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A Novel Practical Synthesis of Benzothiazoles via Pd-Catalyzed Thiol Cross-Coupling

Takahiro Itoh* and Toshiaki Mase

Process Research, PreClinical Development, Banyu Pharmaceutical Co., Ltd., 3 Okubo, Tsukuba, Ibaraki, 300-2611, Japan

takahiro_itoh@merck.com

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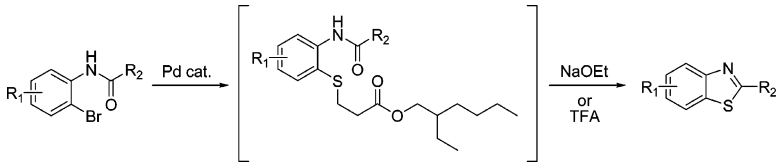
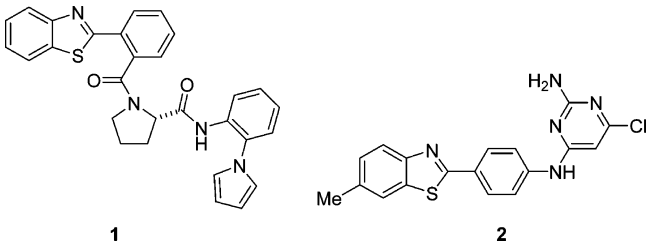
ABSTRACT



A convenient synthesis of substituted benzothiazoles from 2-bromoanilides has been accomplished. The various 2-bromoanilides were reacted with an alkyl thiolate in high yields using a palladium catalyst. The resulting sulfides were easily converted to the corresponding benzothiazoles via the simultaneous generation of thiols and condensation under basic or acidic conditions.

Substituted benzothiazole is an important class of heterocyclic compounds that exhibits a wide range of biological properties such as inhibitors of stearoyl-coenzyme A δ-9 desaturase,[1] antitumor,[2] antimicrobial,[3] LTD_4 receptor antagonist,[4] etc. For example, the investigations of benzothiazole as a key pharmacore led to Merck investigational new drugs such as the orexin receptor antagonist **1**[5] and the Gram-positive selective antibacterials **2**[6] (Figure 1).



1 **2**

Figure 1. Structures of Merck investigational new drugs.

Many reports have appeared in the literature describing the formation of benzothiazoles.[7] Scheme 1 describes the major approaches for assembly of these compounds including a direct conversion of 2-aminothiophenol with carboxylic acids or aldehydes (approach A)[8] and a condensation of thioanilides via copper- or palladium-catalyzed Buchwald−Hartwig-type carbon−heteroatom bond formation (approach

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(6) Ali, A.; Taylor, G. E.; Graham, D. W. PCT Int. Appl. 2001, WO 2001028561.

(7) For example: (a) Couture, A.; Grandclaudon, P. *Heterocycles* **1984**, *22*, 1383−1385. (b) Tale, R. H. *Org. Lett.* **2002**, *4*, 1641−1642.

(8) (a) Cohen, V. I.; Pourabass, S. *J. Heterocycl. Chem.* **1977**, *14*, 1321−1323. (b) Boger, D. E. *J. Org. Chem.* **1978**, *43*, 2296−2297. (c) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395−6396. (d) Abbotto, A.; Bradnmante, S.; Facchetti, A.; Pagani, G. A. *J. Org. Chem.* **2002**, *67*, 5753−5772. (e) Rudrawar, S.; Kondaskar, A.; Chakraborti, A. K. *Synthesis* **2005**, *15*, 2521−2526.

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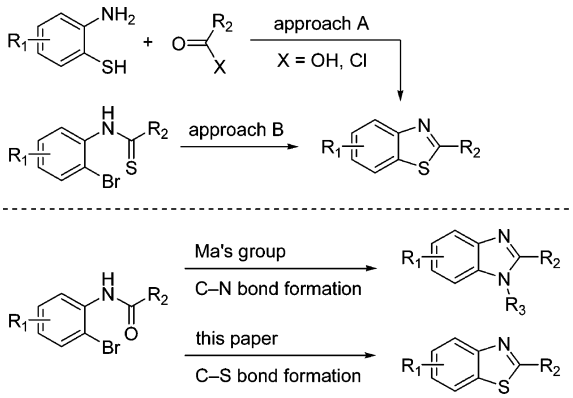
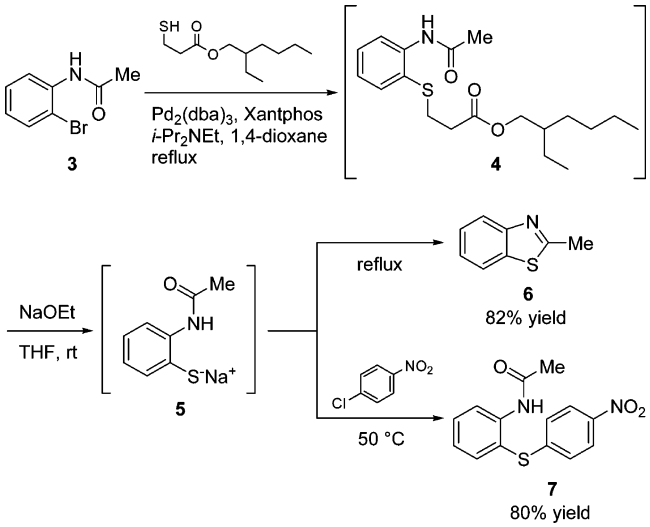
Scheme 1. Major Approaches for the Synthesis of Benzothiazoles



