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Copper-Catalyzed Synthesis of N-Fused Heterocycles through Regioselective 1,2-Aminothiolation of 1,1-Dibromoalkenes

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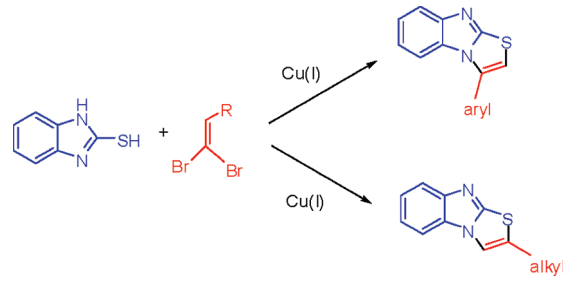
ABSTRACT



The first aminothiolation of 1,1-dibromoalkene is described using an inexpensive copper/*N*,*N*-dimethylethylenediamine catalyst. The method provides a powerful means of using easily available 1,1-dihaloalkenes as precursors to fused heterocycles.

Transition-metal-catalyzed hydroelementation of unsaturated organic compounds represents an atom-economic protocol for the construction of C−heteroatom bonds.[1−3] Catalytic Ullmann-type C−heteroatom coupling is an alternative powerful tool for synthesis of heteroatom-containing compounds.[4−6] Both approaches have found wide application in material science and pharmaceutical chemistry. We envisioned that 1,2-aminothiolation of unsaturated halides would yield compounds with N and S nucleophiles at the 1,2- positions (Scheme 1). Sequential nucleophilic substitution and H−X (X = S, N) addition would simultaneously result in the formation of C−S and C−N bonds. Here we report a concise and practical preparation of imidazol[2,1-*b*]-thiazole and related N-fused heterocyles based on a novel copper-catalyzed 1,2-aminothiolation of 1,1-dihaloalkenes. The starting materials are easily available from aldehydes, and the resulting N-fused heterocyles have shown promising

(1) For recent reviews on hydroelementation of unsaturated compounds, see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(2) Recent examples of hydroamination: (a) Rizk, T.; Bilodeau, E. J.-F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8325. (b) Han, J.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 916. (c) Iska, V. B. R.; Verdolino, V.; Wiest, O.; Helquist, P. *J. Org. Chem.* **2010**, *75*, 1325. (d) Enomoto, T.; Girard, A.-L.; Yasui, Y.; Takemoto, Y. *J. Org. Chem.* **2009**, *74*, 9158. (e) Duan, H.; Sengupta, S.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2009**, *131*, 12100.

(3) For recent examples of hydrothiolation, see: (a) Cao, C.; Fraser, L. R.; Love, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 17614. (b) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108. (c) Yang, J.; Sabarre, A.; Fraser, L. R.; Patrick, B. O.; Love, J. A. *J. Org. Chem.* **2009**, *74*, 182. (d) Sabarre, A.; Love, J. A. *Org. Lett.* **2008**, *10*, 3941.

(4) For recent reviews on C−heteroatom coupling, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Hartwig, J. F. *Nature* **2008**, *455*, 314.

(5) A few examples of C−N coupling: (a) Chen, W.; Zhao, Q.; Xu, M.; Lin, G. *Org. Lett.* **2010**, *12*, 1072. (b) Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766. (c) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (d) Kabir, M. S.; Lorenz, M.; Namjoshi, O. A.; Cook, J. M. *Org. Lett.* **2010**, *12*, 464.

(6) A few examples of C−S coupling: (a) Murru, S.; Ghosh, H.; Sahoo, S. K.; Patel, B. K. *Org. Lett.* **2009**, *11*, 4254. (b) Fernández-Rodríguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (c) Sperotto, E.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *J. Org. Chem.* **2008**, *73*, 5625. (d) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495.

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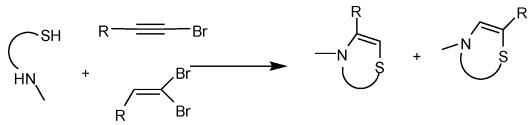
Scheme 1. Aminothiolation of 1,1-Dibromoalkene



biological activities as inhibitors of neurodegenerative disorders and antitumor drugs.[7]

Initially, the aminothiolation of 1,1-dibromodecene and 2-mercaptobenzoimidazole (**1a**) was selected as a model system to optimize the reaction conditions; the results are summarized in Table 1. It was found that the choices of metal

