# A Novel Intramolecular Palladium-Mediated Cyclization for the Synthesis of Substituted 2-(Aryl- or Benzylamino)-4*H*-1,3-Benzothiazines

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**Abstract:** Synthesis of 2-aryl/benzylamino 4*H*-1,3-benzothiazine derivatives was achieved via an unprecedented intramolecular palladium cyclization for creating a sulfur–aryl bond.

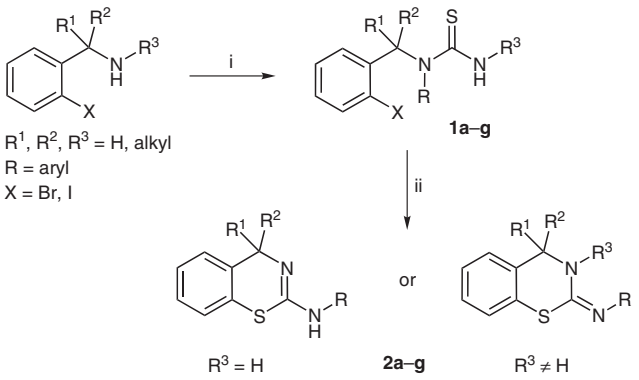
**Key words:** palladium, sulfur, heterocycles, ring closure, catalysis

For one of our research programs, an efficient synthesis of unknown 2-(α,α′-arylamino)-4*H*-1,3-benzothiazine derivatives was needed. A literature survey of 2-substitued amino-4*H*-1,3-benzothiazine systems showed only very limited reported examples and none of them with 2-(arylamino) substituents. Recently, synthetic access of 2-dialkylamino-4*H*-1,3-benzothiazines, via a benzyne intermediate, was reported by Sathunuru and co-workers.[2] Nevertheless, this approach did not appear suitable for our synthesis of 2-(arylamino) derivatives, especially in terms of the potential scaffold's functionalization/substitution. In this communication, we would like to report a new and efficient synthesis of 2-(aryl- and benzylamino)-4*H*-1,3-benzothiazine derivatives allowing general substitution patterns. For this synthesis, an unprecedented intramolecular palladium cyclization creating a sulfur–aryl bond was developed.

The key step of our new synthetic approach was based on a palladium-mediated intramolecular cyclization between an *o*-iodo/bromo aryl and a thiourea. The intermediate thiourea is obtained from the condensation of an *o*-halo-substituted benzylic amine and an aryl/benzylisothiocyanate.

Our hypothesis was that under basic conditions the isothiourea tautomer would be present and be able to achieve intramolecular cyclization under palladium catalysis.

Formation of S–aryl bonds using standard palladium coupling procedures between various thiols and iodo aryl derivatives has been described.[3] In addition, Takagi and coworkers showed that alkylthioamides were able to react under Pd(0) conditions with *o*-iodoanilines to form 2-alkylbenzothiazoles via the formation of a sulfur–aryl bond before cyclization.[4] The same author showed as well that sulfur–aryl bond could be formed between thiourea and iodaryls but this time under nickel catalysis.[5]




**Scheme 1** 2-(Arylamino)benzothiazine synthesis. *Reagents and conditions*: i) RNCS, $Et_3N$, dioxane, r.t., 8 h; ii) $Pd(PPh_3)_4$ (10% mol), $Ph_3P$ (10% mol), $Et_3N$ or DBU (2 equiv), dioxane, reflux.

To test the cyclization process, 1-(2-bromobenzyl)-3-phenyl-thiourea (**1a**) and 1-(2-iodobenzyl)-3-phenyl-thiourea (**1a′**) were prepared by condensation of the corresponding *o*-halobenzylamine and phenylisothiocyanate. These intermediates were then submitted to a standard palladium protocol using 10% mol of $Pd(PPh_3)_4$ in the presence of triethylamine in refluxing dioxane, and the reaction was monitored by LC-MS. (Scheme 1)

When **1a** was used, the benzothiazine adduct **2a** was obtained in a modest 16% isolated yield after 16 hours of reaction whereas with **1a′**, the yield was increased to 55% and the reaction was complete in only 40 minutes. By adding, 10 mol% of triphenylphosphine as a ligand, the yield of benzothiazine was increased up to 67%.[6] From this small pilot screen, several conclusions could be made: a) standard palladium chemistry is able to afford 2-(aminophenyl)-4*H*-1,3-benzothiazine, b) iodine substitution proved essential to ensure a fast and efficient conversion, and c) addition of a co-ligand is improving the chemical yield. It is noteworthy to mention that when applying the nickel catalysis reported by Takagi, no adduct formation was detected.

