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Efficient Copper-Catalyzed Synthesis of *N*-Alkylanthranilic Acids *via* an *ortho*-Substituent Effect of the Carboxyl Group of 2-Halobenzoic Acids at Room Temperature

Liang Zeng,[a,b] Hua Fu,[a,*] Renzhong Qiao,[b,*] Yuyang Jiang,[a,c] and Yufen Zhao[a]

[a] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, People's Republic of China
Fax: (+ 86)-10-6278-1695; e-mail: fuhua@mail.tsinghua.edu.cn

[b] State Key Laboratory of Chemical Resource Engineering, Department of Pharmaceutical Engineering, College of Life Science and Technology, Beijing University of Chemical Technology, Beijing 100029, People's Republic of China
E-mail: qiaorz@mail.buct.edu.cn

[c] Key Laboratory of Chemical Biology (Guangdong Province), Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, People's Republic of China

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Abstract: We have developed an efficient copper-catalyzed method for the synthesis of *N*-alkylanthranilic acids. The protocol uses inexpensive copper(I) iodide/racemic 1,1′-binaphthyl-2,2′-diol (*rac*-BINOL) as the catalyst/ligand system, readily available 2-halobenzoic acids and aliphatic amines as the starting materials, the coupling reactions were performed at room temperature, and various functionalities in the substrates were tolerated.

Keywords: *N*-alkylanthranilic acids; copper; cross-coupling; O,O ligands; Ullmann reaction

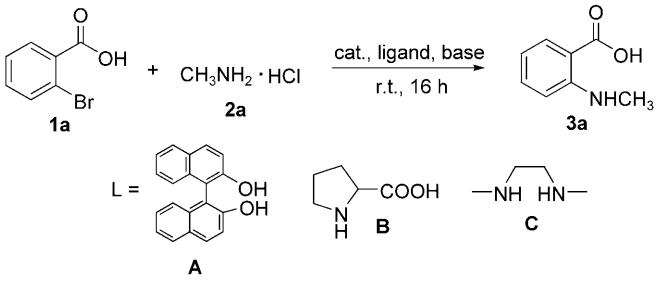
Introduction

The synthesis of *N*-substituted anthranilic acid derivatives has attracted much attention because of their importance as drug molecules and building blocks. *N*-Aralkylanthranilic acid derivatives, such as 2-benzylamino-5-nitrobenzoic acid and 5-nitro-2-phenethylaminobenzoic acid, have been demonstrated to interact with the cystic fibrosis transmembrane conductance regulator causing a blockade of the chloride channel and have therefore potential as novel antiarrhythmic drugs.[1] The copper-catalyzed amination of 2-chlorobenzoic acid was first accomplished by Ullmann.[2] Since then, various copper-catalyzed amination procedures suitable for 2-chlorobenzoic acids have been described.[3] *N*-Substituted anthranilic acids are usually prepared from 2-chlorobenzoic acids or *via* coupling of anthranilic acid and aryl halides.[4] In fact, a wide range of 2-bromobenzoic acid derivatives are readily available, for example, through oxidation of 2-alkyl-1-bromobenzenes[5] or lithiation of dibromobenzenes and subsequent treatment with carbon dioxide.[6] The previous cross-coupling procedures using 2-halobenzoic acids were limited in their applications because a higher reaction temperature (up to 130 °C) was required,[7] and various efforts to improve the efficiency of this reaction by using non-classical energy-supplying methods, such as ultrasound[8] and microwave-assisted[9] modes, have been reported. Recently, copper-catalyzed Ullmann *N*-arylations have made great progress.[4,10] Unfortunately, these methods sometimes cannot be used to construct some functional molecules because the reaction temperaturess are still too high, so it is highly desirable to develop milder copper-catalyzed coupling methods. Recently, Buchwald[11] and we[12] have developed copper-catalyzed *N*-arylations at room temperature, and the results showed that efficiency of the copper-catalyzed coupling reactions highly depended on involvement of suitable ligands, but only aryl iodides as the substrates were often effective. Herein, we report an efficient synthetic procedure providing a convenient access to a range of *N*-alkylanthranilic acids through copper-catalyzed amination of 2-bromo- and 2-iodobenzoic acid derivatives at room temperature.

