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Synthesis of 5-substituted 3-mercapto-1,2,4-triazoles via Suzuki–Miyaura reaction

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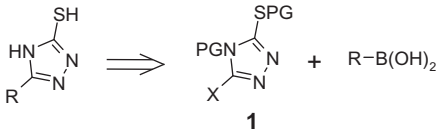
ABSTRACT

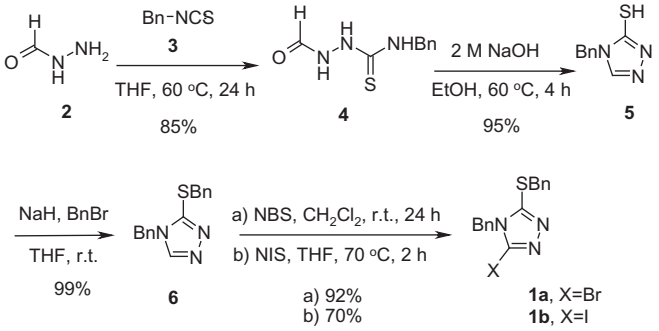
3-Bromo- and 3-iodo-*N*,*S*-dibenzyl-5-mercapto-1,2,4-triazoles were prepared and demonstrated as versatile building blocks for Suzuki–Miyaura cross-coupling with aryl, heteroaryl, and vinyl boronic acid derivatives. Deprotection of the resulting coupling products provided 5-substituted-3-mercapto-1,2,4-triazoles in good overall yields. This represents a novel and convenient approach for the introduction of a 3-mercapto-1,2,4-triazole substructure into target compounds.

Heterocyclic compounds incorporating the 3-mercapto-1,2,4-triazole substructure exhibit a wide spectrum of biological activity.[1–3] In addition, 3-mercapto-1,2,4-triazole has the ability to coordinate metal ions.[4–6] This property has been used to develop non-hydroxamate Zn-dependent enzyme inhibitors based on 3-mercapto-1,2,4-triazoles.[7] Despite the broad utilization potential of 3-mercapto-1,2,4-triazoles, there are a limited number of methods available for their synthesis. The most common approach is an intramolecular cyclization of acyl-thiosemicarbazides under basic conditions.[1–3,7–9] The intermediate acyl-thiosemicarbazides are prepared by the addition of hydrazides to isothiocyanates or by non-selective acylation of thiosemicarbazides. Thus, this approach is limited to hydrazines and carboxylic acid derivatives as starting materials. Another limitation is that substrates that tolerate relatively harsh basic conditions are needed to achieve the cyclization. Moreover, the substituent at position 5 of the resulting triazoles is introduced via a multistep procedure that is not suitable for rapid library generation.

Our synthetic strategy for the synthesis of 5-substituted-3-mercapto-1,2,4-triazoles was based on the Suzuki–Miyaura cross-coupling of N,S-diprotected building block **1** with boronic acid derivatives followed by deprotection (Scheme 1). Benzyl groups were chosen for N,S-protection as they are sufficiently stable to avoid catalyst poisoning by generation of thiol in the reaction mixture.[10]



Scheme 1. Building block strategy for the synthesis of 5-substituted-3-mercapto-1,2,4-triazoles.



Scheme 2. Synthesis of building blocks **1a**,**b**.

Building blocks **1a,b** were obtained in four steps starting from commercially available formylhydrazine (**2**) and benzylisothiocyanate (**3**) according to the reported approach for the synthesis of mercaptotriazoles (Scheme 2).[11] Intermediate acyl thiosemicarba-

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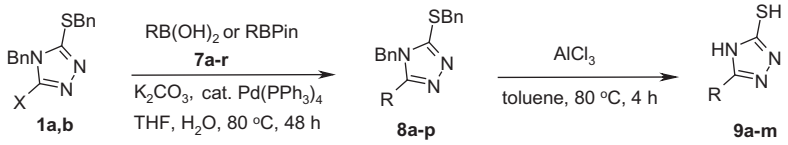

Scheme 3. Suzuki–Miyaura coupling of protected mercaptotriazole building blocks **1a**,**b** and deprotection of the coupling products **8a**–**m**.

Table 1
Suzuki–Miyaura cross-coupling of building block **1** with boronic acid derivatives **7** leading to intermediates **8** and deprotection to give mercaptotriazoles **9**