To establish the scope and limitations of this new reaction with regards to steric hindrance, a selection of 2-(arylamino)-4*H*-1,3-benzothiazine was prepared by combination of *o*-iodobenzylamines and α,α′-arylisocyanates as reported in Table 1.

When this new intramolecular cyclization was applied to α,α′-arylthiourea (**1b** and **1c**), steric hindrance was not detrimental to the reaction, and the benzothiazine deriva-

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**Table 1** Synthesis of 2-(Arylamino)-4*H*-1,3-benzothiazines

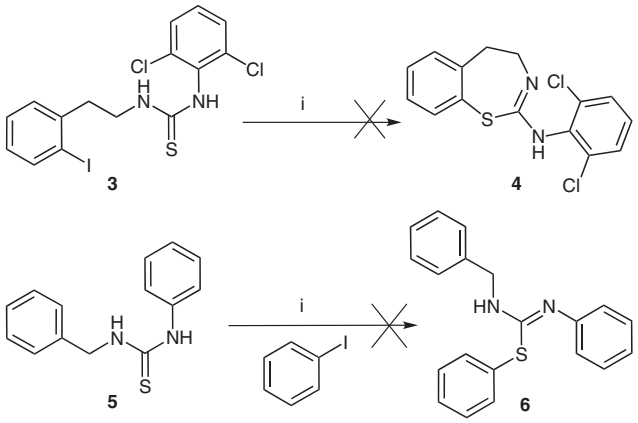
| Entry | Starting thiourea | R | $R^1$, $R^2$ | $R^3$ | X | Benzothiazine adduct[a] | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Ph | H, H | H | Br | **2a** | 16 |
| 2 | **1a′** | Ph | H, H | H | I | **2a** | 67 |
| 3 | **1b** | 2,6-$MeC_6H_3$ | H, H | H | I | **2b** | 75 |
| 4 | **1c** | 2,6-$ClC_6H_3$ | H, H | H | I | **2c** | 63 |
| 5 | **1d** | 2,6-$MeC_6H_3$ | H, Et | H | I | **2d** | 86 |
| 6 | **1e** | 2,6-$ClC_6H_3$ | Me, Me | H | I | **2e** | 32 |
| 7 | **1f** | 2,6-$MeC_6H_3$ | H, H | Me | I | **2f** | 83 |
| 8 | **1g** | 2,6-Cl-4-F-$C_6H_2$ | H, Et | Me | I | **2g** | 63 |

[a] Reaction carried out analogously to the example synthesis reported in ref. 5 except that $Et_3N$ was replaced by DBU for entries 3–8.
[b] Isolated yield.

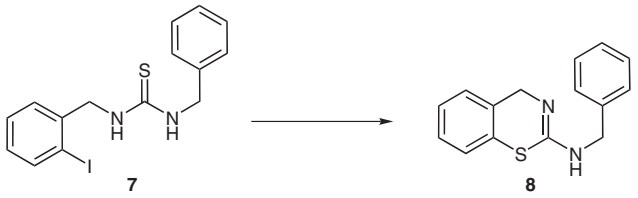
tives **2b** and **2c** were isolated in good yields. Compared to our initial test conditions, the base was switched from triethylamine to DBU which led to better yields. Monosubstitution of the benzylic position (**1d**) was still tolerated but for the *gem*-dimethyl derivative (**1e**) a decreased yield was observed. Interestingly, when a secondary amine (**1f**) was used instead of a primary benzylamine, the cyclization was still very efficient. By combining benzylic and nitrogen susbsituents (**1g**), a highly substituted benzothiazine **2g** was synthesized in a 63% yield.

