ORGANIC LETTERS

2012
Vol. 14, No. 23
5948–5951

Benzazoles from Aliphatic Amines and *o*-Amino/Mercaptan/Hydroxyanilines: Elemental Sulfur as a Highly Efficient and Traceless Oxidizing Agent

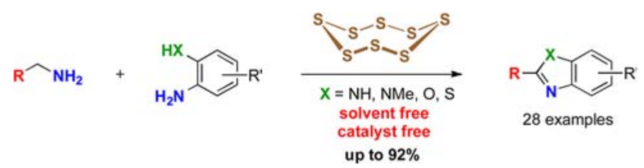
Thanh Binh Nguyen,*,† Ludmila Ermolenko,† William A. Dean,‡ and Ali Al-Mourabit†

Centre de Recherche de Gif-sur-Yvette, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

nguyen@icsn.cnrs-gif.fr

Received October 17, 2012

ABSTRACT



A novel remarkably simple solvent-free and catalyst-free synthesis of benzazoles from alkylamines and *o*-hydroxy/amino/mercaptan anilines using elemental sulfur as traceless oxidizing agent has been developed.

Benzazole moiety plays an important role in chemistry and is also present in a variety of biologically active and therapeutically useful compounds.[1] Development of new methods for its construction is therefore highly desirable. A simple and efficient transformation using readily available reagents under solvent-free and metal-free conditions is considered as a key solution for pollution problems generated by large-scale reactions. In this context, solvent- and metal-free redox reactions promoted by elemental sulfur in organic syntheses appear to be highly desirable to maximize atom economy and to avoid expensive complex metal catalysts. In particular, the elemental sulfur-mediated oxidation represents a useful alternative to other oxidation reactions using its lighter congener, oxygen, because sulfur is readily available, nontoxic, and stable under normal conditions. In contrast to oxygen, which is a biradical in the ground state, sulfur is less reactive. Consequently, the reactions using sulfur present a low risk of explosion, show different and interesting reactivities and selectivities even without metal catalyst, and do not require pressurized reactors. In connection with our interest in C−N bond formation, we sought to explore oxidation reactions of aliphatic amine using elemental sulfur as a convenient alternative to oxygen under solvent-free and catalyst-free conditions.[2]

The interaction between sulfur and amines has been the subject of several studies.[3] When an aliphatic amine, such as benzylamine **1a**, was heated with sulfur, thiobenzamide **3** was obtained as a result of a cascade reaction (Scheme 1).[3] The synthetic utility of this reaction has received little

† Institut de Chimie des Substances Naturelles.
‡ Present address: Harvard University, Cambridge, MA 02138.

(1) For examples, see: (a) Jain, A. K.; Paul, A.; Maji, B.; Muniyappa, K.; Bhattacharya, S. *J. Med. Chem.* **2012**, *55*, 2981. (b) Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 744. (c) Carpenter, R. D.; Andrei, M.; Aina, O. H.; Lau, E. Y.; Lightstone, F. C.; Liu, R.; Lam, K. S.; Kurth, M. J. *J. Med. Chem.* **2008**, *51*, 14. (d) Wang, X.; Sarris, K.; Kage, K.; Zhang, D.; Brown, S. P.; Kolasa, T.; Surowy, C.; El Kouhen, O. F.; Muchmore, S. W.; Brioni, J. D.; Stewart, A. O. *J. Med. Chem.* **2008**, *51*, 170. (e) Aiello, S.; Wells, G.; Stone, E. L.; Kadri, H.; Bazzi, R.; Bell, D. R.; Stevens, M. F. G.; Matthews, C. S.; Bradshaw, T. D.; Westwell, A. D. *J. Med. Chem.* **2008**, *51*, 5135. (f) Alamgir, M.; Black, D. S. C.; Kumar, N. *Top. Heterocycl. Chem.* **2007**, *9*, 87. (g) Bradshaw, T. D.; Westwell, A. D. *Curr. Med. Chem.* **2004**, *11*, 1009.

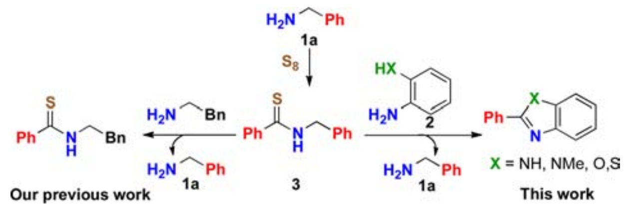
(2) (a) Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 3202. (b) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Heterocycles* **2012** DOI: 10.3987/COM-12-S(N)53.

