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Nitro-Methyl Redox Coupling: Efficient Approach to 2-Hetarylbenzothiazoles from 2-Halonitroarene, Methylhetarene, and Elemental Sulfur

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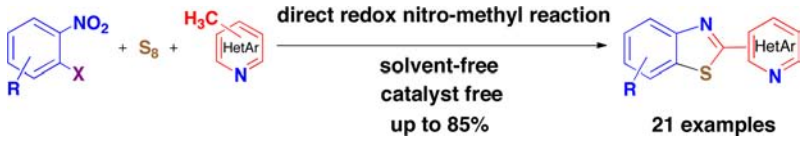
ABSTRACT



A simple, straightforward, and atom economic approach to 2-hetarylbenzothiazoles starting from 2-halonitroarene, methylhetarene, and elemental sulfur under mild conditions is described. The method is highlighted by the direct redox nitro-methyl reaction for carbon−nitrogen bond formation without an added oxidizing or reducing agent.

One of the biggest issues facing modern chemistry is the depletion of natural resources and pollution, especially in large-scale production. To resolve these problems, much effort has been made to develop greener and sustainable processes. In connection with our research program in developing new approaches of carbon−nitrogen and carbon−sulfur bond formations applicable to the process synthesis of biologically active molecules, we are interested in methods which include the following criteria: (i) is operationally simple; (ii) uses readily available starting materials; (iii) accesses a broad scope. In this context, utilization of elemental sulfur, which is nontoxic, stable under ambient conditions, easy to handle, and readily available in pure form, could be an excellent solution. Indeed, elemental sulfur, via its sulfur-containing compounds generated during the course of the reaction, is capable of playing multiple roles together as a redox reagent, catalyst, building block, etc., consequently possibly resulting in unpredictable but interesting reactivities.

As a case study, we report herein a result which demonstrates a novel, efficient, and yet extremely simple application of elemental sulfur in the synthesis of benzothiazoles. This targeted heterocyclic structure is one of the privileged scaffolds widely found in pharmaceutically important compounds[1] as well as functional materials.[2] Different strategies have been developed to achieve efficiently the synthesis of this motif, in which prefunctionalized substrates, such as *ortho*-thiol[3] or -halo anilines/anilides[4] or thioanilides,[5]

(1) For recent examples, see: (a) Serdons, K.; Terwinghe, C.; Vermaelen, P.; Laere; Van, K.; Kung, H.; Mortelmans, L.; Bormans, G.; Verbruggen, A. *J. Med. Chem.* **2009**, *52*, 1428. (b) Ramurthy, S.; Aikawa, M.; Amiri, P.; Costales, A.; Hashash, A.; Jansen, J. M.; Lin, S.; Ma, S.; Renhowe, P. A.; Shafer, C. M.; Subramanian, S.; Sung, L.; Verhagen, J. *Biorg. Med. Chem. Lett.* **2011**, *21*, 3286. (c) Pan, J.; Mason, N. S.; Debnath, M. L.; Mathis, C. A.; Klunk, W. E.; Lin, K.-S. *Biorg. Med. Chem. Lett.* **2013**, *23*, 1720. (d) Kumbhare, R. M.; Kosurkar, U. B.; Janaki Ramaiah, M.; Dadmal, T. L.; Pushpavalli, S. N. C. V. L.; Pal-Bhadra, M. *Biorg. Med. Chem. Lett.* **2012**, *22*, 5424. (e) Bolognesi, M. L.; Bartolini, M.; Tarozzi, A.; Morroni, F.; Lizzi, F.; Milelli, A.; Minarini, A.; Rosini, M.; Hrelia, P.; Andrisano, V.; Melchiorre, C. *Biorg. Med. Chem. Lett.* **2011**, *21*, 2655. (f) Amada, H.; Sekiguchi, Y.; Ono, N.; Matsunaga, Y.; Koami, T.; Asanuma, H.; Shiozawa, F.; Endo, M.; Ikeda, A.; Aoki, M.; Fujimoto, N.; Wada, R.; Sato, M. *Biorg. Med. Chem. Lett.* **2012**, *22*, 2024.

