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Copper(I)-Catalyzed Synthesis of Substituted 2-Mercapto Benzimidazoles

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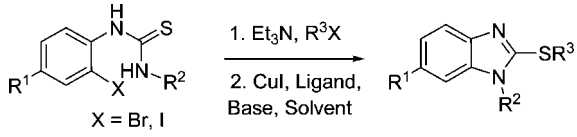

An efficient method for the preparation of various substituted 2-mercapto benzimidazoles from their corresponding thioureas has been developed. *S*-Alkylation of thioureas followed by Cu-catalyzed intramolecular *N*-arylation furnished substituted 2-mercapto benzimidazoles in high yields and short reaction times. Furthermore, 2-mercapto benzimidazoles substituted with a *p*-methoxybenzyl group allowed access to benzimidazole thiones.

2-Mercapto benzimidazoles are an important class of heterocycles that are encountered in a number of natural and nonnatural biologically active compounds. For example, medicinal chemistry applications of such compounds include 2-(benzylthio)-4,6-dichloro-1-[(2-hydroxyethoxy)methyl]benzimidazole as an antiviral compound,[1] 2-mercapto-1-(*β*-4-pyridethyl)-benzimidazole (MPB) as an antitumor agent,[2] and luteinizing hormone-releasing hormone (LHRH) antagonists (Figure 1).[3] The cyclic thioureide structure is recognized for its antithyroid action,[4] and has shown atypical antipsychotic potency when linked to aryl piperazines.[5] Substituted 2-mercapto benzimidazoles can be oxidized into sulfinyl derivatives, which belong to another class of pharmaceutically important molecules.[6] Finally, the mercapto group can be oxidized into sulfonyl, which can act as a leaving group for the synthesis of 2-substituted benzimidazoles.[7]

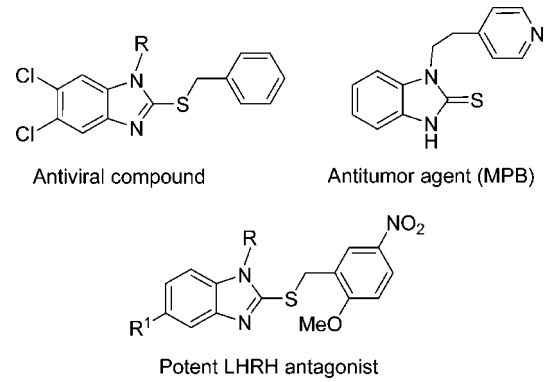

FIGURE 1. Structures of some biologically active substituted 2-mercapto benzimidazoles.

The main methodology for the synthesis of unsymmetrically substituted 2-mercapto benzimidazoles involves the reaction of *o*-phenylenediamine precursors with CS_2, followed by alkylation.[3,5,7b,8] Similarly, benzimidazole thiones are prepared from *o*-phenylenediamine via the formation of benzimidazolones, and thionation of the later with Lawesson's reagent.[9] These methods suffer from a limited number of suitable substrates for diverse synthesis. We felt that a catalytic approach involving C−N bond formation would overcome this drawback.

In the past decade, a great effort has been devoted toward the development of efficient methods for the synthesis of heterocyclic compounds from aryl halides with copper catalysts.[10] Buchwald et al. reported the synthesis of indolines,[11] 2-aryl-4-quinolones,[12] and *N*-alkylbenzimidazoles.[13] The group of Ma developed cascade processes for the preparation of isoquinolines,[14] benzofurans,[15] benzimidazoles,[16] dihydrobenzimidazole-2-ones,[17]indoles,[18] and pyrrolo[1,2-*a*]quinoxaline.[19]

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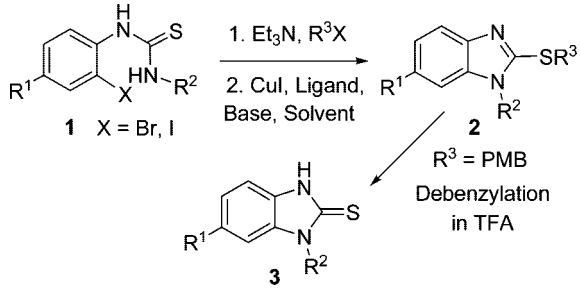
SCHEME 1. Synthesis of Substituted 2-Mercapto Benzimidazoles and Benzimidazole Thiones



Batey's group reported copper-catalyzed intramolecular C−X bond formation to synthesize benzoxazoles,[20] benzothiazoles,[20b] and aminobenzimidazoles.[21] Although C−N bond formation has been well explored for the construction of various heterocycles, there is no report for the preparation of substituted 2-mercapto benzimidazoles employing this strategy.

