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Palladium-catalyzed tandem synthesis of 2-aminobenzothiazoles starting from unreactive 2-chloroanilines

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Palladium-catalyzed tandem synthesis of 2-aminobenzothiazoles starting from unreactive 2-chloroanilines

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A simple and efficient protocol for the synthesis of 2-aminobenzothiazole derivatives is described. 2-Chloroanilines were treated with thiocarbamoyl chloride in the presence of $Pd(dba)_2$ and *t*-BuOK to afford the corresponding 2-aminobenzothiazoles in good to excellent yield *via* a tandem manner.

Heterocycles, that most ubiqutious structural motifs, are existing in natural products and therapeuticals[1-3]. Benzothiazole is an important constituent of various drugs and shows fundamental potential application in the development of novel therapeutics[4-5]. For example, riluzole (**a**) is used as treatment of armyotrophic lateral serotonin[6], R116010 (**b**) exhibits as an anticancer drug[7] and 2-aminobenzothiazole (**c**) acts as anti-HIV agent[8] **(Fig. 1)**.

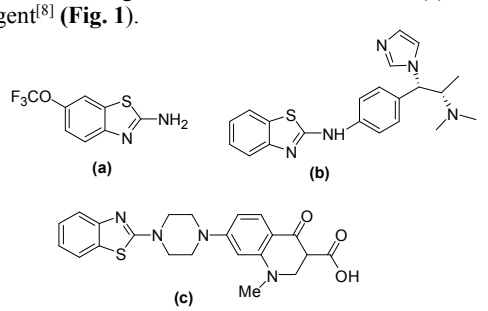
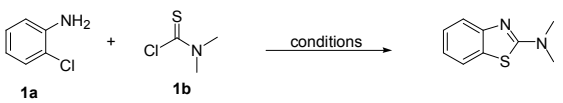


Fig. 1 Examples of bioactive 2-aminobenzothiazoles

The development of efficient methods for the synthesis of benzothiazoles has received considerable attention. Over the last few decades, a wide range of synthetic methods have been developed giving access to benzothiazoles bearing various functionalities. Among the synthetic strategies, a series of transition metal catalyzed reaction were explored to construct benzothiazoles such as Pd[10], Cu[11], Fe[12] and Ag[13]. To the best of our knowledge, there are few reports for the synthesis of benzothiazoles using 2-chloroanilines as starting materials due to the low reactivity of the C-Cl bond, and the reported methods suffer from either long reaction time or low yield[14]. Herein, we present a facile and efficient protocol for the synthesis of 2-aminobenzothiazoles utilizing functionalized 2-chloroanilines in the presence of palladium catalyst.

For our initial studies, 2-chloroanilne (**1a**) and dimethylthiocarbamoyl chloride (**1b**) were investigated under various conditions (**Table 1**). For the catalyst screening, $Fe(OAc)_3$, $NiCl_2$, CuBr, $Cu(OTf)_2$, $PdCl_2$, $Pd(OAc)_2$, and $PdBr_2$ were tested, but they let to no product formation (**Table 1**, **entries 1-7**). Gratifyingly other catalysts, such as $Pd(PPh_3)_4$ and $Pd(dba)_2$, provided the desired product in good yields **(entries 8-9**). The effect of additive was further evaluated (**entries 10-14**), and the results indicated that *t*-BuOK is superior than other bases. Solvents, temperature and the base quantity were further investigated. The transform was conducted in various solvents (DMAC, DMF, DMSO, toluene and acetonitrile) but afforded the 2-aminobenzothiazole in poor to moderate yield (**entries 15-19**). When the reaction was operated under 40 °C or room temperature, it led to poor reactivity (**entries 20-21**). The excess of *t*-BuOK was proved crucial for full conversion. When one or two equivalent of base was used giving lower yield or no product formation (**entry 22-23**).

Table 1. Screening reaction conditions for 2-chloroaniline and dimethylthiocarbamoyl chloride[a].