Results and Discussion

First, 2-bromobenzoic acid and methylamine hydrochloride were chosen as the model substrates to optimize the catalytic conditions, including copper catalysts, ligands, bases and solvents in the *N*-arylation at room temperature as shown in Table 1. Several copper salts, CuCl, CuBr, CuI, $CuSO_4$, $CuCl_2$ and $Cu(OAc)_2$ (entries 1–6), were tested using DMF as the solvent, 20 mol% *rac*-BINOL as the ligand, K_3PO_4 (relative to 2-bromobenzoic acid) as the base, and the results showed that CuI was the most effective catalyst (entry 3). Other ligands, such as L-proline and *N,N′*-dimethylethylenediamine, were tested (entries 7 and 8), and *rac*-BINOL gave the highest yield (96%, entry 3). The reaction provided a 58% yield in the absence of ligand (entry 9). We also investigated the effect of solvents (compare entries 3, 10–12), DMSO was slightly inferior to DMF (entry 10), but the others were bad solvents (entries 11 and 12).

Table 1. Copper-catalyzed coupling of 2-bromobenzoic acid with methylamine hydrochloride: optimization of the catalytic conditions.[a]



Entry	Cat.	Ligand	Solvent	Base	Yield [%][b]
1	CuCl	**A**	DMF	K_3PO_4	trace
2	CuBr	**A**	DMF	K_3PO_4	20
3	**CuI**	**A**	**DMF**	**K_3PO_4**	**96**
4	$CuSO_4$	**A**	DMF	K_3PO_4	0
5	$CuCl_2$	**A**	DMF	K_3PO_4	trace
6	$Cu(OAc)_2$	**A**	DMF	K_3PO_4	0
7	CuI	**B**	DMF	K_3PO_4	25
8	CuI	**C**	DMF	K_3PO_4	67
9	CuI	–	DMF	K_3PO_4	58
10	CuI	**A**	DMSO	K_3PO_4	70
11	CuI	**A**	toluene	K_3PO_4	0
12	CuI	**A**	1,4-dioxane	K_3PO_4	0
13	CuI	**A**	DMF	Cs_2CO_3	35
14	CuI	**A**	DMF	K_2CO_3	trace
15	CuI	**A**	DMF	K_3PO_4	91[c]

[a] *Reaction conditions:* 2-bromobenzoic acid (1.0 mmol), methylamine hydrochloride (1.5 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (3 mmol), solvent (3 mL) at room temperature (~25 °C) under a nitrogen atmosphere.

[b] Isolated yield.

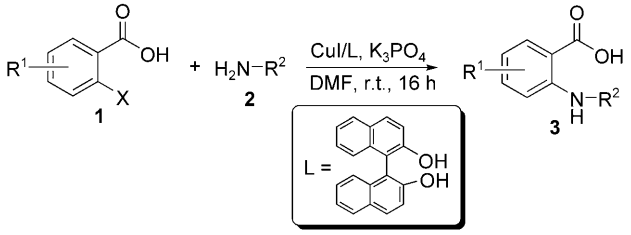
[c] 2.5 equiv. of K_3PO_4 were used as the base.

Bases also influenced the progress of the coupling reaction, and 3 equivalents of K_3PO_4 provided the highest yield (compare entries 3, 13 and 14). Changing the amount of base was also attempted, and the reaction afforded a slightly lower yield when 2.5 equivalents of K_3PO_4 were used (entry 15). After the optimization process of catalysts, ligands, solvents and bases, the following coupling reactions were carried out under our standard conditions: 10 mol% CuI as the catalyst, 20 mol% *rac*-BINOL as the ligand, DMF as the solvent and 2 or 3 equivalents of K_3PO_4 (2 equivalents of base for free amines, 3 equivalents of base for amine hydrochlorides) as the base (relative to 2-halobenzoic acids) at room temperature under a nitrogen atmosphere.

