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Synthesis of 2-substituted-benzothiazoles by palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas and *o*-bromophenylthioamides

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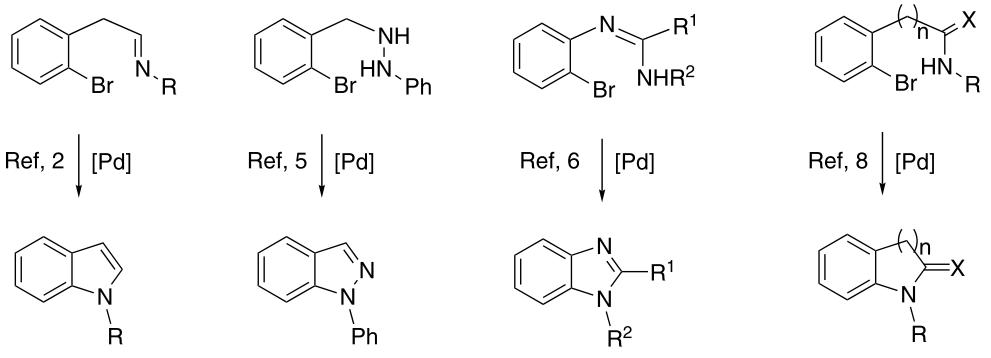
Abstract—2-Amino-, and 2-alkyl-benzothiazoles have been efficiently prepared by palladium catalyzed cyclization of *o*-bromophenylthioureas and *o*-bromophenylthiamides. Results were best with the $Pd_2(dba)_3$/monophosphine catalytic system.

Palladium-catalyzed aryl–nitrogen bond forming reactions[1] are highly useful for synthesizing arylamines and have found numerous applications in organic synthesis. Intramolecular palladium-catalyzed *N*-arylation reactions of aryl halides have been used to prepare indoles,[2] oxoindoles,[3] 2-aryl-2*H*-indazoles,[4] 1-aryl-1*H*-indazoles,[5] imidazoles,[6] oxazepines and thiazepines,[7] indolines,[8] and other heterocycles[9] (Scheme 1).

In contrast, there are fewer studies on the corresponding palladium-catalyzed aryl–sulfur bond formation. The direct nucleophilic substitution of inactivated aryl halides with thiolates requires very drastic conditions, (polar solvents and temperatures often over 150°C).[10] The use of palladium for synthesizing arylthioether was first reported by Murahashi[11] and Migita,[12] and Hartwig[13] subsequently studied the mechanism of the reaction and increased the synthetic scope.[14] General methods for synthesizing arylthioethers starting from aryltriflates,[15] aryliodides,[16] arylbromides[17] and arylchlorides[18] have recently been reported. The synthesis of bispyrimidine thioethers[19] and the use of aryl thiocyanates as starting material[20] have also been reported. Recently, copper catalysts have been shown to be efficient in the synthesis of arylthioethers.[21]



Scheme 1.

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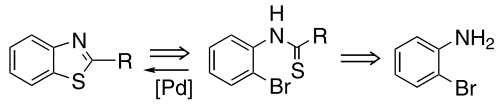


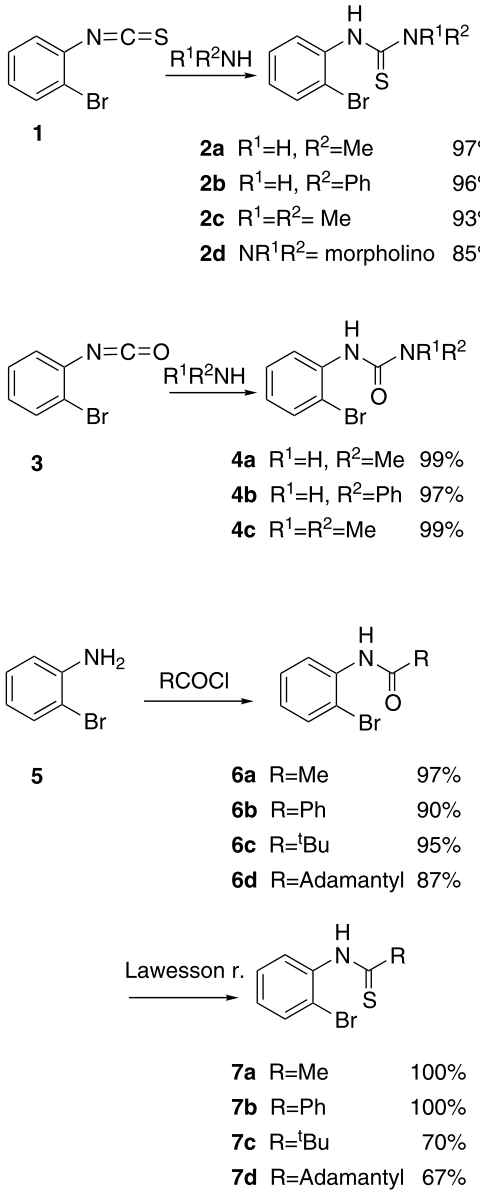
Scheme 2.

