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Ligand-free nickel-catalyzed C-S bond formation: synthesis of 2-aminobenzothiazoles

Mukta Singsardar, Shubhanjan Mitra, Adinath Majee & Alakananda Hajra[1]
Chemistry, Visva-Bharati University, India

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Abstract

A Ni-catalyzed C-S bond forming reaction has been developed for the synthesis of 2-aminobenzothiazole by the coupling of 2-haloanilines (-bromo and -iodo) with isothiocyanates. The key advantages of this procedure are ligand-free condition, inexpensive catalyst, high yields, and simple purification of the products by non-chromatographic technique.

Keywords: *Nickel*; *C-S cross-coupling*; *2-Aminobenzothiazole*; *Ligand-free; 2-Haloaniline; environmentally-benign*

1. Introduction

Transition-metal catalyzed cross-coupling reactions of carbon–heteroatom bond formations are important synthetic reactions in modern organic synthesis and they have emerged as powerful tools in both academics and industrial fields (Diederich & Stang, 1998). Although several metals such as palladium, copper and iron catalysts have proven to be highly effective in such coupling processes, the development of alternative catalyst for the aforementioned transformations is still desirable. Nickel-catalyzed cross-coupling reactions have recently been receiving significant attention from the synthetic community as a way to construct carbon–carbon bonds or carbon–heteroatom bonds (Glorius, 2008) due to their low cost and toxicity (Rosen, Quasdorf, Wilson, Zhang, Resmerita, Garg & Percec, 2011). However, $NiCl_2$ catalyzed C-S cross-coupling reaction is less reported in organic synthesis, particularly under ligand-free conditions (Jammi, Barua, Rout, Saha & Punniyamurthy, 2008). Benzothiazole moieties are an important class of heterocycles due to their pharmacological (Brade, Khadse & Bobade, 1998) and biological activities (Kok, Gambari, Chui, Yuen, Lin, Wong, Lau, Cheng, Lam, Chan, Lam, Cheng, Lai, Yu, Cheung, Tang & Chan, 2008). For example, 2-anilinobenzothiazole (R116010) is a potential inhibitor of retinoic acid metabolism (Van, Van, Bruwiere, Moelans, Janssen, Floren, Van, Van, Sanz, Venet, Dillen, Van, Willemsens, Janicot & Wouters, 2002). 2-Anilinobenzothiazole is found to be active for enhancing the *t*-RNA-induced expression of CYP26B1 (Gomaa, Armstrong, Bobillon, Veal, Brancale, Redfern & Simons, 2008) etc (Figure 1).

Figure 1. Some reported biologically active benzothiazole derivatives.

[1] Corresponding author

Accordingly, these broad utilities have prompted significant efforts towards the synthesis of benzothiazole derivatives. The majority of efficient methods for synthesis of 2-aminobenzothiazole derivatives include transition metal-catalyzed cyclization reactions such as Pd (Inamoto, Hasegawa, Hiroya & Doi, 2008), Cu (Ding, He & Wu, 2009) or Fe salts (Ding, Cao, Liu, Zong & Peng, 2010) (Scheme 1). However, generally these transition metal catalyzed reactions need specific ligands for the transformation.

Scheme 1. Strategy for the synthesis of 2-aminobenzothiazoles

Only a few efficient (Wang, Chen, Yue, Pan & Zao, 2012 and the references cited therein), ligand-free (Shen & Bao, 2009; Guo, Tang, Zhong & Li, 2010; Saha, Ramana, Purkait, Ali, Paul & Punniyamurthy, 2009) and environmentally benign (Rout, Guin, Nath & Patel, 2012; Zhang, Yue, Yu, Song, Xu, Tian & Guo, 2012) approaches have been reported for the synthesis of 2-aminobenzothiazole. However, most of the methods involved longer reaction time and higher temperature. In addition, these protocols are only applicable to 2-iodoanilines. Therefore there is a need for a general and convenient method for the synthesis of 2-aminobenzothiazoles.

In continuation of our research work for the synthesis of heterocyclic compounds using less toxic and inexpensive metal as a catalyst (Bagdi, Santra, Monir & Hajra, 2015), herein we report a convenient and versatile method for the synthesis of 2-aminobenzothiazoles using $NiCl_2$ as catalyst (Scheme 2).

