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Direct Preparation of 2-Benzothiazolylzinc Bromide and its Applications: A Facile Synthetic Route to the Preparation of 2-Substituted Benzothiazole Derivatives

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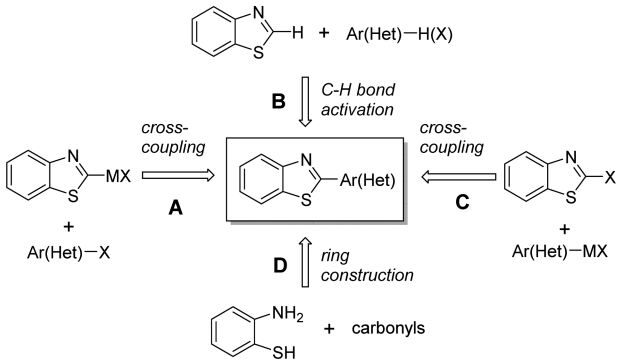
The benzothiazole moiety has been found in a variety of natural products and pharmaceuticals and demonstrates efficient biological activities.[1] Specifically, 2-substituted benzothiazole derivatives have attracted considerable attention in a wide spectrum of chemical applications due to their unique structural properties.[2] Therefore, the diversity of synthetic protocols has been an extensively discussed topic among scientists involved in organic synthesis for the past decades. In general, to build up the 2-substituted benzothiazole complexes, the strategic tools can be categorized as shown in Scheme 1: cross-coupling of benzothiazolylmetallic complexes (method **A**), coupling reaction of benzothiazole via direct oxidative C-H activation (method **B**),[3] cross-coupling of organometallic with halobenzothiazole (method **C**),[4] and ring-construction of N and S-containing compounds with the appropriate substrates (method **D**).[5]

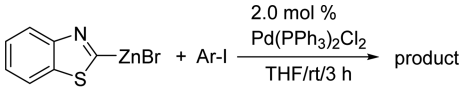
Among these tools, methods **B** and **D** have been extensively explored. In contrast, in spite of the effectiveness and efficiency of the transition metal-containing organometallic complexes, methods **A** and **C** are relatively undeveloped. Interestingly, there is no report of synthesis utilizing method **A**, likely owing to the difficulty of preparing the corresponding organometallic reagents. In our continuing study on the application of organozinc reagents, we found that stable 2-benzothiazolylzinc bromide (**I**) was easily prepared by the direct insertion of highly active zinc[6] into 2-bromobenzothiazole. The subsequent coupling reactions of the resulting organozinc reagent with several different types of electrophiles yielded the desired products in a moderate yield. To the best of our knowledge, this is the first general example of the direct preparation of 2-benzothiazolylzinc bromide and the subsequent transition metal-catalyzed cross-coupling reactions to generate 2-substituted benzothiazole derivatives.

The new organozinc reagent (**I**) was efficiently prepared by the reaction of active zinc[6] with 2-bromobenzothiazole at room temperature in THF. The oxidative addition of active zinc (1.5 equiv used) was completed in 3 h at room temperature. This organozinc reagent has been found to be very effective for cross-coupling reactions with a variety of aryl iodides in the presence of a catalytic amount of $Pd(PPh_3)_2Cl_2$ in THF at room temperature giving rise to corresponding 2-arylbenzothiazoles. The results are summarized in Table 1.

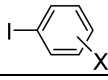
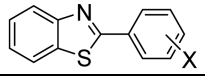


Scheme 1. General approaches for the generation of 2-substituted benzothiazoles.