To further extend the possible scope of this new reaction, cyclization to a seven-membered ring and an intermolecular S–aryl bond formation between a thiourea and iodobenzene were examined under our standard protocol (Scheme 2). In both cases, adducts **4** or **6** were not observed.

After showing that *N*-benzyl-*N*′-arylthioureas were good substrates for intramolecular cyclization, we turned our attention to *N*-benzyl-*N*′-benzyl derivatives (Scheme 3). The first attempt to cyclize *o*-iodo-*N*-benzylthiourea **7** un-



**Scheme 2** Unsuccessful cyclization/addition when using i) $Pd(PPh_3)_4$ (10 mol%), $Ph_3P$ (10 mol%), DBU (2.5 equiv) in dioxane (90 °C).



**Scheme 3** Synthesis of *N*-benzylbenzothiazine **8**. *Reagents and conditions*: palladium catalyst, ligand, DBU (2 equiv), dioxane, reflux (cf. Table 2 for catalyst/ligand charge).

**Table 2** Screening Conditions for the Synthesis of **8**

| Entry | Base | Catalyst (mol%) | Ligand (mol%) | Conversion at 1 h (%)[a] | 16 h (%)[a] |
|---|---|---|---|---|---|
| 1 | $Et_3N$ | $Pd(PPh_3)_4$ (25) | – | 94 | |
| 2 | DBU | $Pd(PPh_3)_4$ (25) | – | 100 | |
| 3 | DBU | $Pd(PPh_3)_4$ (10) | – | 95 | |
| 4 | DBU | $Pd(PPh_3)_4$ (5) | – | 5 | |
| 5 | DBU | $Pd(PPh_3)_2Cl_2$ (10) | – | 5 | |
| 6 | DBU | $Pd(dppf)_2Cl_2$ (10) | – | 45 | |
| 7 | DBU | $Pd_2(dba)_3$ (10) | – | 12 | |
| 8 | DBU | $Pd(OAc)_2$ (10) | – | 35 | |
| 9 | DBU | $Pd(OAc)_2$ (10) | $PPh_3$ (25) | 13 | |
| 10 | DBU | $Pd(OAc)_2$ (10) | dppf (25) | 100 | |
| 11 | DBU | $Pd(OAc)_2$ (5) | dppf (2.5) | 0 | |
| 12 | DBU | $Pd(OAc)_2$ (5) | dppf (5) | 12 | 13 |
| 13 | DBU | $Pd(OAc)_2$ (10) | dppf (5) | 20 | 40 |
| 14 | DBU | $Pd(OAc)_2$ (10) | dppf (10) | 46 | 100 |

[a] Percentage of conversion of **7** to **8** by LC-MS at 254 nm based on peak areas.

der the previously described conditions [$Pd(PPh_3)_4$ (0.1 equiv), $Et_3N$ (2 equiv), dioxane, reflux) afforded **8**[7] in a low isolated yield (10%).

So, we decided to investigate this reaction by looking at the catalyst/ligand source and the base. The reactions were run in screw-capped tubes[8] at 80 °C in dioxane and analyzed by LC-MS after one hour and 16 hours (Table 2).

The lowest amount of catalyst needed was determined to be 10 mol% (entry 3). With 5 mol% no reaction took place. The best reaction conditions were found to be 10 mol% $Pd(OAc)_2$ and 25 mol% dppf [1-1′-bis(diphenylphosphinino)ferrocene)] (entry 10). The ligand was crucial for the reaction rate. When $Ph_3P$ was used instead of dppf (entry 9), only 13% of conversion was observed after one hour. Finally, after refinement of catalyst/ligand charge, the optimal conditions were found when using 10 mol% of $Pd(OAc)_2$ with 10 mol% of dppf.

