


Synthesis of 2-Aminobenzothiazoles *via* Copper(I)-Catalyzed Cross-Coupling with Part-Per-Million Catalyst Loadings

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Abstract: An efficient protocol has been developed for the preparation of 2-aminobenzothiazoles *via* a copper(I)-catalyzed tandem reaction of 2-iodoanilines with isothiocyanates at very low catalyst loadings [typically 50 ppm of copper(I) iodide (CuI)]. A variety of 2-iodoanilines could be cross-coupled with isothiocyanates, affording 2-aminobenzothiazoles in moderate to good yields (49–93%) under the given conditions. The turnover number (TON) of this reaction reaches 67,000 and the reaction could be scaled up, at least, to the gram-scale.

Keywords: 2-aminobenzothiazoles; copper; cross-coupling; low catalyst loadings

Introduction

Utilization of transition metal-catalyzed cross-coupling reactions has been attracting much attention in recent years,^[1] and it has become one of the most versatile strategies for the synthesis of natural products,^[2] pharmaceuticals,^[3] organic functional materials,^[4] and so on. Despite the successful applications in many research areas, the inherent limitations of these metal-catalyzed cross-coupling reactions cannot be neglected, e.g., the use of high catalyst loadings [therefore, with low turnover numbers (TONs) and turnover frequencies (TOFs)] and difficulties in purification of products from residual metal catalyst. Accordingly, more efficient catalytic systems working at lower catalyst loadings should be developed to overcome these drawbacks. Of all the metal-catalyzed systems investigated, the palladium-catalyzed cross-coupling reactions have proven successful for working with low catalyst loadings, i.e., usually at the ppm level.^[5]

Very recently, research interest in this area has focused on the possibility of copper-catalyzed cross-couplings with ppm level catalyst loadings. This is because, in comparison with palladium, copper is much cheaper, abundant, and less toxic. In 2009, Bolm and Buchwald^[6] first noticed that the catalyst activity for iron-catalyzed cross-coupling reactions depends on the chemical purity and commercial source of the metal catalysts used. Further research revealed that the residual copper in the iron salt has a dramatic influence on the efficiency of these cross-coupling reactions. For example, only 5 ppm of Cu₂O catalyst could effectively catalyze the *N*-arylation reaction of pyrrole or phenylamide, affording the corresponding product in good yield (77% and 97%, respectively).^[6] Larsson et al.^[7] also found a similar effect and reported on Ullmann-type coupling reactions in the presence of “homeopathic amounts” of copper salts. Moreover, the scope of Ullmann-type reactions could be extended to *N*-, *O*-, and *S*-arylations with sub-mol% amounts of copper.^[7] In 2010, Bolm and his co-workers first investigated the catalytic effect of residual metals (especially the copper) in FeCl₃ on the intramolecular cyclization of aryl 2-bromobenzyl ketones.^[8] They found that even 0.0088 mol% of CuCl₂ catalyst is sufficient to provide benzo[*b*]furans in moderate yields.^[8] With the use of copper/DMEDA (dimethylethylenediamine) at sub-mol% levels, Zuidema and Bolm^[9] further broadened the reaction scope to Castro–Stephens coupling, the case of which is a striking example for ligand-accelerated catalysis. Very recently, a similar result was also found in the copper-catalyzed cross-coupling reaction of pyrazole and iodobenzene.^[10] These research works pioneered the efficient cross-coupling reactions catalyzed by sub-mol% amounts of copper catalyst loadings, although a high reaction temperature and large amount of ligand (usually 20 mol%) are still necessary. Issues yet to be developed are, therefore, the generality and

facility of these cross-coupling reactions with very low catalyst loadings.

We report herein a CuI/Et₃N catalytic system for the efficient preparation of 2-aminobenzothiazoles^[11] with very low catalyst loadings (at *ca.* 50 ppm level) under mild reaction conditions (80 °C for 24 h under air). A variety of 2-iodoanilines could be cross-coupled with isothiocyanates to produce 2-aminobenzothiazoles in moderate to good yields (49–93%) under the given conditions without any additional ligands. The TON of this reaction could reach 67,000 and the reaction could be scaled up, at least, to a 5 mmol scale (1.10 gram).