Our interest in developing methods for the synthesis of heterocyclic compounds from thioureas[22] led us to consider a Cu-catalyzed approach using 2-haloaniline derived thioureas. Recently, Batey and Pan have shown that the cyclization of 2-bromophenylthioureas derivatives leads to substituted 2-aminobenzothiazoles.[23] We envisaged that an *S*-alkylation followed by an intramolecular Cu-catalyzed aryl amination sequence from 2-haloaniline derived thioureas could lead to substituted 2-mercapto benzimidazoles (Scheme 1). The reaction of *S*-*p*-methoxybenzyl thioethers in trifluoroacetic acid in the presence or in the absence of metal salts is known to produce the corresponding thiols or thiones.[24] Therefore, we expected that our approach could be extended for the preparation of benzimidazole thiones from 2-mercapto benzimidazoles substituted with a *p*-methoxybenzyl group (PMB) (Scheme 1).

1-(2-Bromophenyl)-3-phenylthiourea (**1a**), prepared quantitatively from 2-bromoaniline and phenyl isothiocyanate, was first evaluated as a model substrate. *S*-Alkylation of 1,3-disubstituted thioureas is known to occur selectively on the sulfur atom, and is quantitative with alkyl halides and bases at room temperature.[22,25]

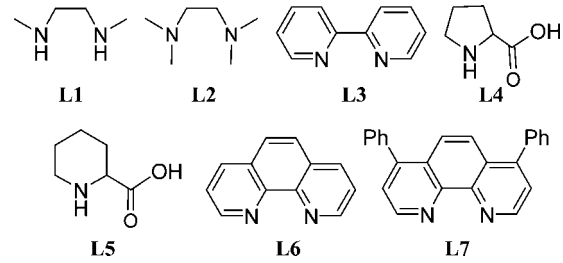


FIGURE 2. Ligands examined for Cu-catalyzed intramolecular amination.

We began our investigation using MeI and NEt_3 for alkylation, and by evaluating different ligands (0.1 equiv) (Figure 2), using CuI (0.05 equiv) as precatalyst, K_2CO_3 (2 equiv) as base, and 1,4-dioxane as solvent. The reaction was inefficient in the absence of ligand or in the presence of diamine ligands and bipyridine (**L1**−**3**). Low conversion (<50%) was observed with L-proline (**L4**) and L-pipecolinic acid (**L5**). The best results were obtained with 1,10-phenanthroline (**L6**) and 4,7-diphenyl-1,10-phenanthroline (**L7**) that led to nearly 95% conversion at 85 °C. 1,10-Phenanthroline (**L6**) was finally selected as the ligand due to easy availability and cost consideration. The one-pot sequence *S*-alkylation/Cu-catalyzed intramolecular *N*-arylation of **1a** led to **2a** in 75% yield within 4 h. With use of this procedure, the scope of the method was then explored.

As shown in Table 1, a variety of aryl and alkyl groups in diversified positions are well tolerated. The aryl-substituted thioureas **1b**−**k**, prepared from the corresponding 2-haloanilines and aryl isothiocyanate, were converted smoothly into their corresponding 2-mercapto benzimidazoles **2b**−**k** in shorter reaction times compared to their alkyl-substituted analogues **2*l***−**o**. The relevance of bis-heterocycles in drug discovery has been recently acknowledged.[26] Thus, we have explored the reactivity of thioureas bearing heterocycles such as furan, morpholine, and pyridine. Noteworthy, the Cu-catalyzed cyclization is compatible with such compounds and bis-heterocycles **2m**, **2p**, and **2q** were obtained in good yields. In addition, cyclization of bisthiourea **1w** prepared from 1,3-bis(isothiocyanatomethyl)benzene was also achieved and afforded **2w** in moderate yield. *S*-Alkylations have been performed with different electrophiles such as alkyl, benzyl, and allyl halides leading to **2b**−**q**, **2r**−**t**, and **2u**−**v**, respectively. Halogenated compounds can be elaborated from the corresponding haloanilines, allowing further coupling reactions for the elaboration of more complex compounds. Indeed, 2,4-dibromoaniline was reacted with phenyl isothiocyanate to produce the corresponding thiourea and then cyclized to afford **2v** in 81% yield. 1-(2-Bromophenyl)-3-(2-iodophenyl)thiourea **1y** led, under standard conditions, to a mixture of bromo and iodo derivatives **2y**/**2y′**. However, when the reaction was performed at lower temperature, 1-(2-bromophenyl)-2-(methylthio)benzimidazole **2y** was produced with good selectivity (Scheme 2).