Table 1. Optimization of Copper-Catalyzed Aminothiolation of 1,1-Dibromodecene[a]

entry	catalyst	solvent	base	ligand[b]	t (°C)	yield (%) (**3**/**4** ratio)
1		DMF	Cs_2CO_3		110	
2		dioxane	DBU		75	
3		toluene	DBU		75	
4	CuI	DMF	Cs_2CO_3	DMEDA	110	43 (1/6)
5	CuI	toluene	$CsCO_3$	DMEDA	110	
6	CuI	DMF	Cs_2CO_3	DMEDA	rt	
7	CuI	DMF	Cs_2CO_3	DMEDA	50	19 (1/4)
8	CuI	dioxane	K_3PO_3	DMEDA	65	27 (1/4)
9	CuI	DMF	DBU	DMEDA	65	70 (1/7)
10	CuI	DMF	TBAF	DMEDA	65	81 (1/7)
11	CuI	DMF	TBAF	DMEDA	110	80 (1/7)
12	CuI	DMF	Et_3N	DMEDA	110	
13	Cu_2O	DMF	K_3PO_3	DMEDA	110	37 (1/7)
14	Cu_2O	DMF	TBAF	DMEDA	65	80 (1/7)
15	Cu_2O	DMF	DBU	DMEDA	65	74 (1/7)
15	$CuSO_4{\cdot}5H_2O$	DMF	K_3PO_3	phen	110	47 (1/6)
16	$CuSO_4{\cdot}5H_2O$	DMF	TBAF	DMEDA	65	78 (1/7)
17	$CuSO_4{\cdot}5H_2O$	DMF	DBU	DMEDA	65	76 (1/7)
18	$NiCl_2$	DMF	Cs_2CO_3	dmdi	110	trace
19	$Pd(AcO)_2$	DMF	Cs_2CO_3	dppf	110	trace
20	$Pd(dba)_2$	DMF	Cs_2CO_3	PPh_3	110	trace
21	$FeCl_3$	DMF	Cs_2CO_3	DMEDA	110	trace

[a] Reactions were carried out using 2-mercaptobenzimidazole (1 mmol), 1,1-dibromodecene (1.2 mmol), base (5 mmol), catalyst (0.1 mmol), ligand (0.15 mmol), and solvent (3 mL), 24 h, under N_2. [b] DMEDA = *N*,*N*′-dimethylethanediamine; phen =1,10-phenanthroline; dppf =1,1′-bis(diphenylphosphino)ferrocene; dmdi =1,1′-dimethyl-3,3′- methylenedi- imidazolium dibromide.

catalysts, bases, and solvents are critical to the reaction. In the absence of a metal catalyst, the cyclization reaction did not procceed no matter what inorganic and organic bases were used. When Bu_4NF was used as the base, the dehydrohalogenation of 1,1-dibromodecene and subsequent hydrothiolation of 1-bromoalkyne was observed, giving (*Z*)-2-(1-bromooct-1-en-2-ylthio)-1*H*-benzo[*d*]imidazole as the major product. Pd, Fe, and Ni salts together with various N- and P-donors were found ineffective using Cs_2CO_3 or DBU (1,8-diazabicyclo[5.4.0] undec-7-ene) as bases in either polar or nonpolar solvents, and these reactions yielded complicated mixtures. Sulfur compounds are often considered to be poisons to transition metal catalysts, and thus the catalytic reactions of thiols are less explored. To our delight, the aminothiolation reaction took place smoothly using Cu salts as catalysts, leading to the desired cyclization product. CuI is more suitable than other copper salts, and DMEDA is the best ligand. As shown in Table 1, the aminothiolation of **1** has a significant dependence on the nature of the bases. Inorganic bases such as K_3PO_4 and Cs_2CO_3 and organic bases DBU and Bu_4NF are efficient. The organic bases gave better yields of octylbenzoimidazo[2,1-*b*]thiazole, whereas inorganic bases required higher temperature and gave lower conversions. The results showed that the regioselectivity is not sensitive to the copper sources, bases, and temperature. Under the optimized conditions, a total yield of 2- and 3-octylimidazo[2,1-*b*]thiazole was obtained in ca. 7:1 ratio.