Results and Discussion

Reaction Test with the Loading of CuI at ppm Level

Initially, we found that the cross-coupling reaction of 2-iodoaniline (**1a**) and isothiocyanatobenzene (**2a**) could be efficiently catalyzed by CuI (Alfa Aesar, purity of 99.999%) with the catalyst loading of 0.001–5 mol% (Table 1). In the presence of Et₃N (2.0 equiv.) as base and DMSO as solvent, the reaction was carried out at 80 °C for 24 h under air. In order to rule out possible effects of impurities, special measures were taken during the experimental procedure. For example, all the glassware and stirrer bars were thor-

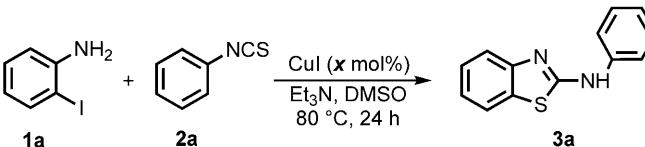
oughly cleaned and all the solvents used were freshly distilled (see Experimental Section for more details). When 5 mol% of CuI was applied as the catalyst, the desired product, 2-aminobenzothiazole (**3a**) could be obtained in 95% yield (Table 1, entry 1). Interestingly, this yield remained constant even when the loading of CuI was decreased to 1 mol% (entry 2). Encouraged by this result, we tested the reaction output at the given conditions when the amount of CuI was further lowered from 0.1 mol% to 0.001 mol% (entries 3–7). The reaction yield was kept as 91–92% when the CuI loading was varied from 0.1 mol% to 0.01 mol% (entries 3–5). Remarkably, the reaction still gave the product **3a** in the yields of 88% (TON of 17,600) and 67% (TON of 67,000), when the CuI loading was further decreased to 0.005 mol% (entry 6) and 0.001 mol% (entry 7), respectively. The control experiment showed that, in the absence of CuI, the product **3a** could only be obtained in the yield of 27% (entry 8), which confirms the promoting effect of CuI catalyst.

Scope of the Reaction Catalyzed by CuI at ppm Level

We, therefore, start out to investigate the scope of this reaction, in which the CuI catalyst at ppm level could also be applied. We found that the reaction of 2-iodoaniline (**1a**) with a variety of substituted isothiocyanates (**2b–2i**) could also be effectively conducted in the presence of 0.005 mol% of CuI catalyst (Table 2). The catalytic system shows good tolerance of functional groups, such as trifluoromethyl (Table 2, entry 1), methyl (entry 3), methoxy (entry 4), and nitro (entry 5) groups. Both electron-rich and electron-poor aryl isothiocyanates could afford the desired products **3** in moderate to good yields (62–93%, entries 1–6). However, the alkyl isothiocyanates, such as cyclohexyl isothiocyanate (**2h**) and 1-butyl isothiocyanate (**2i**) gave the corresponding products in the low yields of 26% and 46%, respectively (entries 7 and 8), even when the larger amount of CuI catalyst (0.01 mol%) and longer reaction time (48 h) were applied.

Furthermore, the reaction of substituted anilines (**1**) and isothiocyanates (**2**) was examined to explore the generality of using the CuI catalyst at a ppm level (Table 3). To our delight, most of the tested systems worked well with 0.005 mol% of CuI as the catalyst, giving the desired products (**3**) in moderate to good yields (49–91%, Table 3, entries 1–8). For example, the 2-iodo-4-methylbenzenamine (**1b**) results in the desired products in yields of 71–76% (Table 3, entries 1–3). On the other hand, the fluoro-substituted iodoaniline (**1c**) has the highest reactivity under the given conditions, and affords the product in 91%

Table 1. Efficient synthesis of 2-aminobenzothiazole (**3a**) from 2-iodoaniline (**1a**) and isothiocyanatobenzene (**2a**) in the presence of 0.001%–5 mol% of CuI.^[a]



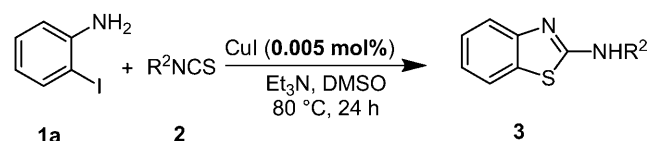
Entry	CuI (x mol%)	Yield [%] ^[b]	TON ^[c]
1	5	95	19
2	1	95	95
3	0.1	92	920
4	0.05	91	1,820
5	0.01	92	9,200
6	0.005	88	17,600
7	0.001	67	67,000
8	0	27	–

^[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.22 mmol), CuI (x mol%, 5.0 mM in CH₃CN), Et₃N (2.0 equiv.) in DMSO (2.0 mL) at 80 °C for 24 h under an air atmosphere.