The above-mentioned procedures for synthesizing heterocycles by creating carbon–nitrogen and carbon–sulfur bonds usually involve simple amino and thiol functionalities. We hypothesize that a thiocarbonyl group is nucleophilic enough to be used in the reaction (Scheme 2). Here we report a new procedure for synthesizing benzothiazole derivatives[22] by a palladium-catalyzed intramolecular cyclization of *o*-bromoarylthioureas and *o*-bromoarylthioamides.

Thioureas **2a**–**d**[23] were easily prepared in excellent yields from *o*-bromophenylisothiocyanate (**1**) by reaction with methylamine, aniline, dimethylamine and morpholine, respectively (Scheme 3). Amides **6a**–**d** were prepared from *o*-bromoaniline (**5**) by reaction with acyl chlorides, and were then efficiently transformed into the corresponding thioamides **7a**–**d** by reaction with the Lawesson reagent. For the sake of comparison, we also prepared ureas **4a**,**c** by reacting *o*-bromophenylisocyanate (**3**)[24] with methylamine, aniline, and dimethylamine.

We studied the effect of the ligand on the reaction starting from the thiourea **2a** and using Pd_2dba_3 as palladium precursor. The diphosphine dppf has been used efficiently in several palladium catalyzed aminations.[25] When the reaction was performed in dioxane with Pd_2dba_3/dppf and K*t*-BuO as the base we obtained 87% of the benzothiazole **8a** (entry 1, Table 1).[26] We tried the monophosphine *o*-biphenylP(*t*-Bu)$_2$[27] (entry 2) and it also provided a very active catalytic system, which afforded the benzothiazole in very high yield. The synthesis of benzothiazole from *o*-bromophenylthioureas by nucleophilic substitution has been reported, although it requires very drastic conditions.[28] In order to discard the substitution reaction we carried out the reaction in the standard conditions and in the absence of the palladium catalytic system, and we recovered the starting material unaltered, proving that the palladium catalyst is necessary to drive the reaction (entry 3).

Unexpectedly, the thiourea **2b** did not give the benzothiazole derivative: rather mass spectrometry and ^{1}H NMR identified compound **9** as the main product (entries 4 and 5). Since isothiocyanate, *o*-bromoisothiocyanate, aniline, and *o*-bromoaniline were also identified in the reaction mixture, we believe that the initial reaction involves the nitrogen and that the imidazolone obtained reacts further with the isothiocyanate present in the medium. In fact, the compound is also formed in the absence of catalyst (entry 6), at lower temperatures and in the presence of other bases.

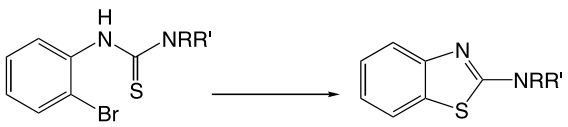


Scheme 3.

Then we explored the reaction of urea **2c**, which has a disubstituted amine. In this case, the use of dppf gave a very low yield (entry 7), although it was improved by using Cs_2CO_3 as base (entry 8). However, the monophosphine *o*-biphenylP(*t*-Bu)$_3$ provided excellent yields of the benzothiazole **8c** (entry 9). We also tried the monophosphines P(*t*-Bu)$_3$[29] and *n*-BuPAd$_2$[30] which also gave excellent yields at shorter reaction times (entries 10 and 11).

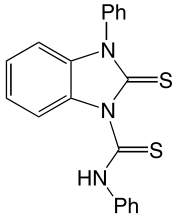
The morpholino derivative **2d** was cyclized by using Pd/*o*-biphenylP(*t*-Bu)$_3$ to give the benzothiazole **8d** but in this case the yield was moderate (entry 12).

Table 1. Cyclization reaction of 2-bromophenylthioureas **2a–d** catalyzed by Pd_2dba_3/ligand[a] (see Ref. 31)



2a R= H, R'=Me
2b R= H, R'= Ph
2c R=R'= Me
2d R=R'= morpholino

8a R= H, R'=Me
8b R= H, R'= Ph
8c R=R'= Me
8d R=R'= morpholino



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Entry	Substrate	Ligand	Base	Time (h)	Product	Yield (%)[b]
1	**2a**	dppf	K*t*-BuO	18	**8a**	87
2	**2a**	*o*-BiphenylP(*t*-Bu)$_2$	K*t*-BuO	18	**8a**	88
3	**2a**	–[c]	K*t*-BuO	18	–	–
4	**2b**	dppf	K*t*-BuO	18	**9**	100[d]
5	**2b**	*o*-BiphenylP(*t*-Bu)$_2$	K*t*-BuO	18	**9**	100[d]
6	**2b**	–[c]	K*t*-BuO	18	**9**	34[d]
7	**2c**	dppf	K*t*-BuO	18	**8c**	17
8	**2c**	dppf	Cs_2CO_3	18	**8c**	52
9	**2c**	*o*-BiphenylP(*t*-Bu)$_2$	Cs_2CO_3	18	**8c**	90
10	**2c**	P(*t*-Bu)$_3$	Cs_2CO_3	2	**8c**	92
11	**2c**	*n*-BuPAd$_2$	Cs_2CO_3	1	**8c**	97
12	**2d**	*o*-BiphenylP(*t*-Bu)$_2$	K*t*-BuO	18	**8d**	55