1a 1b

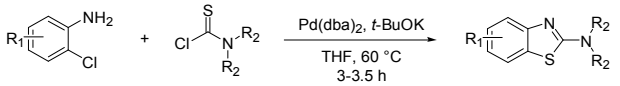
Entry	Catalyst	Base (equiv)	Solvent	Temp (°C)	Yield[b] (%)
1	$Fe(OAc)_3$	*t*-BuOK (3.0)	THF	60	-
2	$NiCl_2$	*t*-BuOK (3.0)	THF	60	-
3	CuBr	*t*-BuOK (3.0)	THF	60	-
4	$Cu(OTf)_2$	*t*-BuOK (3.0)	THF	60	-
5	$PdCl_2$	*t*-BuOK (3.0)	THF	60	-
6	$Pd(OAc)_2$	*t*-BuOK (3.0)	THF	60	-
7	$PdBr_2$	*t*-BuOK (3.0)	THF	60	-
8	$Pd(PPh_3)_4$	*t*-BuOK (3.0)	THF	60	83
9	$Pd(dba)_2$	*t*-BuOK (3.0)	THF	60	91
10	$Pd(dba)_2$	NaH (3.0)	THF	60	62
11	$Pd(dba)_2$	K_2CO_3(3.0)	THF	60	54
12	$Pd(dba)_2$	NEt_3 (3.0)	THF	60	31
13	$Pd(dba)_2$	Cs_2CO_3 (3.0)	THF	60	73
14	$Pd(dba)_2$	CH_3ONa (3.0)	THF	60	67
15	$Pd(dba)_2$	*t*-BuOK (3.0)	DMAC	60	19
16	$Pd(dba)_2$	*t*-BuOK (3.0)	DMF	60	25
17	$Pd(dba)_2$	*t*-BuOK (3.0)	DMSO	60	53
18	$Pd(dba)_2$	*t*-BuOK (3.0)	$PhCH_3$	60	65
19	$Pd(dba)_2$	*t*-BuOK (3.0)	CH_3CN	60	-
20	$Pd(dba)_2$	*t*-BuOK (3.0)	THF	40	69
21	$Pd(dba)_2$	*t*-BuOK (3.0)	THF	rt	-
22	$Pd(dba)_2$	*t*-BuOK (2.0)	THF	60	51
23	$Pd(dba)_2$	*t*-BuOK (1.0)	THF	60	-

[a] Reaction conditions: 1a (1.0 mmol), 2a (1.2 mmol), [Cat.] (5 mmol%) solvent (3.0 mL) for 3.5 h; [b] Isolated yield.

Under optimal conditions, various functionalized 2-chloroaniline derivatives and thiocarbamoyl chloride were converted to desired benzothiazoles as shown in **Table 2**. 2-Chloroanilines bearing a substitution at the 4-position tended to cyclize well with dimethylthiocarbamoyl chloride (**1b**) in 71-

90% yield (**entry 2-5**). When 5-substituted 2-chloroanilines were used, palladium mediated benzothiazole formation providing desired product **6c-8c** in 58-92% yield (**entry 6-8**). Subsequently, the thiocarbamoyl chloride **2b** was examined under the same condition and afforded corrsponding product **9c** and **10c** in 84% and 82% yield, respectively.

Table 2. Palladium-catalyzed synthesis of substituted 2-aminobenzothiazoles[a].



Entry	2-Chloroaniline	Thiocarbamoyl chloride	Product	Yield[b] (%)
1	**1a**	**1b**	**1c**	91
2	**2a**	**1b**	**2c**	80
3	**3a**	**1b**	**3c**	90
4	**4a**	**1b**	**4c**	86
5	**5a**	**1b**	**5c**	71
6	**6a**	**1b**	**6c**	92
7	**7a**	**1b**	**7c**	58
8	**8a**	**1b**	**8c**	81
9	**1a**	**2b**	**9c**	84
10	**3a**	**2b**	**10c**	82

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.5 mmol), $Pd(dba)_2$ (5 mol%), *t*-BuOK (3.0 mmol), and THF (3 mL) at 60 °C; [b] Isolated yield.

As for the reaction mechanism, a tandem pathway is proposed. The first step is the base-promoted formation of aryl thioureas, the second one is the palladiun-catalyzed intra-molecular cross-coupling reaction which let the arylthioureas afford the 2-aminobenzothiazoles smoothly.

In conclusion, we present a useful protocol for the preparation of various substituted 2-aminobenzothiazoles starting from cheap 2-chloroaniline derivatives and thiocarbamoyl chloride. The broad substrate scope, short reaction time, mild react condition and good to excellent yield make this approach attractive. Further investigation on the synthesis of various heterocyclic compounds is under research in our laboratory.

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