Table 1. Cross-coupling reaction of **I** with aryl iodides



I 1.0 eq 0.8 eq

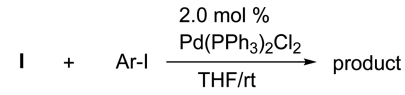
Entry	Ar-I	Product (%)[a]	
			
1	X : 4-OCH_3	**1a**	(70)
2	4-CO_2Et	**1b**	(95)
3	4-Br	**1c**	(15)
4	4-Cl	**1d**	(53)
5	3-CN	**1e**	(38)
6	3-F	**1f**	(58)
7	3-Cl, 4-CH_3	**1g**	(50)
8	3,4-Me_2	**1h**	(23)

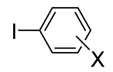
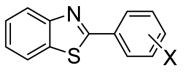
[a]isolated yield (based on ArI)

This catalytic system was also effective for the coupling reaction with haloaromatic compounds containing relatively acidic protons. As shown in Table 2, the cross-coupling products (**2a-2d**, Table 2) were obtained in moderate yields from the Pd(II)-catalyzed coupling reaction with the corresponding iodinated anilines and phenols.

Compared to the outstanding progress of the synthetic protocol for 2-arylbenzothiazole as summarized in Scheme

Table 2. Cross-coupling reaction of **I** with iodoaniline and iodophenol derivatives

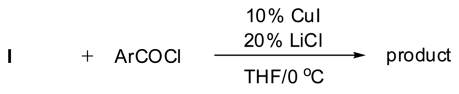


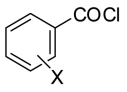
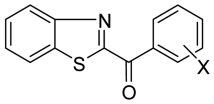
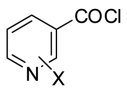
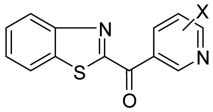
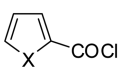
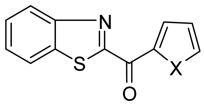
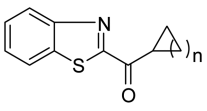
Entry	Ar-I	Product (%)[a]
		
1	X : 4-NH_2	**2a** (42)
2	3-NH_2	**2b** (46)
3	4-OH	**2c** (46)
4	3-OH	**2d** (77)

[a]isolated yield (based on ArI)

1, introducing a carbonyl moiety at the 2-position of benzothiazoles is relatively difficult even though these derivatives possess a wide range of biological activities.[7] Because of this inconvenience, only a few synthetic methodologies utilizing the oxidative cyclization have been developed.[8] Therefore, development of a new facile synthetic route for the preparation of 2-acylbenzothiazole derivatives is highly desirable.

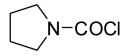
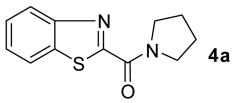
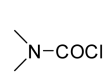
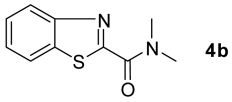
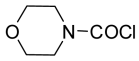
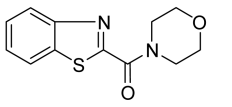
Table 3. Preparation of ketones



Entry	ArCOCl	Product (%)[a]
		
1	X : H	**3a** (43)
2	3-Br	**3b** (67)
3	4-Br	**3c** (34)
4	4-CF_3	**3d** (29)
		
5	X : 2-Cl	**3e** (28)
6	6-Cl	**3f** (26)
		
7	X : S	**3g** (0)[b]
8	O	**3h** (0)[b]
		
9	n : 1	**3i** (53)
10	2	**3j** (52)
11	4	**3k** (60)

[a]isolated yield (based on ArCOCl). [b]obtained as a mixture of desired and unidentified products

Table 4. Preparation of amide derivatives

Entry	Electrophile	Product	Yields (%)[a]
1		 **4a**	52
2		 **4b**	29
3			NR[b]

[a]isolated yield (based on electrophile). [b]no coupling reaction

To expand the scope of our methodology, a series of copper-catalyzed coupling reactions were performed.[9] A traditional reaction conditions, 10 mol % CuI and 20 mol % of LiCl, was employed to carry out the coupling reactions of 2-benzothiazolylzinc bromide with an appropriate acid chloride. A variety of aromatic acid chlorides were reacted with the organozinc reagent in THF at 0 °C leading to the formation of the corresponding aryl heteroaryl ketones (**3a**-**3**d, Table 3) in moderate yields (entries 1-4, Table 3).

