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Synthesis of 3-Substituted Aryl[4,5]isothiazoles through an All-Heteroatom Wittig-Equivalent Process

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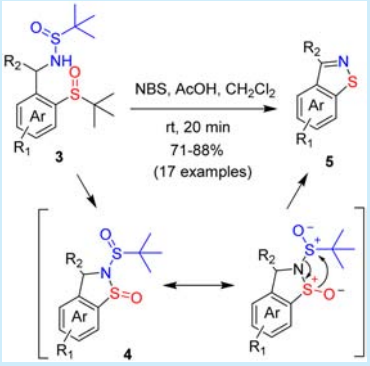
Supporting Information

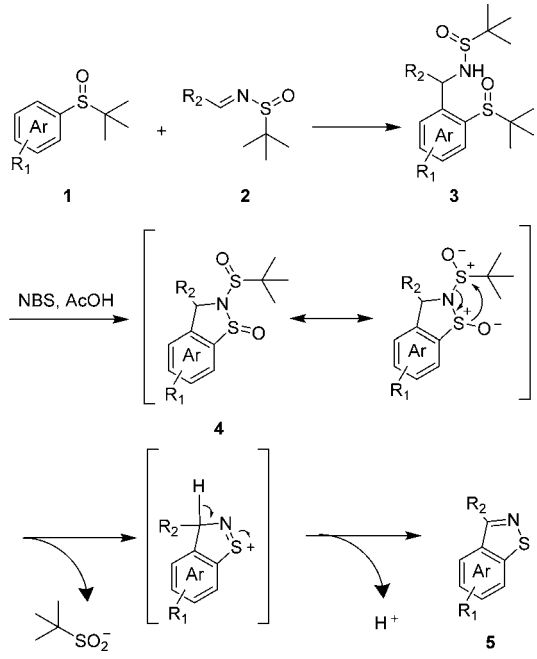
ABSTRACT: Extending the previous use of *tert*-butyl sulfoxide as the sulfinyl source, intramolecular sulfinylation of sulfonamides was successfully performed. The resulting sulfinimides were not isolated and instead were believed to go through an all-heteroatom Wittig-equivalent process to eventually afford aryl[4,5]isothiazoles in high yields.



Isothiazole is an important structural scaffold in medicinal chemistry. A primary example is the benzisothiazole group in the U.S. Food and Drug Administration-approved drug lurasidone, which can be used to treat adults with schizophrenia and bipolar 1 depression.[1] Other isothiazole-containing compounds have been studied in a variety of drug development projects.[2] Traditionally, the synthesis of aryl-fused isothiazoles requires multiple manipulations of the S or N sources,[3] and protocols that employ direct ring formation using readily available starting materials are limited.[4] Two recent reports of benzisothiazole synthesis are notable improvements in the field: a cyclization method starting from *o*-mercaptoacylphenones through S-nitrosation followed by an aza-Wittig procedure[5a] and direct ring fusion through aryne and 1,2,5-thiadiazoles.[5b] Here we present another efficient synthesis of aryl-fused isothiazoles using *tert*-butyl sulfoxide and *tert*-butylsulfinamide as the S and N sources, respectively.

We recently reported a mild and general procedure for the synthesis of sulfoxides, sulfinic acid esters, and sulfonamides that uses *tert*-butyl sulfoxides as the sulfinyl source through activation by *N*-bromosuccinimide (NBS) and acetic acid at room temperature.[6] To expand the application of this procedure, we utilized it for the synthesis of chiral 2,3-dihydrobenzisothiazole-1-oxide **4** (Scheme 1) from the starting material, **3**, which is readily accessible from ortho metalation of aryl sulfoxides **1** and asymmetric addition to imines **2**.[7] However, upon treatment of **3a** (R_1 = none, R_2 = Ph in Scheme 1; also see Table 1) with NBS and acetic acid, the corresponding compound **4** was not isolated. Instead, the corresponding isothiazole **5a** (Table 1) was obtained.