Scheme 2. Synthesis of Benzothiazole via C−S Bond Formation



B).[9,10] Approach A is the classical approach; however, it suffers from difficulties in the preparation of readily oxidizable 2-aminothiophenols. By comparison, the alternative approach B suffers from functional group compatibility in the preparation of the starting materials. Especially, functional groups such as ketones, esters, and amides are often incompatible with the method commonly used to prepare the thioanilides.[11] Therefore, a new alternative methodology for the synthesis of benzothiazoles needs to be explored. Recently, we have developed the Pd-catalyzed cross-coupling reaction of aryl bromide/triflates and alkyl/aryl thiols.[12] We have also been interested in developing protocols that would allow for the preparations of aryl thiols from aryl halides via a thiol surrogate.[13] In this regard, Ma et al. have recently reported a Cu-catalyzed cascade process for the synthesis of 1,2-disubstituted benzimidazoles.[14] Herein, we wish to report a new convenient method of benzothiazoles from 2-bromoanilides with a thiol surrogate coupling reaction.

In the initial study for the preparation of sulfide, we carried out the reaction of 2′-bromoacetanilide (**3**) with a very inexpensive and odorless 2-ethylhexyl 3-mercaptopropionate as a thiol surrogate catalyzed by $Pd_2(dba)_3$/Xantphos to afford the corresponding sulfide **4** (Scheme 2). The resulting sulfide **4** was treated with NaOEt at room temperature to afford the corresponding sodium thiolate **5** followed by heating at reflux to form 2-methylbenzothiazole (**6**) in 82% yield via intramolecular condensation. In the meantime, thiolate **5** can be intercepted with an electrophile. For example, quenching thiolate **5** with 4-chloronitrobenzene in situ gives sulfide **6** in 80% yield via a S_NAr mechanism. Encouraged by these results, the synthesis of benzothiazoles from 2-bromobenzanilides via Pd-catalyzed C−S bond formation with thiol surrogates was further investigated.

As shown in Table 1, the various 2-bromobenzanilides could be converted into the corresponding benzothiazoles in good yields via Pd-catalyzed C−S bond formation followed by deprotection and the condensation. The yields of C−S bond formation did not depend on the substrates; however, the yields and the conditions of the intramolecular condensation depended on the substrates. The substrates possessing an electron-deficient (entries 1 and 2) or neutral (entry 3) carbonyl group of amides were rapidly cyclized under basic conditions at reflux temperature. When the amide was electron rich (entry 4), on the other hand, the yield of the condensation under basic conditions was quite low. The basic condensations of some anilides possessing electron-withdrawing groups on the benzene ring were also sluggish (entries 5 and 6). Unlike the basic conditions, the acidic conditions were more effective (shorter reaction time and higher yield). It was found that trifluoroacetic acid (TFA) was the best reagent. An intermediate for the antitumor agent,[2] 2-(3-methyl-4-nitrophenyl)benzothiazole, was obtained in 77% yield under acidic condensation (entry 1). The substrates possessing a ketone group gave the corresponding benzothiazoles in high yield (entries 3, 6, and 8). In the case of the pyridine substrate, higher reaction temperature and longer reaction time were necessary for the condensation even by using TFA (entry 7).

This new methodology was successfully applied using an unprotected secondary amine (entry 10) and an unprotected phenol (entry 11). In the case of 2-bromophenylurea, intramolecular cyclization did not proceed during the intermolecular C−S coupling reaction, and the following intramolecular cyclization took place to afford 2-hydroxybenzothiazole instead of the formation of 2-aminobenzothiazole (entry 12). Formamide was also converted into the benzo-

(9) (a) Couture, A.; Granclaudon, P. *Heterocycles* **1984**, *22*, 1383−1385. (b) Benedí, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073−6077. (c) Joyce, L. L.; Evindar, G.; Batey, R. A. *Chem. Commun.* **2004**, 446−447. (d) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802−1808.