(2) (a) Raposo, M. M. M.; Castro, M. C. R.; Belsley, M.; Fonseca, A. M. C. *Dyes Pigm.* **2011**, *91*, 454. (b) Li, M.; Zeng, H.; Meng, Y.; Sun, H.; Liu, S.; Lu, Z.; Huang, Y.; Pu, X. *Dalton Trans.* **2011**, *40*, 7153. (c) Lee, B. C.; Kim, J. S.; Kim, B. S.; Son, J. Y.; Hong, S. K.; Park, H. S.; Moon, B. S.; Jung, J. H.; Jeong, J. M.; Kim, S. E. *Bioorg. Med. Chem.* **2011**, *19*, 2980.

(3) For examples, see: (a) Charton, J.; Girault-Mizzi, S.; Sergheraert, C. *Chem. Pharm. Bull.* **2005**, *53*, 492. (b) Seijas, J. A.; Vazquez, T.; Pilar, M.; Carballido, R.; Raquel, M.; Crecente, C. J.; Romar-Lopez, L. *Synlett* **2007**, 313.

(4) Ma, D.; Xie, S.; Xue, X.; Zhang, J.; Dong, J. H.; Jiang, Y. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 4222.

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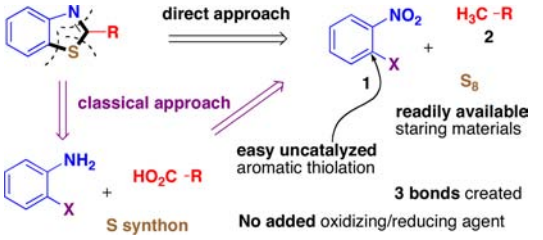
were used. These methods however suffer from low atom and/or step efficiency, therefore making them less attractive as sustainable chemical transformations.

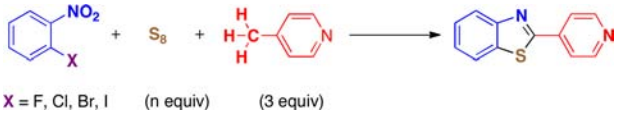
Scheme 1. Benzothiazole from 2-Halonitrobenzene **1**, Methylhetarene **2**, and Elemental Sulfur



We reasoned that a multicomponent approach appears to be a good choice and the creation of up to three bonds in one operation is highly desirable (Scheme 1). The simplest and most straightforward synthetic equivalent of the sulfur synthon (brown moiety) should unquestionably be elemental sulfur.[6] Based on the same atom- and step-economic principle previously applied,[7] we wish to develop conditions to shuffle directly up to six electrons from a methyl group in **2** as a carbon synthon (red moiety) to a nitro group in **1** as a nitrogen synthon (blue moiety). Consequently, no additional oxidizing or reducing agent would be necessary. Moreover, this functional group selection is justified by (i) the easy and direct introduction of the nitro group into an aromatic ring and (ii) the high availability of chemicals bearing a methyl group. The presence of a halogen atom at the *o*-position of the strongly electron-withdrawing nitro group in the nitroarene **1** would facilitate the nucleophilic introduction of a sulfur atom, even without a metallic catalyst.

We initiated our study by examining the cascade reaction using 2-halonitrobenzenes, elemental sulfur, and 4-picoline **2a** (Table 1) at 120 °C under solvent-free conditions. To our delight, all four 2-halonitrobenzenes yield the desired benzothiazole **3aa** in high conversions (entries 1−4) although 2-fluoro- and 2-chloronitrobenzenes displayed

Table 1. Reaction of 2-Halonitrobenzenes, 4-Picoline, and S



entry[a]	X	*n*	temp (°C)	conversion (%)[b]
1	F	1.5	120	>95
2	Cl	1.5	120	>95
3	Br	1.5	120	90
4	I	1.5	120	87
5	Cl	1	120	80
6	Cl	2	120	>95
7	Cl	2	110	92