Scheme 1. Formation of Aryl[4,5]isothiazole



The formation of **5** from **4** may be explained by a process equivalent to an aza-Wittig reaction through the loss of *tert*-butylsulfinic acid (Scheme 1). Such an all-heteroatom Wittig

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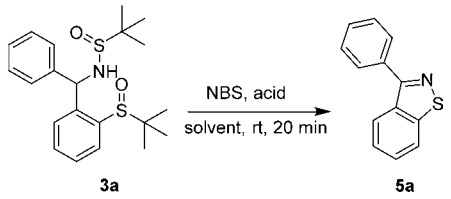
Table 1. Exploration of Optimal Conditions for Activation of the *tert*-Butyl Sulfinyl Group



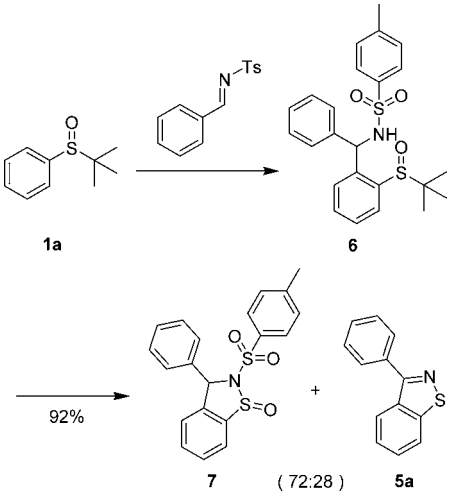
3a 5a

entry	acid	solvent	reagent ratio (3a/NBS/acid)	yield of 5a (%)
1	AcOH	CH_2Cl_2	1.0/2.0/1.2	75
2	AcOH	CH_2Cl_2	1.0/2.0/1.5	82
3	AcOH	CH_2Cl_2	1.0/2.0/2.0	81
4	$PhCO_2H$	CH_2Cl_2	1.0/2.0/1.5	71
5	TsOH	CH_2Cl_2	1.0/2.0/1.5	31
6	TFA	CH_2Cl_2	1.0/2.0/1.5	45
7	AcOH	toluene	1.0/2.0/1.5	20
8	AcOH	THF	1.0/2.0/1.5	none
9	AcOH	DMF	1.0/2.0/1.5	47

process has been reported before.[8] This mechanism is supported by the fact that after the completion of reaction, the ^{1}H NMR spectrum of the reaction mixture indicated the presence of 1 equiv of *tert*-butyl protons (the *tert*-butyl group of the sulfoxide was released from the reaction as isobutene). This suggests that the *tert*-butylsulfinyl group attached to the nitrogen atom was retained during the reaction and did not go through NBC/acid activation to release isobutene.

To provide further evidence of the Wittig-like reaction pathway, we reasoned that replacing the sulfinyl group in **4** with a sulfonyl group should slow the conversion of the intermediate to **5** and thus might allow isolation of the sulfonamide equivalent of **4**. Indeed, as shown in Scheme 2, when *p*-

Scheme 2. Additional Evidence for the Reaction Pathway Using a Sulfonyl Derivative



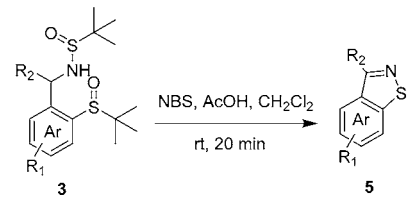
1a 6 7 5a

toluenesulfonyl-protected **6** was treated with NBS and acetic acid, both cyclized **7** (equivalent to **4**) and the further-transformed benzisothiazole **5a** were isolated in 92% total yield with a **7**:**5a** ratio of 72:28. In addition, *p*-toluenesulfonic acid could be detected and isolated from the reaction. The direct conversion of **7** to **5a** was possible by heating, which also afforded *p*-toluenesulfonic acid. All of these observations support an all-heteroatom Wittig-equivalent process for the formation of **5**.