Scheme 2. Synthesis of 2-aminobenzothiazoles

2. Results and Discussion

We started our investigation taking 2-iodoaniline (1 mmol) and phenyl isothiocyanate (1 mmol) as the model substrates as summarized in Table 1. Initially, the reaction was carried out in presence of 10 mol% $NiCl_2$ employing 2 equiv. K_2CO_3 as base in DMSO at 80 ^oC. The *N*-phenylbenzo[*d*]thiazol-2-amine was obtained in 72% yield (Table 1, entry 1). Inspired by this result, various bases like DBU, DABCO and KOH were employed (Table 1, entries 2, 3 & 4); among them DABCO furnished the best result. Furthermore, other high boiling solvents like DMF and toluene were also screened (Table 1, entries 5 & 6). Among them, DMSO appeared to be the best choice. No significant increase in yield was observed when the amount of catalyst was increased from 10 mol% to 15 mol%, whereas lower yield was observed while lowering the amount of catalyst (Table 1, entries 6, 7 & 8). Consequently, the optimum amount of base was also tested, and 2 equiv of DABCO was found to furnish the highest product yield. Next, the

scope of other nickel catalysts was also tested. It was observed that $Ni(NO_3)_2$ (10 mol%) and $NiSO_4$ (10 mol%) furnished lower yields of the product. It was interesting to note that only 62% yield was obtained at 60 ^oC whereas the reaction did not proceed at room temperature (Table 1, entries 14 & 15). The reaction afforded lower yield in absence of base (entry 16). Only 14% yield was obtained in absence of any catalyst (entry 13). Finally, the optimized reaction conditions were obtained using the combination of both Lewis acid ($NiCl_{2)}$ and base (DABCO) using DMSO as solvent at 80 ^oC.

Table 1. Optimization of the reaction conditions

Entry

1

With the optimized reaction conditions in hand, we investigated the substrate-scope as summarized in Table **2**. Both electron-withdrawing and electron-donating groups present in 2-haloanilines as well as in isothiocyanates afforded moderate to good yields. Several functionalities such as -Me, -OMe, -NO_2 remain unaffected under the optimized reaction conditions. It has been observed that presence of electron withdrawing groups in haloanilines and/or isothiocyanates lowered the product yields, whereas presence of electron donating groups increased the yields. It is worthy to mention that 2-bromoaniline reacted well under the present reaction conditions (Table 2, entries 9 & 10). Benzyl isothiocyanate also afforded the desired products in good yields (Table 2, entries 4, 13 & 14). In general the reactions were clean and products were obtained in high yields.

Table 2. $NiCl_2$-catalyzed synthesis of 2-aminobenzothiazoles

Entry	
1	

3. Conclusion

In summary, we have developed a $NiCl_2$-catalyzed convenient strategy for the synthesis of 2-aminobenzothiazole by the coupling between 2-haloanilines and isothiocyanates. Both 2-bromo and 2-iodoanilines worked well under the present reaction conditions. The protocol is mild, straightforward and ligand-free. General applicability, operational simplicity (nonchromatographic technique) and high yields are the key advantages of the present procedure. We believe this methodology will gain much importance in organic synthesis and industrial field as a powerful tool for the synthesis of various 2-aminobenzothiazole derivatives.

4. Experimental Section

^1H and ^{13}C NMR spectra were recorded at 300/400/500 MHz and 75/100/125 MHz respectively in DMSO-d_6 or $CDCl_3$ solutions. Coupling constant are given in Hz and the signals were reported as s (singlet), d (doublet), t (triplet), m (multiplet). Thin layer chromatography was done on silica gel coated glass slide (Merck, Silica gel G for TLC). Commercially available substrates were freshly distilled before the reaction. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck, SRL, Spectrochem and Process Chemicals. All reactions involving moisture sensitive reactants were executed using oven dried glassware. Known compounds were characterized by comparing their spectral data (IR, ^1H NMR, and ^{13}C NMR) found in the literature.

4.1. General Experimental Procedure

A mixture of 2-haloaniline or substituted 2-haloanilines (2 mmol) and phenyl isothiocyanate or substituted phenyl isothiocyanates (2 mmol) was stirred in presence of $NiCl_2$ (10 mol%) and DABCO (2 equiv.) in DMSO (3 mL) at 80 ^oC for 20h. After completion as monitored by TLC, brine solution (3 x 10 mL) was added into the reaction mixture. Then the reaction mixture was extracted with ethyl acetate (2 x 10 mL) and dried over Na_2SO_4. Evaporation of the solvent furnished the crude product which was recrystallized from the mixture dichloromethane and diethyl ether to afford the analytically pure product.
Spectral data of the new compounds with some other important compounds are given below. All the interpreted spectra based on the skeleton as below.