As the general nature and the efficiency of the reaction protocol has been proven, the debenzylation of the compounds bearing a *p*-methoxybenzyl group was investigated in order to extend our methodology to the preparation of benzimidazole

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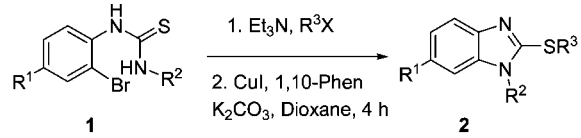
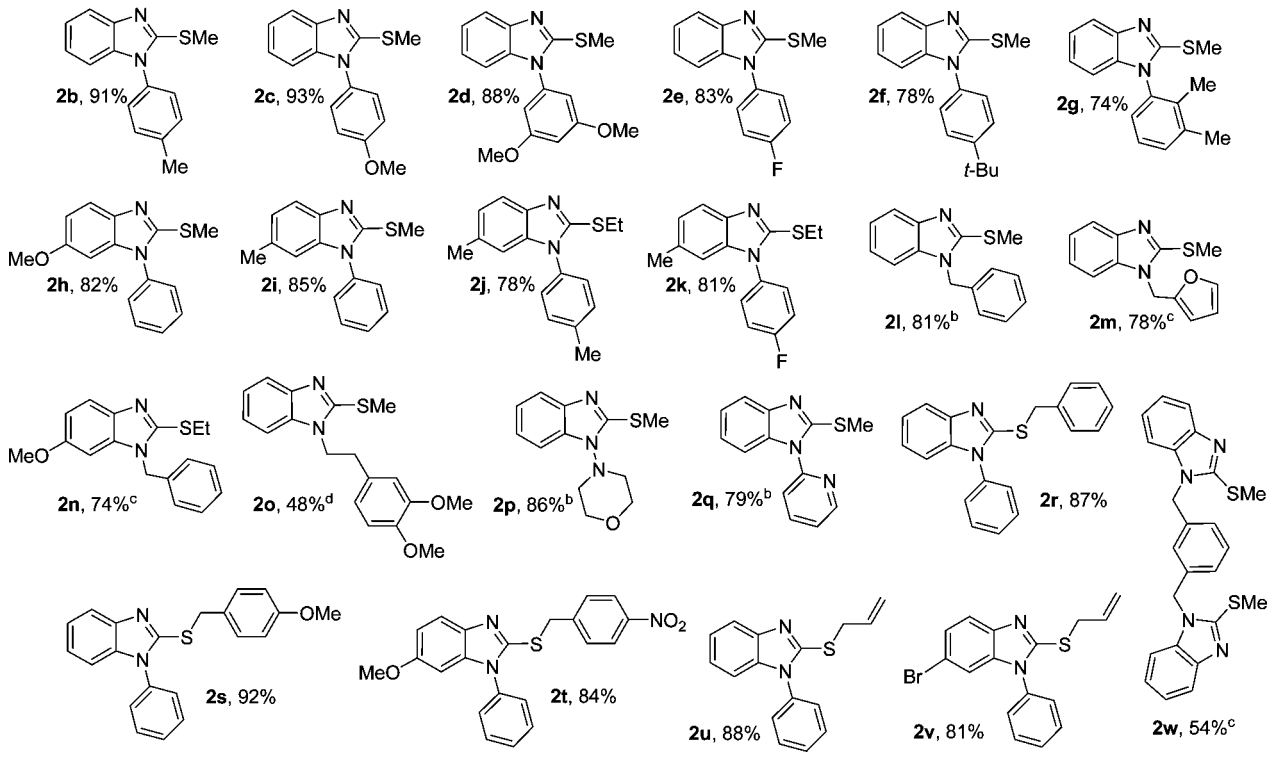
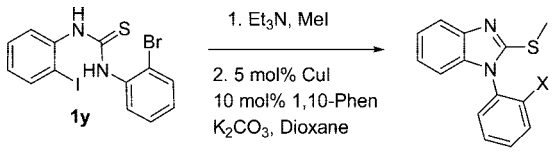
TABLE 1. Synthesis of Substituted 2-Mercapto Benzimidazoles 2[a]