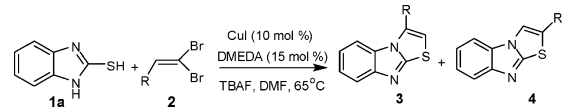
The scope of the copper-catalyzed aminothiolation was examined by reacting **1a** with different aromatic 1,1-dibromoalkenes with various substituents and aliphatic 1,1-dibromoalkenes of different chains. As shown in Table 2, under the optimized conditions (10 mol % of CuI, 15 mol % of DMEDA, and 2−5 equiv of Bu_4NF), the aminothiolation of **2** and **1a** appeared to be quite general with respect to the substituents. Thus, aromatic olefins bearing electron-donating and -withdrawing groups and heteroaromatic olefins were smoothly aminothiolated to give N-fused heterocycles **3a**−**j** in good to very high yields (entries 1−10). The isomers **4a**−**j** were not obtained. Electron-deficient substrates gave better yields. Aromatic halides are tolerated, and no amination or thiolation was observed, so that this offers additional opportunity for further functionalization. The olefins bearing heteroaryl groups could also be aminothiolated to afford cyclization products in good yields. Unlike aromatic alkenes, the linear aliphatic olefins underwent aminothiolation to furnish isomers **4k**−**n** as the major products. However, bulky **2o** yielded a mixture of **3o** and **4o** in a 3:1 ratio (entries 16). It should be noted that in the absence of CuI, the reaction of aliphatic olefin **2k** yielded only **5k** in addition to the desired cyclization product (entry 12).[8] In addition, under the same reaction conditions, both aromatic and aliphatic alkynyl bromides could be aminothiolated in comparable yields and regioselectivities (entries 17−19).

The methodology was also applied to the aminothiolation of unsubstituted and substituted 2-mercaptoimidazole, perimidine, and pyrimidine derivatives with aromatic and aliphatic dibromoalkenes (Table 3). Good yields of the expected N-fused heterocycles, 10-phenylthiazolo[3,2-*a*]perimidine, 3-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one, and imidazothiazine derivatives were obtained in most cases. However, the cyclization of **1c** with **2k** did not occur under

(7) (a) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Welsh, W.; Arora, S.; Farruggia, G.; Masotti, L. *J. Med. Chem.* **2005**, *48*, 5604. (b) Venkatesan, A. M.; Gu, Y.; Santos, O. D.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R. *J. Med. Chem.* **2004**, *47*, 6556. (c) Pietrancosta, N.; Moumen, A.; Dono, R.; Lingor, P.; Planchamp, V.; Lamballe, F.; Bähr, M.; Kraus, J.-L.; Maina, F. *J. Med. Chem.* **2006**, *49*, 3645. (d) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L.; Radin, N. S.; Shoemaker, R. H. *J. Med. Chem.* **2008**, *51*, 809.

(8) The structures of compounds **5k** and **3z** were confirmed by X-ray single crystal diffraction analysis. See Supporting Information.

Table 2. Copper-Catalyzed Regioselective Aminothiolation[a]



entry	R-	product	yield[b] (%)
1	Ph- **2a**	**3a**	75
2	4-MeO-Ph- **2b**	**3b**	74
3	4-NO_2-Ph- **2c**	**3c**	90
4	4-Cl-Ph- **2d**	**3d**	81
5	4-Br-Ph- **2e**	**3e**	86
6	4-Me-Ph- **2f**	**3f**	67
7	2-Naphthyl- **2g**	**3g**	82
8	2-Pyridinyl- **2h**	**3h**	86
9	2-Thiazoyl- **2i**	**3i**	76
10	**2j**	**3j**	80
11	*n*-C_8H_{17}- **2k**	**3k** + **4k**	81 (1:7)
12	**2k**	**5k**	80[c]
13	*n*-C_6H_{13}- **2l**	**3l** + **4l**	72 (1:6)
14	*i*-Bu- **2m**	**3m** + **4m**	79 (1:6)
15	*c*-Hex- **2n**	**3n** + **4n**	70 (1:4)
16	*t*-Bu- **2o**	**3o** + **4o**	70 (3:1)
17	Ph—≡—Br **2p**	**3a**	75
18	*n*-C_6H_{13}—≡—Br **2q**	**3l** + **4l**	74 (1:6)
19	*n*-C_4H_9—≡—Br **2r**	**3p** + **4p**	78 (1:5)

[a] **1a** (1.0 mmol) and **2** (1.2 mmol) for 24 h. [b] Isolated yields and **3** and **4** ratio in bracket. [c] No copper was used.

the conditions described above but gave the hydrothiolated product **5c** as the sole isolated product. When a stronger base (DBU) was used, the expected **4t** could be obtained in a moderate yield. 2-Thioxo-2,3-dihydropyrimidin-4(1*H*)-ones **1e** and **1f** also reacted with dibromoalkenes, giving the corresponding cyclization. In the case of aliphatic alkene, the regioselectivity is low. Finally, (1*H*-benzo[*d*]imidazol-2-yl)methanethiol (**1g**) reacted with **2a**, yielding 8*H*-benzimidazo[2,1-*c*][1,4]thiazine **3z**.[8]