The optimized amination procedure was then applied to a variety of 2-halobenzoic acids and aliphatic amines to evaluate the synthetic potential of this method as shown in Table 2. For 2-bromo- and 2-iodobenzoic acid derivatives, the coupling reactions provided good to excellent yields (entries 1–22), but 2-chlorobenzoic acid was a poorer substrate (entries 23 and 24). Importantly, the copper-catalyzed amination proceeded with regioselectivity, and the reactions only occurred on the carbon-halogen bonds adjacent to the carboxyl group at room temperature, which was probably because of the accelerating effect of the adjacent carboxylate group (see reaction mechanism below). For example, couplings of 2-bromo-4-halobenzoic acids (**1d** and **1e**) with aliphatic amines only yielded *N*-alkyl-4-haloanthranilic acids (entries 16–20), however, *N*-alkyl-2-bromoanthranilic acids were not observed. Various functionalities were tolerated including alkenyl (entries 5, 12, 15, 17, 19, 22 and 24), hydroxy (entry 6), and ester groups (entry 10) in the aliphatic amines and nitro (entries 11–15), carbon-halogen bonds (except *ortho* carbon-halogen bonds of carboxylates) (entries 16–20) in the 2-halobenzoic acid derivatives. We attempted to increase the amount of K_3PO_4 for the slow reactions (such as entries 8, 9 and 17–20 in Table 2), but the couplings did not give higher yields. Electronic effects in the 2-halobenzoic acids including electron-rich and electron-deficient groups did not show any evident difference. The procedure is insensitive to moisture. The results above show that our amination procedure provides a convenient access to a wide range of *N*-alkylanthranilic acids from readily available, unprotected 2-halobenzoic acids and aliphatic amine derivatives.

We also investigated the mechanism of formation of *N*-alkylanthranilic acids. The reaction of 2-(2-bromophenyl)acetic acid with methylamine hydrochloride provided product **3u** in only 34% yield under the catalysis conditions as shown in Scheme 1, Eq. (1), and the structure of **3u** was identified by NMR and IR spectroscopy (see Supporting Information). The results showed the importance of the position of the

Table 2. Copper-catalyzed couplings of substituted 2-halobenzoic acids with aliphatic amines.[a]



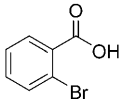
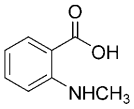
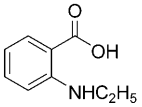
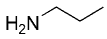
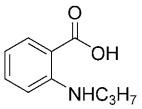
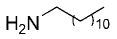
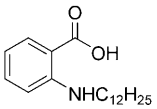
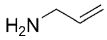
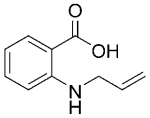
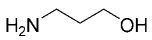
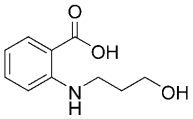
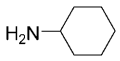
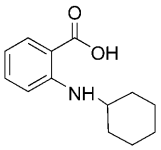
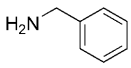
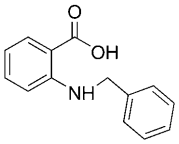
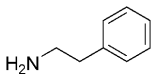
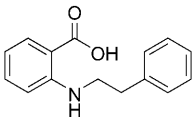
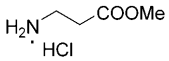
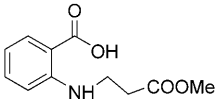
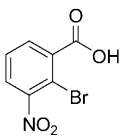
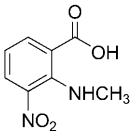
Entry	1		2		Product	Yield [%][b]
1	**1a**		**2a**	$CH_3NH_2 \cdot HCl$	**3a** 	96
2	**1a**		**2b**	$C_2H_5NH_2 \cdot HCl$	**3b** 	86
3	**1a**		**2c**		**3c** 	68
4	**1a**		**2d**		**3d** 	64
5	**1a**		**2e**		**3e** 	80
6	**1a**		**2f**		**3f** 	71
7	**1a**		**2g**		**3g** 	85
8	**1a**		**2h**		**3h** 	45
9	**1a**		**2i**		**3i** 	62
10	**1a**		**2j**		**3j** 	71
11	**1b**		**2a**		**3k** 	68