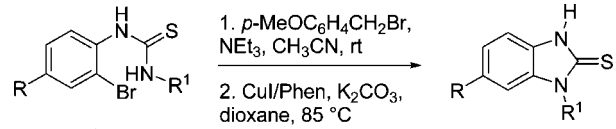
[a] Reaction conditions: **1** (1.0 mmol), Et_3N (1.5 equiv), R^3X (1.0−1.5 equiv), CH_3CN (5 mL), CuI (0.05 equiv), 1,10-phenantroline (0.1 equiv), K_2CO_3 (2 equiv), dioxane (5 mL), 4 h, 85 °C. R^3X: MeI, EtI, allyl iodide (1.5 equiv) or BnBr, *p*-(MeO)$C_6H_4CH_2Br$, *p*-$(NO_2)C_6H_4CH_2Br$ (1 equiv). [b] Performed over 8 h. [c] Performed over 12 h. [d] Performed over 20 h.

SCHEME 2. Selective Intramolecular *N*-Arylation Toward Iodoarene



85 °C, 4 h, **2y** (X = Br)/**2y'** (X = I), 80/20
60 °C, 12 h, **2y**/**2y'**, 95/5

SCHEME 3. Formation of Benzimidazole Thiones 3 from 1



R = H, R^1 = Ph, **1a** — **3a**, 68%
R = H, R^1 = *p*-Tol, **1b** — **3b**, 72%
R = H, R^1 = *p*-FC_6H_4, **1e** — **3e**, 71%
R = OMe, R^1 = Ph, **1h** — **3h**, 75%

thiones **3**. Such compounds cannot be synthesized in a direct manner by a cyclization process.[23] Alkylation of **1a**, **1b**, **1e**, and **1h** with 4-methoxybenzyl bromide, followed by Cu-catalyzed cyclization and debenzylation in TFA afforded **3a**, **3b**, **3e**, and **3h** in fair yields (Scheme 3).[27]

In conclusion, we have developed an alkylation/Cu-catalyzed intramolecular *N*-arylation process to synthesize substituted 2-mercapto benzimidazoles from their corresponding thioureas. A wide range of substrates were easily prepared from 2-haloanilines and were efficiently assembled into these heterocycles. The synthetic approach allows the construction of products from three different components (bromoanilines, isothiocyanates, and alkyl halides) providing a versatile access to these pharmaceutically important compounds. Benzimidazole thiones are also accessible by using a protection (PMB)/deprotection strategy.

Experimental Section

General Procedure for the Synthesis of Substituted 2-Mercapto Benzimidazoles 2. NEt_3 (1.5 mmol, 210 μL) and alkyl halide (1.5 mmol) were successively added to a solution of thiourea **1**

(27) Benzimidazole thiones have two tautomeric forms and can be drawn as either thioenol or as thione. It is believed that these compounds exist primarily in the thione form. Therefore, for the purposes of this publication, we will refer to and draw the products as thiones. For discussions on the tautomerism of thiones, see: (a) Khan, H.; Badshah, A.; Shaheen, F.; Gieck, C.; Qureshi, R. A. *Acta Crystallogr.* **2008**, *E64*, o1141. (b) Öğretir, C.; Öztürk, İ. İ.; Tay, N. F. *Arkivoc* **2007**, *14*, 75. (c) Elzbieta, B.-O.; Lech, S.; Graham, A. W.; Ian, H. S. *Bull Pol. Acad. Sci., Chem.* **1987**, *35*, 81.

(1.0 mmol) in CH_3CN (5 mL), and the resulting solution was stirred for 10 min at room temperature. Solvent was evaporated, then the residue was washed with water and extracted with EtOAc (2 × 15 mL). The organic phase was dried over $MgSO_4$ and concentrated under vacuum to give thioether *S*-alkylated product up to 98% yield, which was used for the next step without any further purification. (In the case of BnBr, *p*-$(MeO)C_6H_4CH_2Br$, and *p*-$(NO_2)C_6H_4CH_2Br$, 1 mmol of halide were used and the reaction time was extended to 20 min).

A round-bottomed flask was charged with thioether *S*-alkylated product (∼1 mmol), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), K_2CO_3 (2 mmol, 276 mg), and 1,4-dioxane (5 mL). The resulting solution was heated at 85 °C until the disappearance of the starting material (TLC). The reaction mixture was then cooled and filtered over Celite with EtOAc. Solvent was evaporated and further purification was achieved by column chromatography.

2-(Methylthio)-1-phenylbenzimidazole (2a): colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.63 (s, 3H), 7.06 (m, 3H), 7.36 (m, 5H), 7.64 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 108.4, 117.2, 121.4, 126.0, 128.1, 129.0, 134.4, 136.6, 142.7, 152.6; IR (KBr) 3052, 2928, 2853, 1596, 1499, 1369, 1270, 1011, 741 cm^{-1}. Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 69.81; H, 5.02; N, 12.02; S, 13.25.