^[b] Average isolated yields after silica gel column chromatography, from two or more experiments. The yields were fluctuated within ±2% for each given set of conditions.

^[c] Turnover numbers.

Table 2. Reaction of 2-iodoaniline (**1a**) with isothiocyanates (**2**) catalyzed by ppm levels of CuI catalyst.^[a]



Entry	Substrate 2	Product 3	Yield [%] ^[b]
1			93 (94 ^[c])
2			72
3			90
4			73
5			72
6			62
7			26 ^[c,d]
8			46 ^[c,d]

^[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.22 mmol), CuI (0.005 mol%, 5.0 mM in CH₃CN), Et₃N (2.0 equiv.) in DMSO (2.0 mL) at 80 °C for 24 h under an air atmosphere.

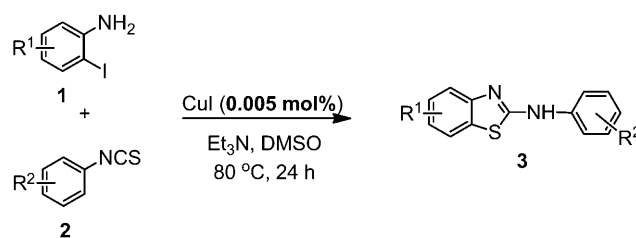
^[b] Averaged isolated yields after silica gel column chromatography.

^[c] 0.01 mol% of CuI.

^[d] Reaction was run for 48 h.

yield with a TON of 18,200 (entry 6). Interestingly, only a trace of product was detected when 2-bromoaniline (**1e**) was applied as the substrate and a yield of 27% could be obtained when the CuI loading was increased to 0.1 mol% (entry 9).

Table 3. Exploring the generality of using CuI catalyst at ppm levels in the tandem reaction of 2-iodoanilines (**1**) and isothiocyanates (**2**).^[a]



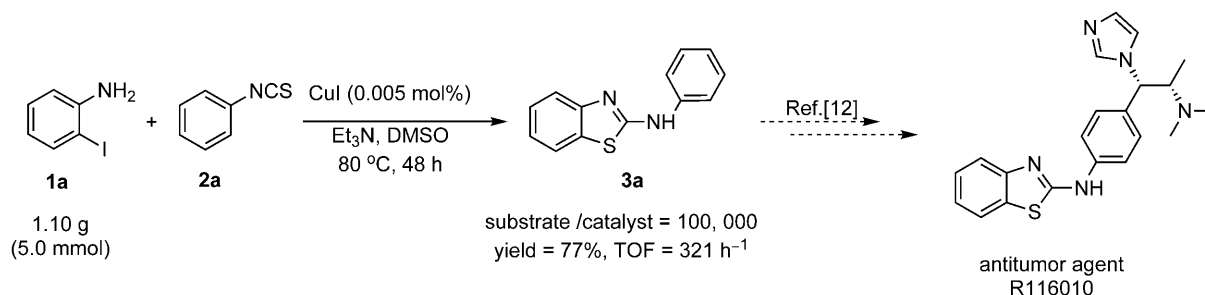
Entry	Substrate 1	Substrate 2	Yield [%] ^[b]
1			71
2			76
3			74
4			80
5			84
6			91
7			58
8			49
9			trace (27 ^[c])

^[a] Reaction conditions: **1** (0.20 mmol), **2** (0.22 mmol), CuI (0.005 mol%, 5.0 mM in CH₃CN), Et₃N (2.0 equiv.) in DMSO (2.0 mL) at 80 °C for 24 h under an air atmosphere.

^[b] Average isolated yields after silica gel column chromatography.

^[c] 0.1 mol% of CuI.