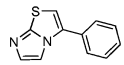
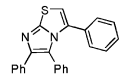
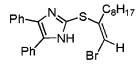
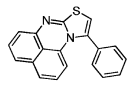
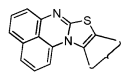
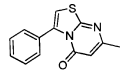
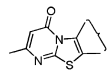
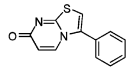
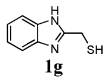
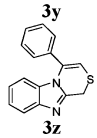
Most probably the reaction involves 1-bromoalkyne *in situ* generated from dehydrohalogenation of 1,1-dibromoalkenes.[9] We propose that the aminothiolation of aromatic alkene takes place via a copper-catalyzed C−S coupling of 1-bromoalkyne to alkynyl thioether **6** and subsequent intramolecular hydroamination (5-*endo-dig* cyclization) of **6**.[10,11] In the case of an aliphatic alkene, the nucleophilic N-alkynylation would occur, leading to ynamide **5** through copper-catalyzed C(sp)−N coupling of 1-bromoalkyne and subsequent formation of a thiazole ring via a 5-*endo-dig* hydrothiolation giving the final product **4** (Scheme 2).[12]

(9) Base-promoted dehydrohalogenation of dihaloalkenes: (a) Okutani, M.; Mori, Y. *J. Org. Chem.* **2009**, *74*, 442. (b) Söederberg, B. C. G.; Gorugantula, S. P.; Howerton, C. R.; Petersen, J. L.; Dantale, S. W. *Tetrahedron* **2009**, *65*, 7357.

(10) Ochiai, M.; Tada, N. *Chem.Commun.* **2005**, 5083.

(11) A few examples of 5-*endo-dig* cyclizations: (a) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (b) Yao, P.-Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275. (c) Sniady, A.; Durham, A.; Morreale, M. S.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2007**, *9*, 1175. (d) Kim, I.; Kim, K.; Choi, J. *J. Org. Chem.* **2009**, *74*, 8492. (e) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559. (f) Yin, Y.; Ma, W.; Chai, Z.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 5731. (g) Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251.

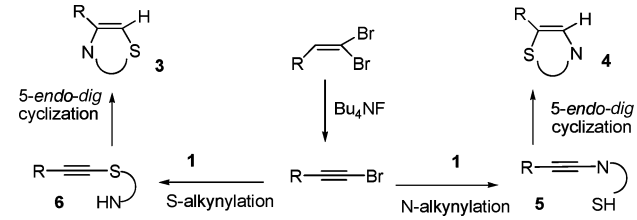
Table 3. Aminothiolation of Various Thiols[a]

entry	thiols	olefin	product	yield (%)
1	 **1b**	 **2a**	 **3q**	74
2	**1b**	 **2k**	 **3r + 4r**	67 (2:5)
3	 **1c**	**2a**	 **3s**	71
4	**1c**	**2k**	 **5c**	80
5	**1c**	**2k**	 **4t**	52[b]
6	 **1d**	**2a**	 **3u**	69
7	**1d**	**2k**	 **3v + 4v**	44 (4:3)
8	 **1e**	**2a**	 **3w**	73
9	**1e**	**2k**	 **3x + 4x**	82 (1:1)
10	 **1f**	**2a**	 **3y**	71
11	 **1g**	**2a**	 **3z**	40

[a] The reaction conditions are the same as denoted in Table 1. [b] DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) was used as the base.

Although 6-*endo-dig* cyclization is also favored,[13] the yield is relatively low (Table 2, entry 11).

Scheme 2. Possible Pathways for Aminothiolation



In conclusion, we have developed a novel copper-catalyzed aminothiolation of 1,1-dibromoalkenes by using a catalytic amount of CuI in combination with DMEDA. The procedure is economical and experimentally simple for the facile preparation of fused heterocyclic compounds having two different heteroatoms from easily available 1,1-dibromoalkenes. The scope and limitations of the reaction itself and the synthetic application of the products obtained are now under investigation.

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Supporting Information Available: Experimental procedures, spectroscopic data, crystallographic data of **3z** and **5k** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For copper-catalyzed C(sp)−N coupling of 1-bromoalkyne, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, Published ASAP April 29, 2010, DOI: 10.1021/cr100003s. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980. (d) Laroche, C.; Li, J.; Freyer, M. W.; Kerwin, S. M. *J. Org. Chem.* **2008**, *73*, 6462. (e) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820. (f) Dooleweerdt, K.; Birkedal, H.; Ruhland, T.; Skrydstrup, T. *J. Org. Chem.* **2008**, *73*, 9447. (g) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (h) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151. (i) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (j) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379–1390. (k) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011.

(13) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.