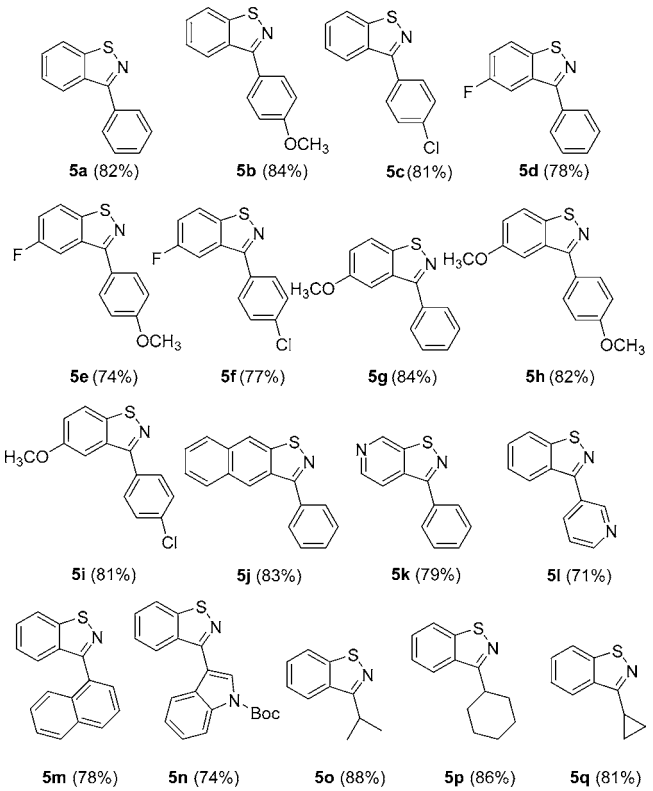
The transformation of **3a** to **5a** was then optimized with regard to reagent ratio, acid used, and solvent. The results are summarized in Table 1. While the use of 1.2 equiv of acetic acid gave a good yield (75%; Table 1, entry 1), increasing the amount of acid to 1.5 equiv produced a better yield (82%; Table 1, entry 2), while using 2.0 equiv of acid gave no further improvement. Similar to the results in our previous report,[6] changing the acid or solvent in every case produced lower product yields than the acetic acid/CH_2Cl_2 combination (Table 1, entries 4–9).

With the optimized reaction conditions in hand, a collection of starting materials **3** bearing various functional groups were subjected to the NBS/acetic acid/CH_2Cl_2 protocol to produce **5**. As shown in Scheme 3, the 3-position of the final aryl[4,5]isothiazole **5** can contain a wide range of aromatic groups (with additional electron-donating or -withdrawing substitutions) or alkyl groups (**5o**–**q**). For the fused aromatic portion, substituted benzene, naphthalene, or pyridine derivatives were obtained (**5d**–**k**).

Scheme 3. Additional Examples of Isothiazole Synthesis[a]



3 5



5a (82%) 5b (84%) 5c (81%) 5d (78%)
5e (74%) 5f (77%) 5g (84%) 5h (82%)
5i (81%) 5j (83%) 5k (79%) 5l (71%)
5m (78%) 5n (74%) 5o (88%) 5p (86%) 5q (81%)

[a]Reaction conditions: a mixture of **3** (0.5 mmol), NBS (1.0 mmol), AcOH (0.75 mmol), and CH_2Cl_2 (2 mL) was stirred at room temperature for 20 min under a nitrogen atmosphere.

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In summary, we have demonstrated an efficient protocol for the synthesis of aryl[4,5]isothiazoles. The key reaction step utilizes NBS/acid activation of aryl *tert*-butyl sulfoxides to allow cyclization by an ortho-placed sulfinamidomethyl group followed by spontaneous transformation to the isothiazole. This new procedure should complement existing methods for accessing this important molecular scaffold in biological and medicinal chemistry. In addition, our experimental evidence strongly supports an all-heteroatom Wittig-equivalent transformation process for the formation of the final products. This transformation may be considered for use in other functional group manipulations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01338.

Procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) George, M.; Amrutheshwar, R.; Rajkumar, R. P.; Kattimani, S.; Dkhar, S. A. *Eur. J. Clin. Pharmacol.* **2013**, *69*, 1497. (b) Sanford, M.; Dhillon, S. *CNS Drugs* **2015**, *29*, 253. (c) Garay, R. P.; Llorca, P. M.; Young, A. H.; Hameg, A.; Samalin, L. *Drug Discovery Today* **2014**, *19*, 1792. (d) Kim, Y.; Tae, J.; Lee, K.; Rhim, H.; Choo, I. H.; Cho, H.; Park, W. K.; Keum, G.; Choo, H. *Bioorg. Med. Chem.* **2014**, *22*, 4587. (e) Woo, Y. S.; Wang, H. R.; Bahk, W. M. *Neuropsych. Dis. Treat.* **2013**, *9*, 1521. (f) Sanford, M. *CNS Drugs* **2013**, *27*, 67.

(2) (a) Lai, H.; Dou, D.; Aravapalli, S.; Teramoto, T.; Lushington, G. H.; Mwania, T. M.; Alliston, K. R.; Eichhorn, D. M.; Padmanabhan, R.; Groutas, W. C. *Bioorg. Med. Chem.* **2013**, *21*, 102. (b) Alex, D.; Gay-Andrieu, F.; May, J.; Thampi, L.; Dou, D.; Mooney, A.; Groutas, W.; Calderone, R. *Antimicrob. Agents Chemother.* **2012**, *56*, 4630. (c) Jorgensen, W. L.; Trofimov, A.; Du, X.; Hare, A. A.; Leng, L.; Bucala, R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4545. (d) Vicini, P.; Crasci, L.; Incerti, M.; Ronsisvalle, S.; Cardile, V.; Panico, A. M. *ChemMedChem* **2011**, *6*, 1199. (e) Geronikaki, A.; Eleftheriou, P.; Vicini, P.; Alam, I.; Dixit, A.; Saxena, A. K. *J. Med. Chem.* **2008**, *51*, 5221.

(3) (a) Lei, N. P.; Fu, Y. H.; Zhu, X. Q. *Org. Biomol. Chem.* **2015**, *13*, 11472. (b) Brown, D. W.; Sainsbury, M. *Sci. Synth.* **2002**, *11*, 573. (c) Wirschun, W. G.; Hitzler, M. G.; Jochims, J. C.; Groth, U. *Helv. Chim. Acta* **2002**, *85*, 2627. (d) Creed, T.; Leardini, R.; McNab, H.; Nanni, D.; Nicolson, I. S.; Reed, D. *J. Chem. Soc., Perkin Trans 1* **2001**, *9*, 1079.

(4) (a) Brieaddy, L. E.; Donaldson, K. H. *J. Heterocycl. Chem.* **1995**, *32*, 1683. (b) McKinnon, D. M.; Lee, K. R. *Can. J. Chem.* **1988**, *66*, 1405. (c) Lawson, A. J. *Phosphorus Sulfur Relat. Elem.* **1982**, *12*, 357. (d) Lawson, A. J. *J. Chem. Soc., Chem. Commun.* **1981**, *23*, 1238. (e) Markert, J.; Hagen, H. *Liebigs Ann. Chem.* **1980**, *1980*, 768.

(5) (a) Devarie-Baez, N. O.; Xian, M. *Org. Lett.* **2010**, *12*, 752. (b) Chen, Y.; Willis, M. C. *Org. Lett.* **2015**, *17*, 4786.

(6) Wei, J.; Sun, Z. *Org. Lett.* **2015**, *17*, 5396.

(7) Le Fur, N.; Mojovic, L.; Ple, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006**, *71*, 2609.

(8) Schwöbel, A.; Kresze, G.; Perez, M. A. *Liebigs Ann. Chem.* **1985**, *1985*, 72.

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