The reaction was run on a gram scale at 0.25 M in an open vessel with the above-mentioned conditions found during the screening. After 30 hours, only 40% conversion was observed. Concentration turned out to be a crucial factor for this type of cyclization as well as high energy required. Indeed, when we switched from an open vessel to the screw-capped vessel system we used during the screening, the cyclization run (at 0.25 M) was completed after 24 hours, and the cyclized material was obtained in an improved isolated yield of 45%. This result showed that this particular type of cyclization needs some high energy accessible by increasing the pressure. Finally, by running the reaction at 0.5 M (still in screw-capped vessels), the conversion was complete in less than two hours with an isolated yield of 72%.[9] When the optimized conditions for the synthesis of 2-benzylamino benzothiazines was applied back to the synthesis of 2-(arylamino) derivatives, the compounds were obtained only in low yields.

In conclusion, a new, simple, and efficient synthetic access to aryl- and benzylamino-substituted 4*H*-1,3-benzothiazines has been developed, allowing a wide range of possible diversification points. This new synthesis was realized through an unprecedented palladium coupling reaction for the generation of an S–aryl bond.

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(6) **Synthesis of 2a**
To a mixture of 1-(2-iodobenzyl)-3-phenylthiourea (**1a′**, 500 mg, 1.4 mmol) and $Et_3N$ (0.38 mL, 2 equiv) in dioxane (20 mL), $Ph_3P$ (158 mg, 0.1 equiv), and $Pd(PPh_3)_4$ (36 mg, 0.1 equiv) were added under argon. The resulting mixture was refluxed for 40 min. The solvent was removed in vacuo, and the crude was partitioned between EtOAc and sat. $NaHCO_3$ soln. The organic phase was separated, washed with sat. $NH_4Cl$, dried over $Na_2SO_4$, and concentrated in vacuo to afford a crude brown oil (520 mg). The crude material was purified by flash chromatography on $SiO_2$ using hexanes–EtOAc (100:0 to 60:40) as solvent system. From the purification, **2** (220 mg, 67.4% yield) was isolated as a light yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.00–7.50 (m, 9 H), 4.52 (s, 2 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 152.6, 149.2, 134.6, 131.7, 129.7, 128.1, 127.7, 127.6, 127.4, 123.7, 120.6, 53.1. IR (solution in $CH_2Cl_2$): 3418, 3054, 1638, 1590, 1518, 1498, 1437, 1311, 1252, 1031, 1025 $cm^{-1}$. HRMS: *m/z* calcd for $C_{14}H_{12}N_2S$: 241.07940 [M + $H^+$]; found : 241.07935 [M + $H^+$].

(7) Klatsmanyi-Gabor, P.; Meisel, T.; Erdey, L. *Acta Chim. Acad. Sci. Hung.* **1964**, *40*, 99.

(8) A 40 mL clear vial, screw top hole cap with PTFE/silicone septa form SUPELCO (ref 27180).

(9) **Synthesis of 8**
In a screw-capped vial, to a suspension of 1-benzyl-3-(2-iodobenzyl)-thiourea (**7**, 945 mg, 2.5 mmol) and DBU (0.76 mL, 2 equiv) in dioxane (5 mL), dppf (141 mg, 0.1 equiv), and $Pd(OAc)_2$ (57 mg, 0.1 equiv) were added under argon. The resulting mixture was stirred at 80 °C for 2 h. The solvent was removed in vacuo, and the crude material was purified by flash chromatography on $SiO_2$ using hexanes–EtOAc (70:30) as solvent system. The fractions containing the product were concentrated in vacuo to afford 570 mg of a light yellow solid. This solid was sonicated in hexanes and the resulting precipitate was filtered off, washed with hexanes, and after high-vacuum drying, **8** (452 mg, 71.9% yield) was isolated as a white powder. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 7.41 (br m, 1 H, NH), 7.15–7.36 (m, 9 H), 4.36 (d, *J* = 4.8, 2 H), 4.27 (s, 2 H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 154.9, 139.0, 135.5, 131.8, 129.3, 128.6, 128.2, 127.8, 127.6, 127.5, 127.4, 54.3, 48.3. IR (solution in $CH_2Cl_2$): 3427, 3034, 1633, 1483, 1468, 1251, 1205, 1192, 1129, 1066 $cm^{-1}$. HRMS: *m/z* calcd for $C_{15}H_{14}N_2S$: 255.09505 [M + $H^+$]; found: 255.09503 [M + $H^+$].