Nicotinoyl chlorides worked well providing the ketones (**3e** and **3f**, Table 3) in a relatively low yield. Unfortunately, both coupling reactions with thiophenecarbonyl chloride and furoyl chloride resulted in the formation of an inseparable mixture of the desired product with unidentified products (entries 7 and 8, Table 3). Cycloalkyl acid chlorides were also good coupling partners and these reactions gave rise the corresponding products (**3i**, **3j** and **3k**, Table 3), respectively.

With these promising results in hand, we expanded our studies to examine whether this protocol could be used for a broader range of amides. Carbamoyl chloride was employed as a coupling partner and the results are summarized in Table 4. Such a strategy was successful in developing a facile protocol for the synthesis of tertiary amides (**4a** and **4b**, Table 4). Unfortunately, no product was obtained from the reaction of morpholinecarbonyl chloride (entry 3, Table 4).

In conclusion, we have developed a novel approach for the direct preparation of 2-benzothiazolylzinc bromide and its application in organic synthesis. This protocol is a new tool for the convenient synthesis of 2-substituted benzothiazole derivatives. The resulting products obtained from this work can be utilized for further applications in the synthesis of many biologically active compounds.

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9. Representative procedures: (a) 1-(4-benzo[*d*]thiazol-2-yl)phenyl)-propan-1-one (**1b**). In a 25 mL round-bottomed flask, $Pd(PPh_3)_2Cl_2$ (0.035g, 2.0 mol %) and 0.5 M solution of 2-benzothiazoylzinc bromide (**I**) in THF (5.0 mL, 2.5 mmol) were added into the flask at room temperature. Next, ethyl-4-iodobenzoate (0.55 g, 2.0 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl ether (30 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$(aq), $Na_2S_2O_3$(aq) solution and brine, successively, and dried over anhydrous $MgSO_4$, filtered and concentrated. A flash column chromatography (5% EtOAc/95% Heptane) gave 0.54 g of **1b** as a white solid in 95% isolated. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, *J* = 5 Hz, 2H), 8.10 (d, *J* = 5 Hz, 2H), 7.90 (d, *J* = 5 Hz, 1H), 7.51 (t, *J* = 5 Hz, 1H), 7.41 (d, *J* = 5 Hz, 1H), 7.39 (d, *J* = 5 Hz, 1H), 4.42 (q, *J* = 5 Hz, 2H), 1.42 (t, *J* = 5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.9, 154.0, 137.3, 135.2, 132.4, 130.2, 127.4, 126.6, 125.7, 123.6, 121.7, 61.3, 14.4. (b) **Benzo[*d*]-thiazol-2-yl(phenyl)methanone (3a).** In a 25 mL round-bottomed flask, CuI (0.05 g, 10 mol %), LiCl (0.02 g, 20 mol %) and 0.5 M solution of 2-benzothiazoylzinc bromide (**I**) in THF (5.0 mL, 2.5 mmol) were added into the flask. The resulting mixture was then cooled down to 0 °C using an ice-bath. Next, benzoyl chloride (0.28 g, 2.0 mmol) was added. The resulting mixture was stirred at ambient temperature for 12 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl ether (30 mL × 3). The combined organic layers were washed with saturated $NaHCO_3$(aq), $Na_2S_2O_3$(aq) solution and brine, successively, and dried over anhydrous $MgSO_4$, filtered and concentrated. A flash column chromatography (1% EtOAc/99% Heptane) gave 0.06 g of **3a** as a yellow solid in 43 % isolated. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12 (d, *J* = 5.0 Hz, 1H), 7.93 (d, *J* = 5.0 Hz, 1H), 7.91 (d, *J* = 5.0 Hz, 2H), 7.69 (t, *J* = 5.0 Hz, 1H), 7.58 (t, *J* = 5.0 Hz, 1H), 7.51 (d, *J* = 5.0 Hz, 1H), 7.48-7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 164.7, 152.3, 140.1, 135.6, 133.9, 130.3, 128.7, 126.4, 125.6, 123.9, 121.6.