[a] Reaction conditions: 2-halonitrobenzene **1** (5 mmol), 4-picoline **2a** (15 mmol), S (*n* equiv, 32 g/mol), 24 h. [b] Determined by ^{1}H NMR of the reaction mixture.

somewhat better reactivity than their heavier congeners. A slightly lower conversion was observed when 2-chloronitrobenzene **1a** and sulfur were used in an equimolar quantity (entry 5). When sulfur (2 equiv) was used, although a full conversion of **1a** was obtained (entry 6), the reaction mixture is less clean than in the previous case (entry 2). Lowering the reaction temperature results in a lower conversion (entry 7).

Once the optimal conditions had been identified, the scope of the reaction is demonstrated by 22 examples presented in Table 2 in which 2-chloronitrobenzene derivatives were used extensively. The reactions of 2-chloronitrobenzene **1a** and sulfur with 2- and 4-methylpyridines **2a**−**f** proceeded smoothly with good to excellent yields (entries 1−6). When 3-picoline **2g** was used, no trace of the desired product **2ag** was observed (entry 7); both **1a** and **2g** were recovered unchanged. This is in full agreement with previously described results.[7,8] This difference in reactivity was applied to regioselectively synthesized 4-(benzothiazol-2-yl)-3-picoline **3ah** (entry 8). Similarly, **3ai** was obtained in good yield (entry 9). Various functional 2-chloronitrobenzenes were shown to be suitable substrates. Methyl, chloride, methoxy, trifluoromethyl, nitro, and bromide functionalities are all competent in this transformation (entries 10−21).

When dichlorinated nitrobenzenes were used (entries 11−13), the yield was lower for 2,4-dichloronitrobenzene (entry 12), possibly due to the side reaction on the 4-chloro group, which is activated by the nitro group. Interestingly, even the reaction between 2,4-dinitrochlorobenzene **1h** and 4-picoline **2a** could be achieved (Table 2). Other methyl heteroaromatic systems such as 2-methylbenzimidazole **2j**, 1,2-dimethylimidazole **2k**, and methylpyrazine **2l** were also used successfully in the presence of a pyridine stable to reaction conditions to facilitate the stirring (pyridine, entries 17 and 18) or to play the role of a base

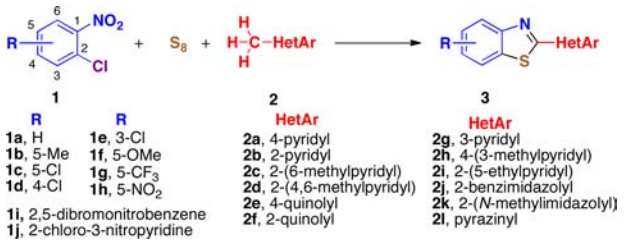
(5) For examples of the Jacobson reaction, see: (a) Jacobson, P. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1067. For recent applications of this reaction, see: (b) Hu, W.; Chen, Y. K.; Yu, H. S.; Huang, S. M.; Tsai, F. Y.; Chang, L. S.; Liao, C. C.; Tsai, Y. M.; Shen, H. C.; Wang, J. J. *Bioorg. Med. Chem.* **2010**, *18*, 6197. (c) Kozlov, V. A.; Aleksanyan, D. V.; Nelyubina, Y. V.; Lyssenko, K. A.; Petrovskii, V.; Odinets, I. L.; Vasil'ev, A. A. *Organometallics* **2011**, *30*, 2920. For related reactions using other oxidizing agents, see: (d) Mu, X. J.; Zou, J. P.; Zeng, R. S.; Wu, J. C. *Tetrahedron Lett.* **2005**, *46*, 4345. (e) Bose, D. S.; Idrees, M. *J. Org. Chem.* **2006**, *71*, 8261. (f) Bose, D. S.; Idrees, M.; Srikanth, B. *Synthesis* **2007**, 819. (g) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2007**, *63*, 10276. (h) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (i) Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792. (j) Inamoto, K.; Hasegawa, C.; Kawasaki, J.; Hiroya, K.; Doi, T. *Adv. Synth. Catal.* **2010**, *352*, 2643. (k) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 76. (l) Cheng, Y.; Yang, J.; Qu, Y.; Li, P. *Org. Lett.* **2012**, *14*, 98. (m) Inamoto, K.; Nozawa, K.; Kondo, Y. *Synlett* **2012**, *23*, 1678.