Table 2. (Continued)

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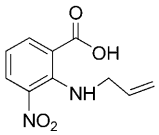
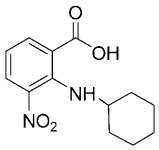
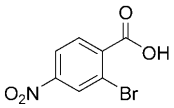
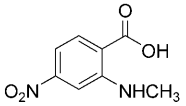
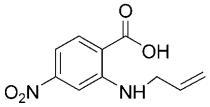
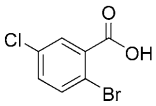
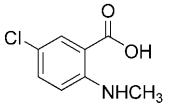
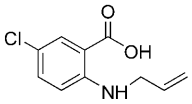
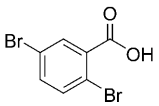
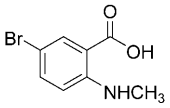
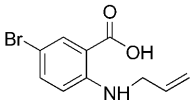
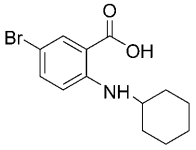
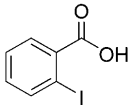
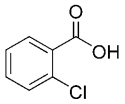
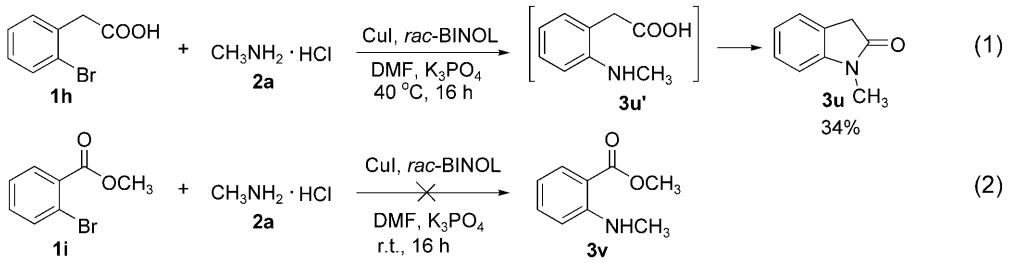
12	**1b**	**2e**	**3l** 	86
13	**1b**	**2g**	**3m** 	85
14	**1c** 	**2a**	**3n** 	77
15	**1c**	**2e**	**3o** 	65
16	**1d** 	**2a**	**3p** 	84
17	**1d**	**2e**	**3q** 	59
18	**1e** 	**2a**	**3r** 	66
19	**1e**	**2e**	**3s** 	59
20	**1e**	**2a**	**3t** 	40
21	**1f** 	**2a**	**3a**	95
22	**1f**	**2e**	**3e**	85
23	**1g** 	**2a**	**3a**	20
24	**1g**	**2e**	**3e**	16