Benzothiazol-2-yl-(4-fluoro-phenyl)-amine (entry 10, Table 2):
White solid; Mp ^oC: 160-165 ^oC; IR (KBr): 3236, 3197, 2925, 2846, 1623, 1562 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.37 (s, 1H), 7.84-7.80 (m, 2H), 7.70 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.30 (t, J = 7.5, 1H), 7.14-7.08 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.1 (C2), 157.9 (C4′) (d, J_{C-F} = 237.9 Hz), 152.6 (C3a), 137.5 (C1′), 130.5 (C7a), 126.1 (C5), 122.5 (C4), 121.2 (C6), 119.8 (2 C2′)(d, J_{C-F} = 7.5 Hz), 119.6 (C7), 115.8 (2 C3′) (d, J_{C-F} = 22.1 Hz). Anal. Cald for $C_{13}H_9FN_2S$: C, 63.92; H, 3.71; N, 11.47%. Found: C, 64.08; H, 3.88; N, 11.60%.
(5-Chloro-benzothiazol-2-yl)-phenyl-amine (entry 11, Table 2):
White solid; Mp ^oC: 236-238 ^oC; IR (KBr): 3234, 3182, 2927, 2835, 1610, 1552 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 10.59 (s, 1H), 7.79 (m, 3H), 7.62 (s, 1H), 7.37 (t, J = 7.9 Hz, 2H), 7.18-7.15 (m, 1H), 7.08-7.02 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.8 (C2), 153.8 (C3a), 140.8 (C1′), 131.1 (C5), 129.4 (C7a), 129.3 (2 C3′), 122.9 (C6), 122.7 (C7), 122.4 (C4), 119.2 (C4′), 118.6 (2 C2′). Anal. Cald. for $C_{13}H_9ClN_2S$: C, 59.88; H, 3.48; N, 10.74%. Found: C, 60.00; H, 3.60; N, 10.90%.

Benzyl-(5-chloro-benzothiazol-2-yl)-amine (entry 14, Table 2):
White solid; Mp ^{o}C: 178-180 ^{o}C. IR (KBr): 3201, 3168, 2893, 2840, 1606, 1556 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 & $CDCl_3$): δ 8.37 (s, 1H), 7.48-7.45 (m, 1H), 7.38-7.22 (m, 6H), 6.97 (m, 1H), 4.61 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6 & $CDCl_3$): δ 166.9 (C2), 152.6 (C3a), 137.1 (C1′), 129.6 (C5), 127.9 (C7a), 127.2 (C4′), 126.4 (2 C2′), 126.0 (C6), 120.2 (2 C3′), 119.5 (C7) , 116.7 (C4), 46.7 (–CH_2-Ph). Anal. Cald. for $C_{14}H_{11}ClN_2S$: C, 61.20; H, 4.04; N, 10.20%. Found: C, 61.29; H, 4.20; N, 10.35%.

(5-Chloro-benzothiazol-2-yl)-(4-methoxy phenyl)-amine (entry 15, Table 2):
White solid; Mp ^{o}C: 202-204 ^{o}C; IR (KBr): 3232, 3182, 2902, 2835, 1633, 1558 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 & $CDCl_3$): δ 10.02 (s, 1H), 7.57-7.24 (m, 4H), 6.99-6.71 (m, 3H,), 3.70 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6 & $CDCl_3$): δ 163.7 (C2), 154.8 (C4′), 153.3 (C3a), 133.3 (C1′), 130.5 (C5), 128.3 (C7a), 121.1 (C6), 120.9 (C7), 120.0 (C4), 118.1 (2 C2′), 113.6 (2 C3′),54.8 (-OCH_3). Anal. Cald. for $C_{14}H_{11}ClN_2OS$: C, 57.83; H, 3.81; N, 9.63%. Found: C, 57.72; H, 3.95; N, 9.77%.

