilines **1′**, **2′**, **4′**,**5′**, **6′**, and **7′** are equally effective (Table 1). The current catalytic system for double S-arylation is effective for aryl iodide and substituted aryl iodides containing activating and deactivating substituents (**a**−**h**) (Table 1). Although iodoarenes works efficiently, bromo- and chloroarenes were found not to be effective as the intermolecular coupling partners.

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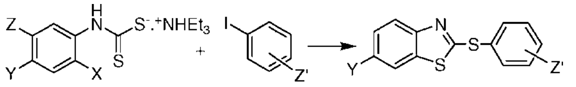
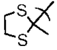
(13) (a) Wong, R.; Dolman, S. J. *J. Org. Chem.* **2007**, *72*, 3969. (b) Li, G.; Tajima, H.; Ohtani, T. *J. Org. Chem.* **1997**, *62*, 4539. (c) Emami, S.; Foroumadi, A. *Chin. J. Chem.* **2006**, *24*, 791. (d) Sattigeri, V. J.; Soni, A.; Singhal, S.; Khan, S.; Pandya, M.; Bhteja, P.; Mathur, T.; Rattan, A.; Khanna, J. M.; Mehta, A. *Arkivoc* **2005**, *11*, 46.

(14) See for applications and synthesis of MBT: As vulcanizing accelerator: (a) Carr, E. L.; Smith, G. E. P. J.; Alliger, G. *J. Org. Chem.* **1949**, *14*, 921. As a reagent in Julia-olefinations: (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. In catalysis: (c) Kozikowski, A. P.; Tückmantel, W.; Böttcher, G.; Romanczyk, L. J., Jr. *J. Org. Chem.* **2003**, *68*, 1641. (d) Aimar, M. L.; Rossi, R. H. *Tetrahedron Lett.* **1996**, *37*, 2137. (e) Aimar, M. L.; Rossi, R. H. *Synthesis* **2000**, 1749. As anticancer compounds: (f) Xanthopoulou, M. N.; Hadjikakou, S. K.; Hadjiliadis, N.; Schürmann, M.; Jurkschat, K.; Michaelidis, A.; Skoulika, S.; Bakas, T.; Binolis, J.; Karkabounas, S.; Charalabopoulos, K. *J. Inorg. Biochem.* **2003**, *96*, 425. Industrial preparation: (g) Isaacs, N. S.; Ismail, Y.; Hilton, M. J.; Coulson, M. *J. Phys. Org. Chem.* **1998**, *11*, 1. Classical synthesis: (h) Somerville, W. T.; Andersen, C. N. *J. Org. Chem.* **1960**, *25*, 656. (i) Aichaoui, H.; Lesieur, D.; Henichart, J. P. *J. Heterocycl. Chem.* **1992**, *29*, 171. (j) Tajima, H.; Li, G. *Synlett* **1997**, 773.

Table 1. Synthesis of 2-Arylthiobenzothiazoles via Sequential Cu-Catalyzed Intra- and Intermolecular *S*-Arylations[a]

