

## Short communication

## Regioselective copper-catalyzed amination of halobenzoic acids using aromatic amines

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## Abstract

Copper dipyrindine dichloride ( $\text{CuPy}_2\text{Cl}_2$ ) has been found to be an efficient catalyst for the synthesis of *N*-aryl anthranilic acids from *ortho*-halobenzoic acids and aromatic amines. Some of the advantages of this method are high chemo selectivity, ease of operation, and high yields (56–92%).

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## 1. Introduction

A chemo- and regioselective copper-catalyzed cross-coupling procedure for amination of 2-halobenzoic acids is described. The method eliminates the need for acid protection and produces *N*-aryl anthranilic acid derivatives in up to 92% yield. *N*-aryl anthranilic acids have received considerable attention during recent years because they are important nonsteroidal anti-inflammatory drugs and candidates for the therapy of neurodegenerative and amyloid diseases [1]. *N*-Aryl anthranilic acids are also synthetic precursors of acridines, which have been utilized as antimalarial and anticancer drugs [2]. Because of their excellent solubility in water, intriguing stereodynamic properties in peptide chains and potential use in drug development, *N*-aryl anthranilic acids and other nonnatural achiral amino acids have found various biomedical applications [3]. Achiral amino acids have been incorporated into biologically active peptides to alter secondary protein structures and biochemical properties or to investigate the stereochemical control of peptide folding [4]. Recently, helicity of achiral peptide chains has been induced through asymmetric noncovalent domino effects using an external chiral stimulus [5]. The first direct synthesis of *N*-aryl anthranilic acids from 2-chlorobenzoic acid was accomplished

by Ullmann [6]. Since then, various copper-catalyzed amination procedures suitable to *ortho*-chlorobenzoic acids have been described by others [7]. Palladium-catalyzed amination of aryl halides exhibiting free carboxylic acid groups in the *meta* or *para* position has also been explored [8]. *N*-Aryl anthranilic acids are usually prepared from 2-chlorobenzoic acids or via coupling of anthranilic acid and arylhalides [9]. A wide range of 2-bromobenzoic acid derivatives are readily available, as variety of methods like oxidation of 2-alkyl-1-bromobenzenes [10] or lithiation of dibromobenzenes and subsequent treatment with carbon dioxide [11], have been explored. The drawbacks of cross-coupling procedures using bromobenzoic acids are due to their limited tolerance of functional groups to very high reaction temperatures and low yields were reported with sterically hindered arylamines [12].

## 2. Results and discussion

We therefore wish to report a highly regioselective synthetic procedure providing convenient access to a range of *N*-aryl anthranilic acids exhibiting various functional groups through Cu-catalyzed amination of 2-halobenzoic acids. Initially, we employed  $\text{CuPy}_2\text{Cl}_2$  as catalyst in the reaction of 2-bromobenzoic acid, and *para*-toluidine, using *n*-butanol, 2-ethoxyethanol, and ethylene glycol as solvent. Further screening of bases ( $\text{Na}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$ ,  $\text{K}_2\text{CO}_3$ ) showed that the best results for the synthesis of *N*-(4-methyl phenyl)anthranilic acid, are

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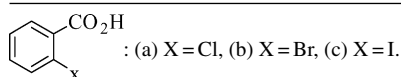
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obtained in the presence of potassium carbonate and catalytic amounts of dipyridine copper chloride in ethylene glycol at 130 °C. Ethylene glycol acts as a ligand in stabilizing or solubilizing the copper complex. Control experiment revealed that no reaction was observed in the absence of ethylene glycol. The yields were significantly less when 2-methoxy ethanol, diethyleneglycol, ethoxyethanol and glycerol were employed. The optimized amination procedure was then applied to a variety of arylamines and halobenzoic acids to evaluate the synthetic potential of this method (Table 1). Reaction of halobenzoic acid with aromatic amines gave the corresponding *N*-aryl anthranilic acids in 56–92% yields. Importantly, the copper-catalyzed ami-

nation proceeds with remarkable chemo- and regioselectivity because only the bromide adjacent to the carboxylic acid moiety is replaced. The most striking advantage of this method is that this reaction can be conducted at ordinary pressure in the presence of air. No inert atmosphere is needed for conducting the experiment. It is also observed in course of our reaction that the yields are more with *ortho*-iodobenzoic acids. Amination of dibromobenzoic acid with aniline yielded *N*-phenyl-5-bromo anthranilic acid. Aryl halide bonds located in the aniline ring are also not affected. *N*-(3-Chlorophenyl)- and *N*-(3-bromophenyl)anthranilic acids were obtained through cross-coupling of halobenzoic acids with 3-chloro and 3-bromo