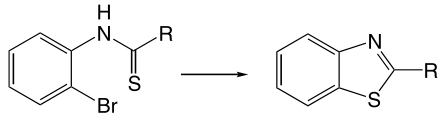
[a] *Conditions*: Substrate (1 mmol), dioxane (4 ml), Pd_2dba_3 (0.05 mmol), ligand (0.055 mmol), base (1.5 mmol), temperature 80°C.
[b] Isolated yield.
[c] In the absence of Pd_2dba_3.
[d] Conversion, yield not determined.

Afterwards, we explored the synthesis of 2-alkylbenzothiazole derivatives by palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas (Table 2). We selected Pd_2dba_3/*o*-biphenylP(*t*-Bu)$_3$ as the catalytic system, using Cs_2CO_3 as the base and dioxane as the solvent. In order to test the efficiency of the procedure we selected both simple thioamide derivatives, such as **7a** and **6b**, and the more hindered **7c** and **7d**. Yields were good to excellent in all cases, and the formation of *tert*-butyl and adamantyl derivatives **10c–d** (entries 3 and 4, Table 2), and benzothiazole **10b** are especially remarkable (entry 2).

In order to check the scope of the reaction, we also explored the reaction of the amide **6a** and ureas **4a**,**c** in the conditions previously optimized. No reaction was observed in the case of amide **6a**, but the behavior of ureas **4a** and **4b** was more interesting: cyclization involved the nitrogen to give corresponding benzoimidazolones **11a**,**b**. Results were best when diphosphines were used (Table 3), whilst monophosphines provided very low conversions. The dimethylamino derivative **4c** did not react even in drastic conditions. These results are in agreement with those previously reported by Buchwald.[8]

In conclusion, the palladium-catalyzed intramolecular cyclization of *o*-bromophenylthioureas and *o*-bromophenylthioamides is a direct and efficient procedure for synthesizing 2-substituted benzothiazoles. Highly hindered alkyl monophosphines proved to be the most efficient ligands.

Table 2. Cyclization reaction of 2-bromophenylthioamide **7a–d** catalyzed by Pd_2dba_3/*o*-biphenylP(*t*-Bu)$_2$[a]



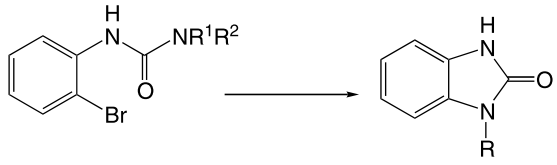
7a R= Me
7b R= Ph
7c R= ^{t}Bu
7d R= adamantyl

10a R= Me
10b R= Ph
10c R= ^{t}Bu
10d R= adamantyl

Entry	Substrate	Product	Yield (%)[b]
1	**7a**	**10a**	77
2	**7b**	**10b**	100
3	**7c**	**10c**	88
4	**7d**	**10d**	68

[a] Conditions: Substrate (1 mmol), dioxane (4 ml), Pd_2dba_3 (0.05 mmol), *o*-biphenylP(*t*-Bu)$_2$ (0.055 mmol), Cs_2CO_3 (1.5 mmol), temperature 80°C, time 18 h.
[b] Isolated yield.

Table 3. Cyclization reaction of **4a**,**c** catalyzed by palladium[a]



4a R^1=H, R^2=Me **11a** R=Me
4b R^1=H, R^2=Ph **11b** R=Ph
4c R^1=R^2=Me **11c** R=Me

Entry	Substrate	Product	Yield (%)[b]
1	**4a**	**11a**	70
2	**4b**	**11b**	32
3	**4c**	**11c**	0

[a] Conditions: Substrate (1 mmol), dioxane (4 ml), Pd_2dba_3 (0.05 mmol), dppf (0.055 mmol), K*t*-BuO (1.5 mmol), temperature 80°C, time 18 h.
[b] Isolated yield

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31. *General procedure*: To a solution of 2-bromophenylisocyanate (1 mmol) in anhydrous dioxane (3.5 ml) under argon, $Pd_2(dba)_3$ (0.05 mmol), dppf (0.075 mol), and KO^{t}Bu or Cs_2CO_3 (1.5 mmol) were added. The resulting solution was heated to 80°C until the starting material had disappeared. The reaction mixture was then cooled, filtered over Celite, evaporated to dryness and purified by column chromatography.