After checking the generality of using CuI catalyst at the ppm level in the cross-coupling reaction of iodoanilines with isothiocyanates, we further explored the possibility for large-scale synthesis. As shown in Scheme 1, we scaled up the reaction of 2-iodoaniline



Scheme 1. Scaling up the reaction of 2-iodoaniline (**1a**) with isothiocyanatobenzene (**2a**) to a 5-mmol scale. The reaction was carried out at 80 °C for 48 h under an air atmosphere, in the presence of 0.005 mol% of CuI, with Et₃N (2.0 equiv.) as base and DMSO (50.0 mL) as solvent. The product **3a** is an important intermediate for the preparation of antitumor agent R116010.^[12]

(**1a**) to 1.10 g (5.00 mmol) in the presence of 0.005 mol% of CuI catalyst with 50.0 mL of DMSO as solvent. The reaction took place smoothly under the given conditions and afforded the desired product, *N*-phenyl-2-benzothiazolamine (**3a**), in 77% yield. The substrate/catalyst ratio was 100,000 and the TOF was 321 h⁻¹. The product **3a** is an important intermediate for the preparation of the antitumor agent R116010.^[12] It is worthy of mention that the residual copper content in the product **3a** was 0.95 ppm (ICP analysis) after silica gel column chromatography and that this content well meets the pharmaceutical requirements.^[13]

Conclusions

In summary, we have developed a CuI/Et₃N system for the efficient synthesis of 2-aminobenzothiazoles with very low copper catalyst loadings (typically at 50 ppm of CuI). This system has shown broad substrate scope, moderate to good yields (49–93%), and high catalytic efficiency (TON up to 67,000). The reaction could be scaled up, at least, to the gram-scale, which may be applicable in the practical or industrial synthesis of 2-aminobenzothiazoles. Further applications of similar catalytic systems to other cross-coupling reactions are currently under investigation in our laboratory.

Experimental Section

General Comments

Unless otherwise noted, all experiments were carried out under an air atmosphere. CuI was purchased from Alfa Aesar (Lot No.: C26N01) with a purity of 99.999%. CuBr was purchased from Sigma–Aldrich (Lot No.: MKBC3138 V) with a purity of 99.999%. All the solvents, such as DMSO (≥99%), CH₃CN (≥98%), and Et₃N (≥99%), were freshly distilled over calcium hydride before

use. Cs₂CO₃ (99.9%), K₂CO₃ (≥99%) were chosen as inorganic bases. The metal content of 2-iodoaniline was determined by ICP, and was found to contain 8 ppm of Fe, and less than 10 ppb of Cu. Isothiocyanates were purchased from Aldrich and J&K Chemical and used without further purification. Considering possible effects of metal impurities, all the equipment (glassware, stirrer bar, and so on) was washed with HNO₃ (20%, v/v)⁻¹ and KOH/isopropyl alcohol, followed by rinsing with distilled water and drying overnight at 150 °C. DMSO was taken *via* pipette (2 mL), and solid compounds were taken *via* ox horn spoons in order to avoid the contamination with metal items. ¹H and ¹³C NMR spectra were recorded in CDCl₃ or DMSO-*d*₆ solution on a Bruker 400 MHz NMR spectrometer, and the coupling constants *J* are given in Hz. In the case of CDCl₃ as solvent, TMS served as the internal standard (chemical shift δ = 0.00 ppm) for ¹H NMR and CDCl₃ was used as the internal standard (δ = 77.0 ppm) for ¹³C NMR. In the case of DMSO-*d*₆ as solvent, chemical shifts δ are given from residual non-deuterated solvent peak, i.e., 2.50 ppm for ¹H NMR and 39.5 ppm for ¹³C NMR. MS and HR-MS were performed on Bruker Daltonics esquire6000 mass instrument (ESI) and Bruker Daltonics APEX II 47e FT-ICR mass spectrometer, respectively.

General Procedure for the Tandem Reaction of 2-Iodoaniline (**1**) and Isothiocyanate (**2**) in the Presence of CuI Catalyst at ppm Level

Into a 10-mL test tube, a CuI solution (0.005 mol%, 2.0 μL, 5.0 mM CuI in CH₃CN) was added, then CH₃CN was removed under vacuum. 2-Iodoaniline (**1**, 0.20 mmol), isothiocyanate (**2**, 0.22 mmol), Et₃N (58 μL, 2.0 equiv.), DMSO (2.0 mL) and a teflon coated stirrer bar were added. The tube was placed in a preheated oil bath at 80 °C. The mixture was stirred for 24 h under an air atmosphere, and then cooled to room temperature. The solution was diluted with ethyl acetate, and washed with water (10 mL), brine (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over anhydrous Na₂SO₄. After evaporating under vacuum, the corresponding product **3** was obtained by purification on silica gel (petroleum ether/ethyl acetate = 15:1 to 4:1).

Acknowledgements

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