(6-Fluoro-benzothiazol-2-yl)-(4-fluoro-phenyl)-amine (entry 16, Table 2):
White solid; Mp ^{o}C: 170-172 ^{o}C. IR (KBr): 3201, 3087, 2920, 2856, 1625, 1575, 1510, 1456 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.26 (br, 1H), 7.81-7.76 (m, 2H), 7.53-7.45 (m, 2H), 7.09-7.03 (m. 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 159.9 (C2), 156.6 (C6) (d, $J_{C\text{-}F}$ = 240 Hz), 156.0 (C4′) (d, $J_{C\text{-}F}$ = 232.5 Hz), 147.3 (C3a), 135.5 (C1′) (d, $J_{C\text{-}F}$ = 2 Hz), 129.6 (C7a) (d, $J_{C\text{-}F}$ = 10.5 Hz), 118.2 (2 C2′) (d, $J_{C\text{-}F}$ = 8.25 Hz), 117.9 (C4), 113.7 (2 C3′) (d, $J_{C\text{-}F}$ = 22.5 Hz), 111.7 (C5) (d, $J_{C\text{-}F}$ = 23.2 Hz), 105.9 (C7) (d, $J_{C\text{-}F}$ = 24 Hz). Anal. Cald. For $C_{13}H_8F_2N_2S$: C, 59.53; H, 3.07; N, 10.68%. Found: C, 59.55; H, 3.10; N, 10.69%.

(5-Chloro-benzothiazol-2-yl)-(4-fluoro-phenyl)-amine (entry 17, Table 2):
White solid; Mp ^{o}C: 207-209 ^{o}C. IR (KBr): 3238, 3195, 2931, 2848, 1623, 1558 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.2 (br, 1H), 7.76-7.72 (m, 2H), 7.56 (m, 2H), 7.09-7.01 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.8 (C2), 157.2 (C4′) (d, $J_{C\text{-}F}$ = 240 Hz), 152.6 (C3a), 135.9 (C1′), 130.3 (C5), 127.8 (C7a), 121.1 (C6), 120.4 (C7), 119.2 (2 C2′) (d, $J_{C\text{-}F}$ = 7.5 Hz), 118.2 (C4), 114.4 (2 C3′) (d, $J_{C\text{-}F}$ = 21.3 Hz). Anal. Cald. for $C_{13}H_8ClFN_2S$: C, 56.02; H, 2.89; N, 10.05%. Found: C, 56.12; H, 2.95; N, 10.17%.

Phenyl-(5-trifluoromethyl-benzothiazol-2-yl)-amine (entry 18, Table 2):
White solid; Mp ^{o}C: 210-212 ^{o}C. IR (KBr): 3226, 3197, 2943, 2842, 1612, 1569 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.64 (br, 1H), 7.91 (d, J = 8 Hz, 1H), 7.77 (s, 1H), 7.70 (d, J = 8 Hz, 2H), 7.39-7.31 (m, 3H), 7.03 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.0 (C2), 152.3 (C3a), 140.3 (C1′), 134.7 (C7a), 129.5 (2 C3′), 127.3 (C4′) (q, $^{2}J_{C\text{-}F}$ = 32 Hz), 124.8 (CF_3) (q, $^{1}J_{C\text{-}F}$ = 270 Hz), 123.3 (C5), 122.3 (C4), 118.7 (C6), 118.7 (C7), 115.5 (2 C2′). Anal. Cald. For $C_{14}H_9F_3N_2S$: C, 57.14; H, 3.08; N, 9.52%. Found: C, 57.17; H, 3.10; N, 9.54%.

(4-Fluoro-phenyl)-(6-methyl-benzothiazol-2-yl)-amine (entry 19, Table 2):
White solid; Mp ^{o}C: 218-220 ^{o}C. IR (KBr): 3195, 3082, 2974, 2844, 1620, 1569 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.33 (br, 1H), 7.71-7.67 (m, 2H), 7.49 (s, 1H), 7.41 (d, J = 8 Hz, 1H), 7.15-7.08 (m, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 161.7 (C2), 157.7 (C4′) (d, $^{1}J_{C\text{-}F}$ = 238 Hz), 149.9 (C3a) , 137.3 (C1′), 133.3 (C7a), 130.2 (C6), 127.4 (C5), 121.2 (C7), 119.9 (2 C2′) (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 119.1 (C4), 115.9 (2 C3′) (d, $^{2}J_{C\text{-}F}$ = 23 Hz), 21.0 (-CH_3). Anal. Cald. For $C_{14}H_{11}FN_2S$: C, 65.09; H, 4.29; N, 10.84%. Found: C, 65.12; H, 4.33; N, 10.88%.

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