(3) (a) Davis, R. E.; Nakshbendi, H. F. *J. Am. Chem. Soc.* **1962**, *84*, 2085. (b) Hodgson, W. G.; Buckler, S. A.; Peters, G. *J. Am. Chem. Soc.* **1963**, *85*, 543. (c) Thomson, J. W.; Nagashima, K.; Macdonald, P. M.; Ozin, G. A. *J. Am. Chem. Soc.* **2011**, *133*, 5036. (d) McMillan, F. H. *J. Am. Chem. Soc.* **1948**, *70*, 868. Mechanistic study of the room temperature reaction of sulfur with benzylamine: (e) Sasaki, Y.; Olsen, F. P. *Can. J. Chem.* **1971**, *49*, 283. (f) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012**, *14*, 4274. (g) Aghpoor, K.; Darabbi, H. R.; Tabar-Heydar, K. *Phosphorus, Sulfur Silicon* **2002**, *177*, 1183.

10.1021/ol302856w
Published on Web 11/21/2012

attention. We reasoned that if another amine stable to sulfur-mediated oxidation is added to the reaction mixture and is capable of participating in the trans-thioamidation with **3**, a cross-coupled product could be obtained. The driving force of this transformation is obviously the consumption of released benzylamine **1a**. In contrast to transamidation which required high temperature and/or catalytic conditions, trans-thioamidation is likely to proceed at lower temperature even without added catalyst.[4] In our previous work,[3f] by using an aliphatic amine such as 2-phenethylamine which is less oxidizable than **1a**, we obtained selectively cross-coupled thiobenzamides. By applying this one-pot transformation to aromatic amines, activation energy of the trans-thioamidation step should be higher because aromatic amines are less nucleophilic. This difficulty could be overcome by using an aniline *ortho*-substituted by a cyclizable group such as amino, hydroxy or mercaptan. The fomation of benzazoles in this case would be considerably facilitated by both energetically favored processes: cyclization and aromatization.

Scheme 1. Sulfur-Mediated Cross-Coupling Reaction of Two Amines

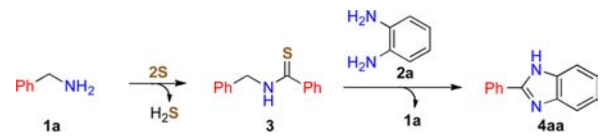


Herein, we report a chemoselective method for an oxidative coupling reaction of alkylamines with *o*-amino/mercaptan/hydroxyanilines for the formation of benzimidazoles, benzothiazoles, and benzoxazoles.

At the start of our studies, we investigated the reaction of benzylamine **1a** with *o*-phenylenediamine **2a** as a model system under solvent-free conditions (Table 1). First, the reactivity of **1a** and **2a** with sulfur was investigated separately. Compound **1a** reacted readily and cleanly with sulfur to yield homocoupled thioamide **3a** (entry 1, Table 1) as the only observable product even at moderate temperature (entry 2, Table 1). On the contrary, **2a** was stable in the presence of sulfur, even at high temperature (entry 3, Table 1). Next, we decided to heat an equimolar mixture of both amines **1a** and **2a** at 150 °C. Gratifyingly, these conditions afforded benzimidazole **4aa** in excellent yield (entry 4, Table 1). The reaction temperature could be lowered by using a slight excess of **1a**. Interestingly, even in the absence of solvent, the reaction mixture was homogeneous and **4aa** was progressively crystallized out from the liquid reaction mixture. Compound **4aa** could be isolated in high yield and purity by washing the reaction mixture with toluene to remove excess sulfur and other products.

(4) Schlatter, M. J. *J. Am. Chem. Soc.* **1942**, *64*, 2722.

Table 1. Reaction Conditions Screening[a]



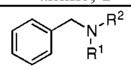
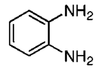
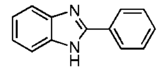
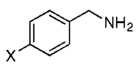
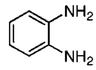
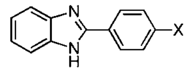
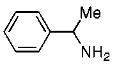
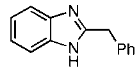
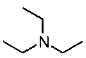
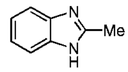
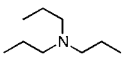
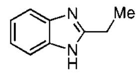
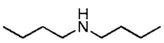
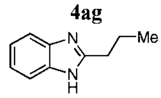
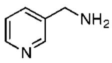
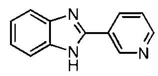
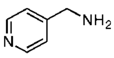
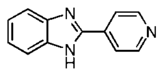
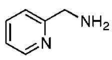
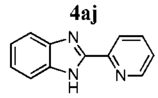
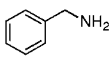
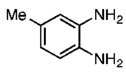
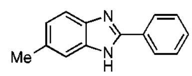
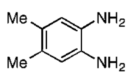
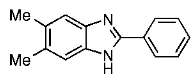
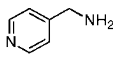
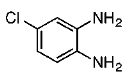
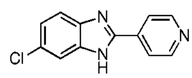
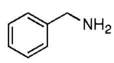
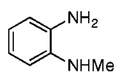
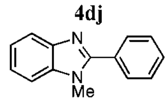
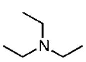
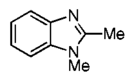
entry[a]	**1a**:**2a** (mmol/mmol)	temp (° C)	time (h)	conversion (%)[b] **3**	**4aa**
1	5:0	150	8	100	
2	5:0	120	8	100	
3	0:5	150	8		0[c]
4	5:5	150	8	<5	>95
5	**7.5:5**	**130**	**20**	**nd**[d]	>95 (92)[f]
6	7.5:5	120	20	nd[d]	80 (71)[f]