Entry	Building block **1**	Boronic acid derivative, **7**	**8**, Yield[a] (%)	**9**, Yield[a] (%)
1	**1a**	$C_6H_5B(OH)_2$, **7a**	**8a**, 99	**9a**, 90
2	**1b**	$C_6H_5B(OH)_2$, **7a**	**8a**, 70	
3	**1b**	4-(Me)$C_6H_4B(OH)_2$, **7b**	**8b**, 89	**9b**, 85
4	**1a**	4-(*t*-Bu)$C_6H_4B(OH)_2$, **7c**	**8c**, 86	**9c**, 95
5	**1b**	4-(*t*-Bu)$C_6H_4B(OH)_2$, **7c**	**8c**, 71	
6	**1a**	3,5-(di-Me)$C_6H_3B(OH)_2$, **7d**	**8d**, 77	**9d**, 94
7	**1b**	3,5-(di-Me)$C_6H_3B(OH)_2$, **7d**	**8d**, 72	
8	**1a**	4-(F)$C_6H_4B(OH)_2$, **7e**	**8e**, 91	**9e**, 96
9	**1b**	4-(F)$C_6H_4B(OH)_2$, **7e**	**8e**, 79	
10	**1a**	2-(MeO)$C_6H_4B(OH)_2$, **7f**	**8f**, 74	**9f**, 95[b]
11	**1b**	2-(MeO)$C_6H_4B(OH)_2$, **7f**	**8f**, 85	
12	**1b**	3-(MeO)$C_6H_4B(OH)_2$, **7g**	**8g**, 81	**9g**, 91[b]
13	**1b**	4-(MeO)$C_6H_4B(OH)_2$, **7h**	**8h**, 89	**9h**, 93[b]
14	**1b**	2-(H_2N)C_6H_4BPin, **7i**	**8i**, 77	**9i**, 86
15	**1b**	3-(HO)$C_6H_4B(OH)_2$, **7j**	**8j**, 80	**9j**, 91
16	**1b**	3-PyBPin, **7k**	**8k**, 43	**9k**, 72
17	**1b**	3-Quinolinyl-BPin, **7l**	**8l**, 60	**9l**, 80
18	**1b**	4-(CN)$C_6H_4B(OH)_2$, **7m**	**8m**, 43	**9m**, 95
19	**1b**	*trans*-$C_6H_5CH{=}CHB(OH)_2$, **7n**	**8n**, 51	—
20	**1b**	$CH_2{=}CHBF_3K$, **7o**	**8o**, 79	—
21	**1b**	Cyclohexen-1-ylB$(OH)_2$, **7p**	**8p**, 60	—
22	**1b**	*i*-Pr$CH_2B(OH)_2$, **7q**	**8q**,—	—
23	**1b**	B_2Pin_2, **7r**	**8r**,—	—

[a] Isolated yields.
[b] Cleavage of the Me group occurred.

zide **4** was subjected to base-promoted cyclization to give triazole **5**. Benzylation of compound **5** provided N,S-diprotected mercaptotriazole **6**, which was halogenated at position 5 with NBS or NIS yielding triazole derivatives **1a** and **1b**, respectively.

Mercapto triazole building blocks **1a,b** were subjected to Suzuki–Miyaura cross-coupling with $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base in degassed THF/H_2O (Scheme 3).[12–14] The coupling reactions with a range of boronic acid derivatives **7** are summarized in Table 1. Both aromatic and vinyl boronic acids or their pinacol esters **7a–p** could be used as coupling partners to give 5-substituted N,S-protected mercaptotriazoles **8a–p**. Aliphatic boronic acid **7q** and pinacolate diborane **7r** were also used to couple with building blocks **1a,b**. However, despite the wide range of catalytic systems investigated, no or very low conversion into the desired products and/or dehalogenated *N,S*-dibenzyl-mercaptotriazole was obtained as the major product.

Deprotection of triazole derivative **8a** was investigated under various conditions. No conversion was achieved with: (a) SmI_2 in THF at rt; (b) Mg and Zn, $HCOO^-NH_4^+$ in MeOH or THF at 80 °C. Mixtures of products were obtained with (a) KO*t*Bu, O_2 in DMSO at rt; (b) Na in liquid NH_3 at −78 °C; (c) BBr_3 in CH_2Cl_2. Finally, we were pleased to find that deprotection could be achieved successfully using $AlCl_3$ in toluene at 80 °C.[15] These conditions led to cleavage of both the *N*- and *S*-benzyl protecting groups in coupling products **8a–m** to give mercaptotriazoles **9a–m** in good to high yields. With compounds **8f–h**, concomitant cleavage of the methyl groups took place providing hydroxyphenyl substituted triazoles **9f–h** (Table 1, entries 10–13). The deprotection conditions with $AlCl_3$ were also used for 5-(phenylvinyl)-mercaptotriazole **8n**, however this led to the formation of a mixture consisting of several unidentified decomposition products. Deprotection of other 5-vinyl-mercaptotriazole derivatives **8o** and **8p** were not attempted under these conditions.

In summary, we have demonstrated the synthesis of 5-substituted mercaptotriazoles via Suzuki–Miyaura reaction of specifically designed building blocks **1a,b** followed by deprotection. Building blocks **1a,b** might be useful in other types of coupling reactions to give modified triazoles.

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Supplementary data

Supplementary data (experimental procedures for the synthesis of compounds **1**–**9** and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.067.

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