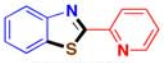
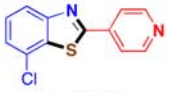
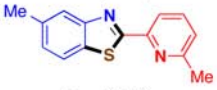
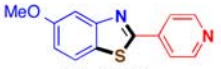
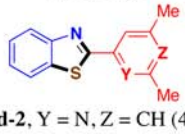
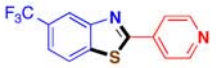
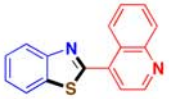
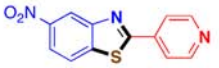
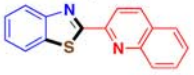
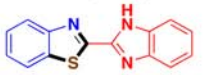
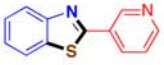
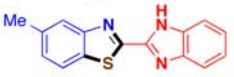
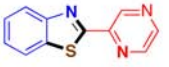
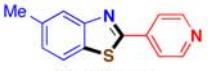
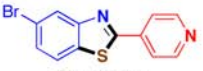
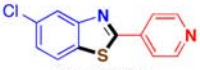
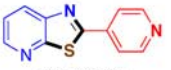
(6) For a recent example using elemental sulfur as the sulfur synthon in the synthesis of benzothiazoles from aldehydes and 2-iodoanilines, see: Deng, H.; Li, Z.; Ke, F.; Zhou, X. *Chem.—Eur. J.* **2012**, *18*, 4840.

(7) Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *J. Am. Chem. Soc.* **2013**, *135*, 118.

(8) (a) Pryor, W. A. *Mechanism of Sulfur Reactions*; McGraw-Hill: New York, 1962. (b) Perregaard, J.; Thomsen, I.; Lawesson, S. O. *Acta Chem. Scand. B* **1975**, *29*, 538.

Table 2. Reaction of 2-Halonitroarene, Methylhetarene, and S[a]



entry	3, yield	entry	3, yield
1	 **3aa** (85%)	12	 **3da** (45%)
2	 **3ab** (75%)	13	 **3ea** (75%)
3[b]	 **3bc** (56%)	14	 **3fa** (65%)
4	 **3ad-2**, Y = N, Z = CH (40%) **3ad-4**, Y = CH, Z = N (22%)	15[c]	 **3ga** (85%)
5[b,d]	 **3ae** (65%)	16[c]	 **3ha** (52%)
6[d]	 **3af** (51%)	17[d]	 **3aj** (72%)
7	 **3ag** (0%)	18[d]	 **3bj** (65%)
8	 **3ah** (82%)	19	 **3ak** (42%)
9	 **3ai** (70%)	20[e]	 **3al** (37%)
10	 **3ba** (85%)	21[f]	 **3ia** (82%)
11	 **3ca** (83%)	22[e]	 **3ja** (67%)

[a] Conditions: **1** (5 mmol), **2** (15 mmol), S (7.5 mmol, 240 mg), 120 °C, 24 h unless otherwise noted. [b] At 140 °C. [c] At 100 °C. [d] **2** (10 mmol) was used; pyridine (1 mL) was added. [e] 150 °C; **2** (10 mmol); 3-picoline (1 mL) was added. [f] 2,5-Dibromonitrobenzene as component **1**.

(3-picoline, entry 20). In general, the presence of an electron-withdrawing group on the phenyl moiety of 2-chloronitrobenzenes significantly accelerated the rate of reaction, as the reactions of **1g** and **1h** with **2a** could proceed at a lower temperature (entries 15–16 and 22).