[a] Sulfur (15 mmol, 480 mg). [b] Determined by ^{1}H NMR spectroscopy. [c] **2a** recovered unchanged. [d] Not determined. [f] Isolated yield.

The scope of the reaction with respect to *o*-phenylenediamines and aliphatic amines was next investigated (Table 2). Under the optimized reaction conditions, various substituted aliphatic amines reacted with *o*-phenylenediamines to yield the corresponding benzimidazoles in good yields. Benzylamines *N*-mono- and disubstituted by methyl or benzyl groups work well as substrates for the oxidative condensation reaction and were readily transformed into 2-phenylbenzimidazole in high yields (entries 1–5, Table 2). When R^1 or/and R^2 = Me, volatile (di)methylamine was released during the course of the reaction (entries 2–3, Table 2), while when R^1 or/and R^2 = Bn, evolved (di)benzylamine was further oxidized and condensed with *o*-phenylenediamine (entries 4 and 5, Table 2). Other benzylamines substituted at the *para* position gave the corresponding benzoxazoles in 85–90% yield (entries 6–8, Table 2). Indeed, there is no sharp difference in reactivity between the strongly electron-donating 4-methoxy group (entry 8, Table 2) with the slightly electron-donating 4-methyl group (entry 6, Table 2) and the electron-deficient 4-chloro group (entry 7, Table 2). In particular, α-methylbenzylamine gave the rearranged coupled product (entry 9, Table 2).[3f] Interestingly, when aliphatic amines other than benzylamines such as triethylamine, tri-*n*-propylamine, and dibutylamine (entries 10–12, Table 2) were used, the corresponding benzimidazoles were obtained in high yields. Similarly, three picolinamines **1i**–**k** gave the benzimidazoles **4ai**–**ak** in preparative yields (entries 13–15, Table 2). It should be noted that in the case of 2- and 4-picolinamines (entries 14–15, Table 2), higher conversions could be achieved even at lower temperature compared to 3-picolinamine (entry 13, Table 2) and benzylamine (entry 1, Table 2). The efficacy of the reaction in the former cases could be explained by the efficient conjugative effect of the heterocycle nitrogen atom in the 2- and 4-positions.

To further investigate the substrate scope, reactions using various *o*-phenylenediamine substrates were carried

Table 2. Sulfur-Mediated Cross-Coupling Reaction of *o*-Phenylenediamines with Aliphatic Amines[a]

entry	amine, **1**	aniline, **2**	temp (°C)	*t* (h)	product, **4**	yield (%)
						
1	**1a**, $R^1 = R^2 = H$	**2a**	130	20	**4aa**	92
2	**1aa**, $R^1/R^2 = H/Me$		130	20		92
3	**1ab**, $R^1 = R^2 = Me$		130	20		90
4	**1ac**, $R^1/R^2 = H/Bn$		140	20		88
5	**1ad**, $R^1 = R^2 = Bn$		150	20		85
						
6	**1b**, X = Me	**2a**	130	20	**4ab**, X = Me	90
7	**1c**, X = Cl		130	20	**4ac**, X = Cl	86
8	**1d**, X = OMe		130	20	**4ad**, X = OMe	85
9	 **1e**	**2a**	130	20	 **4ae**	90
10	 **1f**	**2a**	130	20	 **4af**	90
11	 **1g**	**2a**	140	16	 **4ag**	85
12	 **1h**	**2a**	150	16	 **4ah**	71
13	 **1i**	**2a**	120	20	 **4ai**	83
14	 **1j**	**2a**	110	16	 **4aj**	73
15	 **1k**	**2a**	110	16	 **4ak**	85
16	 **1a**	 **2b**	130	20	 **4ba**	82
17	**1a**	 **2c**	130	20	 **4ca**	78
18	 **1j**	 **2d**	130	20	 **4dj**	81
19	 **1a**	 **2e**	140	16	 **4ea**	85
20	 **1f**	**2e**	130	16	 **4ef**	82

[a] Reaction conditions: *o*-phenylenediamine **2a**–**e** (5 mmol), amine **1a**–**k** (7.5 mmol), and sulfur (15 mmol, 32 g/mol).

out. *o*-Phenylenediamines bearing alkyl or halogen substituents were successful substrates in this reaction and gave the corresponding benzimidazoles in about 80% yields (entries 16–18). Although **2e** is a highly sterically demanding substrate, the oxidation–condensation process was successfully carried out with both benzylamine **1a** and triethylamine **1f** (entries 19 and 20, Table 2).

