Enhanced Parallel Synthesis Efficiency through Tandem Pd-Catalyzed S- and N-Arylation Reactions: Single-Vessel Formation of Aminobenzothiazoles

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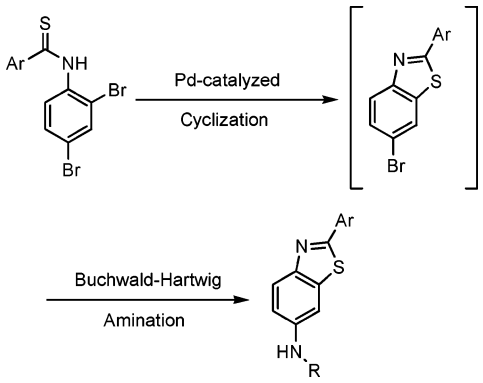
Parallel diversity-oriented synthesis of discrete molecules has become a useful technology for the rapid preparation of focused libraries. Additional handling, purification, and characterization of multiple products and reagents, however, can strain resources and delay productivity. There are several methods adopted by chemists to circumvent these issues including automated handling techniques, synthetic reactions of wide scope, and preparative schemes arranged so that the diversity steps occur late in the sequence. An additional less-explored method directed at improving the efficiency of the parallel synthesis process is the single-vessel multistep synthetic method. Two or more serial steps performed in a single vessel without isolation and purification of intermediates, as well as one time addition of reagents, can drive efficiency. To this end, we explored the combination of two known reactions: catalytic benzothiazole formation from thioamides, followed by catalytic amination of the resulting heterocycle. Both reactions involve catalysis with palladium and additional reagents and offer a purification challenge particularly when the reactions are performed sequentially and on multiple intermediates.

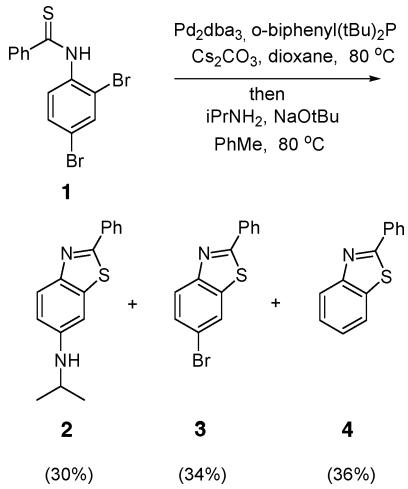
Amino-substituted benzothiazoles have found application in several areas of chemistry.[1−4] Existing methods for their preparation, however, often rely on harsh conditions, limited scope, or multistep procedures with isolation/purification of intermediates.[1,5−6] In fact, the difficulty in obtaining amino-substituted benzimidazoles may explain the paucity of these relatively simple compounds in the literature. Methodology for a mild, generalized approach to substituted benzothiazoles from inexpensive starting materials would be useful in several areas of chemistry, particularly if the method is amenable to parallel library generation.

Palladium-catalyzed cyclization of *o*-bromophenylthioamides and related starting materials has been reported before.[7,8] The palladium-catalyzed amination reaction of aryl halides is well-known and attributed to the efforts of Buchwald and Hartwig. The combination of these reactions into a single-vessel operation would substantially increase the convenience level over a serial two-step process (Scheme 1). Several reports[9] have demonstrated the utility of metal-catalyzed tandem reactions in the one-pot synthesis of polycyclic and heteroaryl compounds. Ideally, the reaction

Scheme 1. Benzothiazole Formation, Followed by Amination



Scheme 2. Stepwise Ring Closure and Amination Reaction



should have broad generality and be sufficiently robust for parallel synthesis. If successful, a one-pot benzothiazole ring closure/Buchwald−Hartwig amination would allow for the rapid elaboration of high value-added compounds from bromoaniline derivatives and require only a single purification step.

Initial attempts to execute the single-vessel reaction involved performing the ring-closure reaction first on *N*-(2,4-dibromophenyl)thiobenzamide **1**, followed by addition of the amination components to the original reaction mixture. This sequential method led to formation of the desired product **2** (30%), as well as the bromobenzothiazole intermediate **3** (34%) and its dehalogenated analog **4** (36%), as shown in Scheme 2.