Although the mechanism of the transformation is not clear at this moment, interesting indications were obtained when following the progress of the reaction between **1a**, **2a**, and sulfur under optimal conditions (entry 1) by ^{1}H NMR analysis. We observed a clean conversion of **1a** and **2a** into **3aa** and small amounts of other unidentified products bearing a 4-picolyl moiety. This result suggests a cascade reaction pathway involving a consecutive series of intramolecular reactions which often proceed via highly reactive intermediates.

To further explore the reaction pathway for the synthesis of benzothiazole **3aa**, some control experiments were performed at 120 °C for 24 h. First, each couple of starting materials was heated together. Reactions of sulfur with **1a** and of **1a** with **2a** did not work; all starting materials were recovered unchanged (Scheme 2, eqs 1, 2). In contrast, when sulfur was heated with **2a**, di-(4-picolyl) **2a$_2$** was formed although in only a low quantity (< 3%) along with unchanged **2a** (eq 3). Because HCl is a byproduct of the global reaction of **1**, **2**, and sulfur, we carried out another test in the presence of HCl (0.3 equiv, the theoretically generated quantity) and obtained a higher conversion of di-(4-picolyl) **2a$_2$** (17%) and tri-(4-picolyl) **2a$_3$** (30%).[9] The formation of these products can be explained by a sequence of sulfuration/sulfur extrusion.[10]

This result combined with the fact that the methyl group involved in the reaction must be located at the 2- or 4-position of the aza heterocycles **2** suggests that the nitrogen atom of the heteroaromatic ring of **2** is responsible for stabilizing the reaction intermediates via imine-enamine tautomerism.[8] When 2-chloroaniline was heated with 4-picoline and sulfur (Scheme 2, eq 4), both organic starting materials were recovered unchanged. From this unsuccessful attempt we conclude that 2-chloroaniline cannot be the intermediate of the reaction. Moreover, when only 1 equiv of sulfur was used in a reaction between **1a** and **2a** (Table 1, entry 5), **3aa** was formed in 80% conversion and 75% yield, suggesting that, theoretically, only 1 equiv of sulfur is required in the transformation.

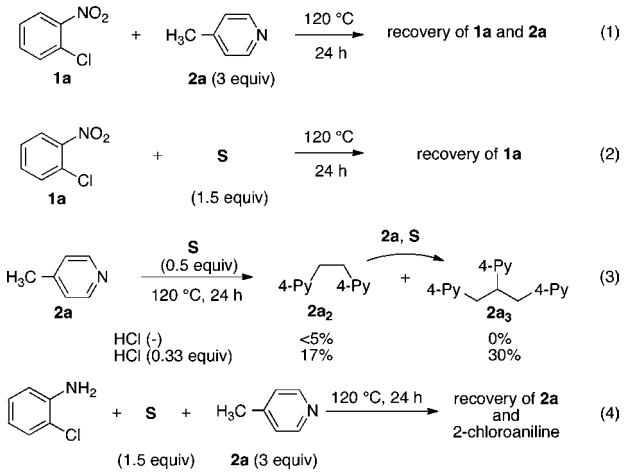
We next tentatively proposed a mechanism for the present reaction (Scheme 3). The first step could be the attack of sulfur on 4-picoline via its more active enamine form **A** to generate **B** which would be subsequently transformed into 4-picolyl radical **C** via sulfur extrusion. This highly active radical, instead of being dimerized, could be trapped by the nitro group of **1a** to yield **D**. Sulfuration the methylene of **D** followed by a cascade reaction of cyclization and reduction[11] would result in **3aa**. The reducing

(9) The formation of **2a$_2$** and **2a$_3$** was observed under more drastic thermal uncatalyzed conditions when a solution of sulfur in 4-picoline (bp 145 °C) was refluxed: Thayer, H. I.; Corson, B. B. *J. Am. Chem. Soc.* **1948**, *70*, 2330.