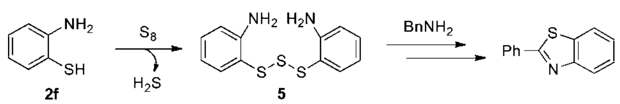
Table 3. Reaction with *o*-Aminothiophenol and *o*-Aminophenol[a]

entry	amine	aniline	conditions	**4**, yield (%)
1	**1a**	**2f**	130 °C, 20 h	**4fa**, 78
2	**1e**	**2f**	130 °C, 20 h	**4fe**, 83
3	**1f**	**2f**	130 °C, 20 h	**4ff**, 75
4	**1g**	**2f**	130 °C, 20 h	**4fg**, 78
5	**1i**	**2f**	120 °C, 20 h	**4fi**, 50
6	**1j**	**2f**	110 °C, 20 h	**4fj**, 68
7	**1a**	**2g**	130 °C, 20 h	**4ga**, 43
8	**1j**	**2g**	130 °C, 16 h	**4gj**, 80

[a] Reaction conditions: aniline **2f**,**g** (5 mmol), amine **1** (7.5 mmol), and sulfur (15 mmol, 32 g/mol).

Finally, we investigated this reaction to prepare thia- and oxa- analogues of benzimidazoles: benzothiazoles and benzoxazoles (Table 3) whose structures are found in various bioactive molecules. In all cases investigated for 2-aminothiophenol **2f**, the desired benzothiazoles were obtained in high yields (entries 1−6, Table 3).

Scheme 2. Reaction of 2-Aminothiophenol



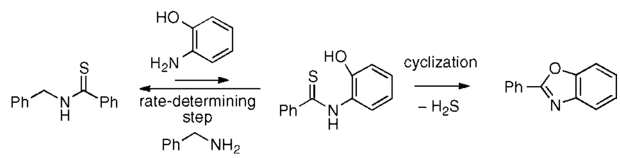
The reaction pathway for **2f** is, however, slightly different. Because of the propensity of thiophenols to form the oligosulfur chain, the first step of the cascade reaction could be the formation of trisulfide **5**. Trisulfide **5** could also oxidize alkylamines in the subsequent steps.[5] Indeed, when **2f** was mixed with elemental sulfur, evolution of H_2S was observed even at rt (Scheme 2).

Benzoxazole **4ga** was obtained in lower yield compared to its aza and thia analogues (**4aa** and **4fa**). This observation could be understood by the fact that, in **2g**, the hydroxy group renders its *o*-amino group less nucleophilic and thus less effective for the trans-thioamidation step, which is also the rate-determining step of benzazole formation (Scheme 3).

When **1j** was used with **2g** (Table 3, entry 8), the yield of **4gj** was significantly higher. In this case, the trans-thioamidation step is favored by the easy oxidation of **1j** which acted as a leaving group in this determining step.

In general, our method is more convenient than other known methods for conversion of alkylamine into 2-substituted benzazoles which inevitably required in all cases expensive/complex catalysts,[6] under high pressure,[6a] irradiation,[6a] high temperature conditions,[6c,d] or expensive oxidizing agent[6b] with limited scope.[6b,c] Moreover, unlike almost reactions involving elemental sulfur and amines which result the incorporation of sulfur in the final products, in the present case, sulfur played the role of a traceless oxidizing agent.

Scheme 3. Reaction of 2-Aminophenol



Overall, in view of the availability of all reaction components including sulfur, and the remarkably simple and catalyst-free reaction conditions at moderate temperature, the present method may possess a highly valuable advantage. The method constitutes a straightforward and efficient proceeding for the large scale synthesis of various biologically active targets without metallic contaminants. Further studies of reaction mechanism and applications are in progress.

Acknowledgment. Financial support from CNRS and ICSN is gratefully acknowledged.

Supporting Information Available. Experimental procedures, product characterization, and copies of the ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

(5) Tweit, R. C. *J. Heterocycl. Chem.* **1970**, *7*, 687.
(6) (a) Su, F. Z.; Antonietti, M.; Wang, X.; Mathew, S. C.; Moehlmann, L.; Blechert, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 657. (b) Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 6106. (c) De Luca, L.; Porcheddu, A. *Eur. J. Org. Chem.* **2011**, 5791. (d) Endo, Y.; Bäckvall, J. E. *Chem.—Eur. J.* **2012**, *18*, 13609.