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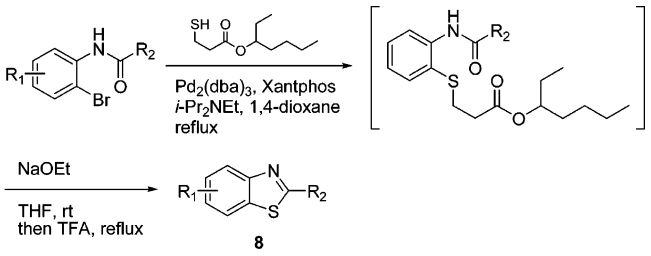
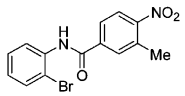
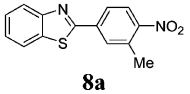
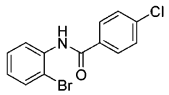
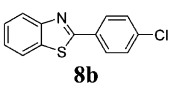
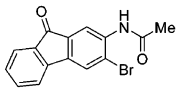
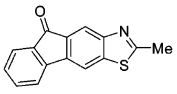
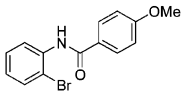
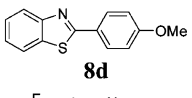
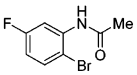
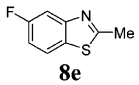
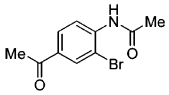
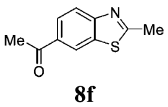
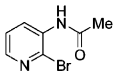
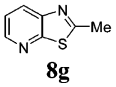
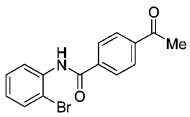
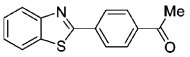
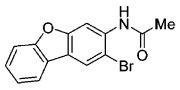
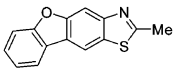
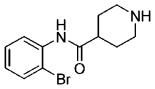
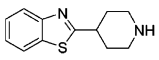
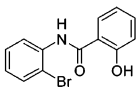
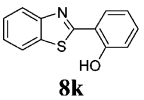
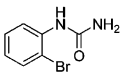
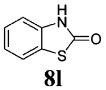
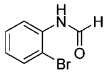
Table 1. Synthesis of Benzothiazoles



8

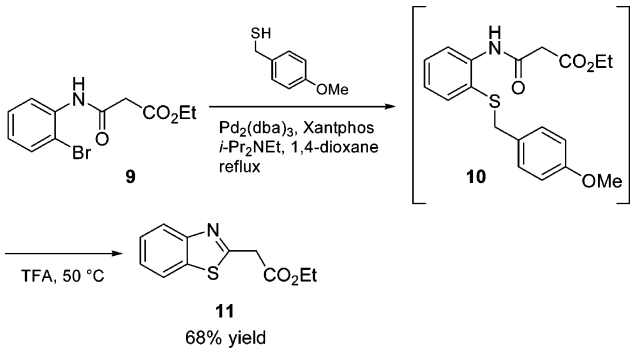
entry	substrate	product	yield (%)
1		 **8a**	77 (75)[a]
2		 **8b**	81 (83)[a]
3		 **8c**	71 (72)[a]
4		 **8d**	85 (low)[a]
5		 **8e**	75 (low)[a]
6		 **8f**	84 (low)[a]
7		 **8g**	67
8		 **8h**	83
9		 **8i**	75
10		 **8j**	80
11		 **8k**	75
12		 **8l**	58
13		 **8m**	88

[a] The condensation was conducted using NaOEt at reflux.

thiazole in high yield under the same conditions (entry 13). The resulting 2-unsubstituted benzothiazole is a versatile intermediate and can be converted to the various substituted products such as 2-amino, 2-halogen, 2-acyl, and so forth by general methodology.[15]

In the case of the reaction of a substrate which is labile for basic conditions such as NaOEt, the alternative thiol surrogate would be used. For example, the C−S bond formation of **9** with 2-ethylhexyl 3-mercaptopropionate proceeded smoothly to give the corresponding sulfide in good yield. But, when the deprotection was conducted under basic conditions using NaOEt, the complex mixture was obtained. In that case, the thiol surrogate that could be deprotected under acidic conditions should be used. The 2-bromobenzanilide **9** was reacted with a (4-methoxyphenyl)methanethiol under typical conditions to obtain the corresponding sulfide **10**. To this solution was directly added TFA to afford the benzothiazole **11** in good yield (Scheme 3).

Scheme 3. Synthesis of Labile Thiazole Using an Alternative Thiol Surrogate



In summary, we have demonstrated that the C−S bond formation of 2-bromoanilides can be catalyzed by $Pd_2(dba)_3$/Xantphos. On the basis of this observation, a novel practical synthetic method for elaborating benzothiazoles has been developed. To our knowledge, this is the first report of the use of thiol surrogates in the synthetic approach for the benzothiazole. Variation at the 2-position of the benzothiazole is possible with variation in the amido groups of the 2-bromoanilides. Therefore, this new methodology allows for the assembly of a wide range of substituted benzothiazoles.

Acknowledgment. We acknowledge Drs. M. Palucki and N. Yasuda, Merck & Co., Inc., for helpful discussions.

Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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