2-(Methylthio)-1-*p*-tolylbenzimidazole (2b): white solid; mp 72−74 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.66 (s, 3H), 7.04−7.29 (m, 7H), 7.65 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 19.7, 107.7, 116.3, 120.6, 125.1, 128.8, 136.0, 137.6, 141.9, 152.1; IR (KBr) 3056, 3029, 2922, 2858, 1604, 1514, 1445, 1270, 811, 744 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01; S, 12.61. Found: C, 70.97; H, 5.57; N, 11.06; S, 12.69.

2-(Methylthio)-1-benzylbenzimidazole (2*l*): white solid; mp 77−79 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.81 (s, 3H), 5.28 (s, 2H), 7.15−7.31 (m, 8H), 7.71 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 48.0, 109.4, 118.6, 122.4, 122.4, 127.4, 128.4, 129.3, 136.0, 136.9, 144.1, 153.6; IR (KBr) 3031, 2932, 2858, 1606, 1493, 1453, 1427, 1374, 1243, 995, 734 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01; S, 12.61. Found: C, 70.98; H, 5.58; N, 11.08; S, 12.76.

2-(Methylthio)-1-(furan-2-ylmethyl)benzimidazole (2m): brown oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.70 (s, 3H), 5.11 (s, 2H), 6.20 (s, 2H), 7.09−7.23 (m, 4H), 7.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 39.1, 108.0, 109.6, 117.2, 121.0, 121.1, 127.0, 131.6, 135.2, 142.0, 147.7, 153.6; IR (KBr) 3118, 3055, 2930, 1612, 1518, 1444, 1367, 1258, 1147, 1012, 923, 740 cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{13}N_2OS$ $(M + H)^+$ 245.0749, found 245.0754.

2-(4-Methoxybenzylthio)-1-phenylbenzimidazole (2s): colorless gum; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.63 (s, 3H), 4.48 (s, 2H), 6.67−6.71 (d, 2H, J = 8.6 Hz), 7.04−7.40 (m, 10H), 7.67 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.5, 60.4, 114.7, 119.2, 123.3, 124.0, 127.5, 127.6, 132.0, 134.2, 135.0, 135.6, 137.6, 140.3, 142.4, 148.7, 157.4, 164.3; IR (KBr) 3062, 2955, 2933, 2834, 1610, 1513, 1434, 1269, 1244, 1028, 832, 744 cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09; S, 9.26. Found C, 73.02; H, 5.25; N, 8.14; S, 9.32.

General Procedure for the Synthesis of Benzimidazole Thiones 3. Thiourea **1** (1.0 mmol) was first alkylated as described above. A round-bottomed flask was charged with the corresponding thioether *S*-alkylated product (∼1.0 mmol), CuI (0.05 mmol, 9.5 mg), 1,10-phenanthroline (0.1 mmol, 18 mg), K_2CO_3 (2.0 mmol, 276 mg), and 1,4-dioxane (5 mL). The resulting solution was heated at 85 °C until the disappearance of the starting material (TLC). The reaction mixture was then cooled and filtered over Celite with EtOAc, then solvent was evaporated. TFA (3−5 mL) was added, and the reaction mixture was heated at 85 °C for 2 h. After completion, TFA was removed under vacuum and the residue was treated with sodium bicarbonate solution. The product was extracted with EtOAc (2 × 15 mL). The organic phase was dried over $MgSO_4$ and then evaporated. The crude product was purified with a short chromatography column.

1-Phenylbenzimidazole-2-thione (3a): white solid; mp 160−163 °C; ^{1}H NMR (250 MHz, $CDCl_3$/DMSO-d_6) δ 6.96 (d, 1H, J = 7.5 Hz), 7.21−7.34 (m, 3H), 7.58−7.71 (m, 5H), 13.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6) δ 109.0, 122.1, 122.8, 126.8, 128.2, 128.6, 134.1, 136.4, 137.6, 138.8, 167.7; IR (KBr) 3138, 3052, 2985, 2926, 1595, 1500, 1462, 1445, 1217, 735 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38; S, 14.17. Found: C, 69.14; H, 4.46; N, 12.43; S, 14.26.

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Supporting Information Available: General information and preparation of 2-halothioureas and analytical data of compounds **2c**−**k**, **2n**−**r**, **2t**−**w**, **2y**, **3b**, **3e**, and **3h** and copies of ^{1}H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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