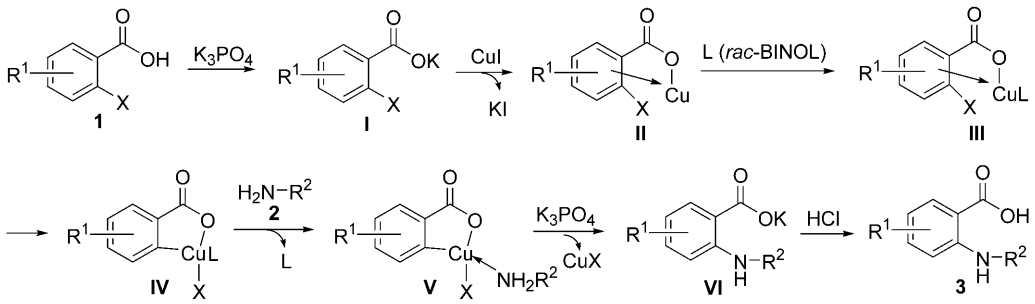
[a] *Reaction conditions:* substituted 2-halobenzoic acid (1.0 mmol), aliphatic amine (1.5 mmol), CuI (0.1 mmol), *rac*-BINOL (0.2 mmol), base (2 mmol for free amines; 3 mmol for amine hydrochloride), DMF (3 mL) at room temperature (~25 °C) under a nitrogen atmosphere.

[b] Isolated yield.

carboxyl group (compare with 2-bromobenzoic acid). When methyl 2-bromobenzoate was used as the substrate instead of 2-bromobenzoic acid, no desired product was observed [Scheme 1, Eq. (2)]. The *ortho*-carboxylate group has been known to effectively accelerate homogeneous copper-catalyzed exchange reactions.[13] Accordingly, a possible mechanism of formation of *N*-alkylanthranilic acids is proposed in



Scheme 1. Reactions of methylamine hydrochloride with 2-(2-bromophenyl)acetic acid [Eq. (1)] and methyl 2-bromobenzoate [Eq. (2)].



Scheme 2. Possible mechanism of formation of *N*-alkylanthranilic acids.

Scheme 2 according to the results above. Reaction of the substituted 2-halobenzoic acid with K_3PO_4 afforded the corresponding potassium benzoate (**I**), and treatment of **I** with CuI forms complex **II**. Coordination of *rac*-BINOL with **II** yields **III**, and oxidative addition of **III** gives **IV**. Treatment of **IV** with amine provides coordinated **V** freeing the ligand, and reductive elimination of **V** in the presence of base affords **VI** releasing the copper catalyst. Acidification of **VI** provides the target product **3**.

Conclusions

We have developed an efficient CuI/racemic 1,1′-binaphthyl-2,2′-diol (*rac*-BINOL)-catalyzed method for the synthesis of *N*-alkylanthranilic acids *via* couplings of 2-halobenzoic acids with aliphatic amines at room temperature. Various functionalities in the substrates were tolerated, and regioselectivity was observed because of the accelerating effect of the adjacent carboxylate group in the 2-halobenzoic acids. This mild and practical method may find broad academic as well as industrial applications.

Experimental Section

General Procedure for Copper-Catalyzed *N*-Arylations of Aliphatic Amines

A two-necked, round-bottomed flask was charged with a magnetic stirrer, evacuated and back-filled with nitrogen. The substituted 2-halobenzoic acid (1.0 mmol) and amine or amine hydrochloride (1.5 mmol) in DMF (3 mL), K_3PO_4 (2 mmol, 424 mg for free amine; 3 mmol, 636 mg for amine hydrochloride), racemic 1,1′-binaphthyl-2,2′-diol (*rac*-BINOL) (0.2 mmol, 57 mg) were added to the flask. After a 10 min stirring, CuI (0.1 mmol, 19 mg) was added under a nitrogen atmosphere. The mixture was allowed to stir at room temperature (~25 °C) under a nitrogen atmosphere for 16 h. 2 N HCl (10 mL) was added to the mixture, and the resulting solution was extracted with ethyl acetate (2×20 mL). The combined organic layer was washed with brine, and dried over anhydrous $MgSO_4$. The solvent was removed from the mixture with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (15:1 to 8:1) as eluent to provide the desired product.

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