We reasoned that the cyclization occurs quickly and under broader reaction conditions than the amination because of the internal nature of this initial step. If so, cyclization and amination may occur under a single set of catalytic conditions designed to promote amination. Hence, *N*-(2,4-dibromophenyl)thiobenzamide **1** was treated with isopropyl amine, cesium carbonate, sodium *tert*-butoxide, $Pd_2(dba)_3$, and *o*-biphenyl-di-*t*-butylphosphine in a 1:1 mixture of toluene and dioxane (80 °C, N_2) for 2 h. The result was formation of the desired product **2** without detection of either the bromobenzothiazole

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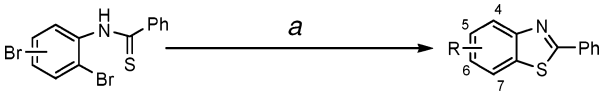
Table 1. Single-Vessel Conversion of Amines and Dibromothioamides to Aminobenzothiazoles



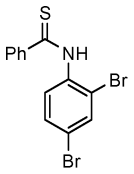
1 or **5-7** **8a-8n**

	ring position	R	yield[b] (%)
8a	4	*i*PrNH	47
8b	5	*i*PrNH	16
8c	5	*n*BuNH	50
8d	5	Et_2N	24
8e	5	BnNH	26
8f	5	$PhCH_2CH_2NH$	44
8g	5	PhNH	27
8h	6	*i*PrNH	50
8i	6	*n*BuNH	51
8j	6	Et_2N	55
8k	6	BnNH	43
8l	6	$PhCH_2CH_2NH$	47
8m	6	PhNH	27
8n	7	*i*PrNH	39

[a] Reaction conditions: Cs_2CO_3, NaO-*t*-Bu, amine, $Pd_2(dba)_3$, toluene-1,4-dioxane (1:1), 80 °C, 2 h. [b] Yields are unoptimized.

intermediate or the debrominated benzothiazole side product. The operational convenience of initial combination of all reagents, in addition to a single purification requirement, makes this reaction ideal for library generation by parallel synthesis.

To examine the scope of this reaction, three other isomeric dibromothioamide substrates (**5**−**7**) were synthesized from the corresponding dibromoanilines[10] by benzoylation, followed by treatment with Lawesson's reagent (see Supporting Information). In each case, catalytic ring closure at the *ortho* bromide was envisioned to give a regioisomeric bromobenzothiazole intermediate, allowing for amination at any of the four remaining ring positions.



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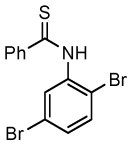

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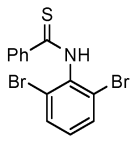

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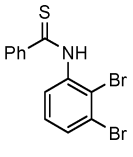

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Substrates **1** and **5**−**7** were reacted with a variety of simple amines under the conditions for single-vessel benzothiazole formation and amination (Table 1). The reactions were carried out in borosilicate vials on a heated orbital shaker block. Fourteen amino-substituted benzothiazoles (**8a**−**n**) were prepared using this method. The convenience of performing two catalytic synthetic sequences in a single vessel, followed by a single purification step, compensated for the modest yields of several products.

As shown in Table 1, the one-pot reaction can be used for placement of the amino substituent at any of the unsubstituted positions of the carbon ring of the benzothiazole. However, the success of the reactions leading to 4- or 7-subsituted benzothiazoles (entries **8a** and **n**, respectively) was limited. While **8a** and **n** were isolated in a straightforward manner, the reaction of other amines with substrates **6** and **7** led to poor conversion to products, based on LC-MS analysis of the reaction mixtures. In contrast, the 5- or 6-substituted benzothiazoles (entries **8b**−**m**) were successfully isolated from the reaction mixtures without exception.

In summary, a one-pot transformation of dibromothioamides to amino-substituted benzothiazoles has been developed using a tandem palladium-catalyzed S- and N-arylation reaction. The immediate combination of all reagents at the outset of the reaction is preferable to stepwise addition in terms of product conversion, operational simplicity, and purification requirements. The procedure outlined here should ease the difficulties associated with the preparation of aminobenzothiazoles particularly in a parallel synthesis setting.

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Supporting Information Available. Experimental details and ^1H and ^{13}C spectra for compounds **8a**−**n** and substrates **1** and **5**−**7** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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