Table 1  
CuPy<sub>2</sub>Cl<sub>2</sub> catalyzed amination of 2-halobenzoic acids using aromatic amines

Entry	Halobenzoic acid	Amine	Product	Yield
1				(a) 72%, (b) 69%, (c) 81%
2				(a) 82%, (b) 90%, (c) 89%
3				(a) 81%, (b) 88%, (c) 90%
4				(a) 69%, (b) 72%, (c) 79%
5				(a) 59%, (b) 61%, (c) 69%
6				(a) 56%, (b) 58%, (c) 64%
7				(a) 78%, (b) 83%, (c) 88%
8				(a) 76%, (b) 80%, (c) 86%
9				(a) 82%, (b) 89%, (c) 91%
10				(a) 84%, (b) 90%, (c) 92%



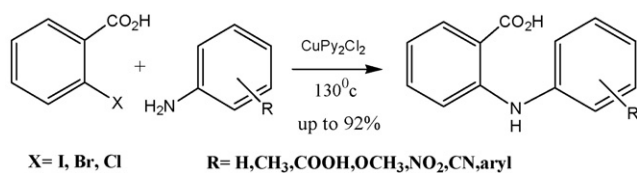


Fig. 1.

anilines, comparison of the results obtained with 4-substituted anilines reveals that incorporation of electron-donating groups facilitates the amination reaction. In particular, the formation of *N*-(4-nitrophenyl)anthranilic acid, proved to be slow and substantial amounts of starting materials were recovered after 24 h.

### 3. Experimental

#### 3.1. General

All materials were obtained from commercial suppliers and used without further purification. Standard distilled water was used throughout the study. All reactions were carried out in air. NMR spectra were recorded at 293 K on a 300 or 400 MHz spectrometer. All products are known and were characterized by comparison of NMR data with that in the literature.

#### 3.2. Typical amination procedure

A mixture of *para*-toluidine (0.96 g, 9.0 mmol), 2-bromobenzoic acid (1.75 g, 8.8 mmol),  $\text{K}_2\text{CO}_3$  (9.0 mmol), dipyridine copper chloride (0.9 mmol), and 3 mL of ethylene glycol was refluxed at 130 °C for 24 h. The cooled reaction mixture was poured into 50 mL of water to which decolorized charcoal was added. The mixture was filtrated through Celite. The crude product was obtained by precipitation upon acidification of the filtrate with diluted HCl. The residue was dissolved in 100 mL of 5% aqueous  $\text{Na}_2\text{CO}_3$ . The solution was filtered through Celite, and *N*-(4-methyl phenyl)anthranilic acid (1.80 g, 7.9 mmol) was obtained in 90% yield as an off-white solid by precipitation as described above (Fig. 1).

#### 3.3. Product characterization data

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.35 (s, 3H), 6.68 (dd,  $J$  = 7.3 Hz, 7.3 Hz, 1H), 6.93 (dd,  $J$  = 8.6 Hz, 8.6 Hz 3H), 7.18 (d,  $J$  = 8.6 Hz, 2H), 7.26–7.32 (m, 1H), 8.0 (d,  $J$  = 8.6 Hz, 1H), 9.60 (bs, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 20.8, 109.9, 113.7, 116.6, 123.7, 129.9, 132.4, 133.9, 135.0, 137.5, 149.5, 173.2; EIMS  $m/z$  227 ( $\text{M}^+$ ).

All the *ortho*-haloaromatic acids were condensed with different aromatic amines following the same procedure.

### 4. Conclusion

In conclusion, it has been observed in our present scheme that  $\text{CuPy}_2\text{Cl}_2$  is an efficient catalyst for the amination of 2-halobenzoic acids. The experimental procedure is very simple and the yields are relatively high.

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