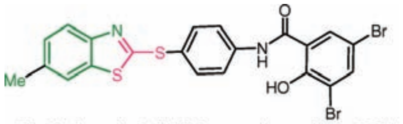


dithiocarbamate	iodoarene	product[b]	yields[c]
X=I, Y=H, Z=H (**1**)	Z'=H (**a**)	(**1a**)[d]	86
X=Br, Y=H, Z=H (**1'**)	Z'=H (**a**)	(**1a**)[e]	82
X=I, Y=H, Z=H (**1**)	Z'=*p*-Me (**b**)	(**1b**)[f]	85
X=Br, Y=H, Z=H (**1'**)	Z'=*p*-Me (**b**)	(**1b**)[f]	79
X=I, Y=H, Z=H (**1**)	Z'=*p*-OMe (**c**)	(**1c**)[f]	74
X=I, Y=H, Z=H (**1**)	Z'=*p*-NO_2 (**d**)	(**1d**)[d]	92
X=Br, Y=H, Z=H (**1'**)	Z'=*p*-NO_2 (**d**)	(**1d**)[e]	87
X=I, Y=H, Z=H (**1**)	Z'= *o*-NO_2 (**e**)	(**1e**)[d]	90
X=I, Y=H, Z=H (**1**)	Z'=*p*-NHAc (**f**)	(**1f**)[e]	72
X=I, Y=H, Z=H (**1**)	Z'=*m*-Cl (**g**)	(**1g**)[e]	86
X=I, Y=H, Z=H (**1**)	Z'=*o*-COOMe (**h**)	(**1h**)[d]	89
X=I, Y=Me, Z=H (**2**)	Z'=H (**a**)	(**2a**)[e]	84
X=I, Y=Me, Z=H (**2**)	Z'=*p*-Me (**b**)	(**2b**)[f]	79
X=Br, Y=Me, Z=H (**2'**)	Z'=*p*-Me (**b**)	(**2b**)[f]	76
X=I, Y=Me, Z=H (**2**)	Z'=*p*-OMe (**c**)	(**2c**)[f]	72
X=I, Y=Me, Z=H (**2**)	Z'=*o*-NO_2 (**d**)	(**2d**)[d]	85
X=I, Y=Cl, Z=H (**3**)	Z'=H (**a**)	(**3a**)[e]	66
X=I, Y=Cl, Z=H (**3**)	Z'=*p*-OMe (**c**)	(**3c**)[e]	72
X=I, Y=Br, Z=H (**4**)	Z'=H (**a**)	(**4a**)[d]	76
X=Br, Y=Br, Z=H (**4'**)	Z'=H (**a**)	(**4a**)[e]	68
X=Br, Y= OMe, Z=H (**5'**)	Z'=H (**a**)	(**5a**)[e]	56
X=I, Y=Me, Z=Me (**6**)	Z'=NO_2 (**e**)	(**6e**)[e]	87
X=Br, Y=Me, Z=Me (**6'**)	Z'=NO_2 (**e**)	(**6e**)[f]	73
X=Br, Y=  , Z=H (**7'**)	Z'=H (**a**)	(**7a**)[e]	65

[a] Reactions were monitored by TLC. [b] Confirmed by IR, ^1H NMR, and ^{13}C NMR spectroscopy. [c] Isolated yields. [d] Reactions were carried out for 4 h. [e] Reactions were carried out for 6 h. [f] Reactions were carried out for 8 h.

The reactions are equally effective irrespective of the nature of the substituents (Y and Z) present in the dithiocarbamate salts. However, an interesting trend in reactivity was observed in its intermolecular coupling partners aryl iodides. The presence of electron withdrawing substituents *p*-NO_2 (**d**), *o*-NO_2 (**e**), *o*-COOMe (**h**) accelerate the rate of the reaction giving products in shorter reaction times, whereas electron donating substituents *p*-OMe (**c**), *p*-Me (**b**) retards the reaction. This fact has been further verified with a substrate containing strongly activating group ($-NH_2$), where no desired product was observed. However when NH_2 group was converted to moderatively activating group NHAc (**f**), good conversion was observed giving product (**1f**) in 72% yield. Thus, from the present study we found the following order of reactivity in aryl iodides *p*-NO_2 > *o*-NO_2 > *o*-COOMe > *m*-Cl > H > *p*-Me > *p*-OMe.

The success of this strategies was finally applied to the synthesis of Cathespin-D inhibitor analogues (**2i**) as shown in Figure 3 demonstrating its potential utility.



2i: Cathepsin-D inhibitor analogue (7 h, 76%)

Figure 3. Synthesis of cathespin-D analogues.

In summary, we have for the first time developed a single catalytic system for two sequential intra- and intermolecular S-arylations leading to a direct synthesis of 2-arylthiobenzothiazoles from dithiocarbamates. Low catalyst loading, inexpensive metal catalyst and ligand, lower reaction temperature, and shorter reaction times make this method superior to all methods reported so far, thus of potential industrial significance.

Acknowledgment. We are grateful to the DST (SR/S1/OC-15/2006) and CSIR [01(2270)/08/EMR-II] for funding. S.M. and H.G. thank the CSIR for fellowships. Thanks are also due to CIF, IIT Guwahati for mass and NMR spectra.

Supporting Information Available: General information, experimental procedures, spectral data, and copies of ^1H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9017535