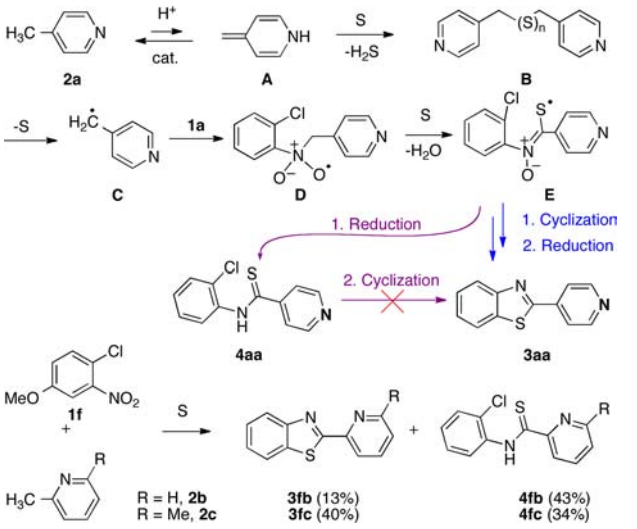
(10) The formation of di-(4-picolyl) and related compounds via a radical mechanism: Pryor, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 2715.

(11) For an example of transformation of *N*,α-diarylnitrones into thiobenzanilides or 2-arylbenzothiazoles using thiolating reagents, see: Yoshifuji, M.; Nagase, R.; Kawashima, T.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 870.

Scheme 2. Investigation of the Reaction Pathway



Scheme 3. Proposed Reaction Pathway



agents involved in this reduction step could be H_2S (from the step **A** → **B**) or 4-picoline. If the reduction step of **E** happens first, thioamide **4aa** would be formed but could not be cyclized into **3aa**.[12] Indeed, in some tested cases wherein the cyclization step is hindered by both of the following factors, the corresponding thioamides were obtained in non-negligible quantities: (i) the presence of an electron-donating group such as MeO at the *para* position of the chlorine atom of **1**; (ii) the reaction of 2-methyl aza heterocycles such as 2-picoline and 2,6-lutidine.

It is important to point out that using elemental sulfur activated by 4-picoline (S_8-**2a**) as a sulfurating agent of **1a** is more beneficial than sulfide salts. Indeed, the combination S_8-**2a** is (i) due to the α effect, which is more nucleophilic (to facilitate the sulfur introduction), and (ii) less reducing toward the nitro group (to avoid the undesirable reduction of the nitro group of **1a** at the early stage prior to the formation of the carbon−nitrogen bond **C** + **1a** → **D**). Indeed, the reactions using sulfide salts (sodium or ammonium) instead of S_8 result in complex mixtures.

In summary, we have developed a simple, straightforward, atom economic, and multicomponent synthesis of 2-hetaryl benzothiazoles derivatives in good to excellent yields using inexpensive, readily available 2-halonitroarenes, sulfur, and methylhetarenes. The reaction conditions are solvent-free, catalyst-free, and relatively mild with high functional group tolerance. Mechanistically, 2- or 4-methyl aza heterocycles are activated by H^+ generated during the course of the transformation. Moreover, the method is highlighted by the direct nitro-methyl reaction for carbon−nitrogen bond formation which proceeds without an added oxidizing or reducing agent.[13] Further investigations of the mechanism and other applications, including the use of other methyl substrates, as well as other reducing partners are underway.

Supporting Information Available. Experimental procedures, product characterization, and copies of the ^1H 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.

(12) When nitrobenzene was heated at 120 °C for 24 h with sulfur in 4-picoline, thioisonicotinanilide (25%) was obtained. This observation is in agreement with the literature report: Emmertt, B.; Holz, A. *Chem. Ber*. **1954**, 676.

(13) For some recent examples of redox condensation of nitro groups, see: (a) Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G. *Org. Lett*. **2012**, *14*, 2722. (b) Xie, Y.; Liu, S.; Liu, Y.; Wen, Y.; Deng, G. *Org. Lett*. **2012**, *14*, 1692.