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Chinese Chemical Letters 20 (2009) 784–788
CHINESE CHEMICAL LETTERS
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Microwave-assisted chemoselective copper-catalyzed amination of *o*-chloro and *o*-bromobenzoic acids using aromatic amines under solvent free conditions

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Received 12 November 2008

Abstract

Copper-catalyzed synthesis of *N*-aryl anthranilic acid derivatives using effective amination of 2-chloro and 2-bromobenzoic acid under microwave irradiation is reported. Some of the advantages of this method are high chemoselectivity, short reaction times, ease of work up procedure and elimination of the need for acid protection.

Keywords: Microwave-assisted; Copper-catalyzed; Solvent free; Amination; *N*-Aryl anthranilic acid

The substituted *N*-phenylanthranilic acid is common intermediate in the synthesis of pharmaceutically important molecules such as antimalarials [1,2], anti-inflammatory [3] and antineoplastics [4]. Non-steroidal anti-inflammatory drugs (NSAIDs), derivatives of *N*-phenyl anthranilic acid such as flufenamic (FLF) 1, tolfenamic (TLF) 2 and mefenamic (MEF) 3 acids (Fig. 1), are wildly used in inflammatory and painful diseases of rheumatic and non-rheumatic origin [5]. Also, among the wide variety of synthetic compounds recognized as potential anticancer drugs, molecules based on the anthranilic acid scaffold have attracted great interest in recent years [6].

The synthesis of these intermediates usually involve the condensation of functionalized anilines and *o*-halobenzoic acid derivatives resulting in the desired *N*-aryl anthranilic acids by either Ulmann–Goldberg/Jordan–Ulmann coupling [7,8] and palladium catalyzed C–N coupling reactions [9,10]. Traditional copper-catalyzed Ulmann-Goldberg or Jordan-Ulmann coupling protocols necessitate the use of higher reaction time and temperature, stochiometric amounts of anilines and copper reagent, which on scale, lead to problems of waste disposal [11–14]. These reactions can be carried out under milder conditions than the classical Ulmann condensation by using appropriate ligand [15]. Recent developments of this reaction led to utilization of *o*-halobenzoic acids with anilines, or other amino aryls, in the presence of a base and a source of copper as a catalyst [16].

In many cases, microwave irradiation has been successfully applied in solvent free heterogeneous reactions, which is especially advantageous from environmental aspects [17]. Development of environmentally benign organic reactions has become a crucial and demanding research area in modern organic chemical research. In this concern, we

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1001-8417/$ – see front matter © 2009 Published by Elsevier B.V. on behalf of Chinese Chemical Society.
doi:10.1016/j.cclet.2009.02.013

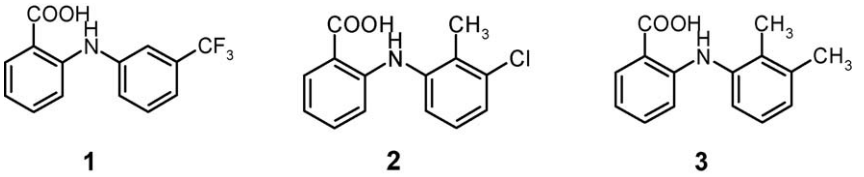


Fig. 1. Structures of *N*-aryl anthranilic acids.

wish to report a simple, convenient, efficient, economic and environmentally friendly method for the synthesis of *N*-aryl anthranilic acid derivatives by the copper acetate catalyzed reaction of *o*-chloro and *o*-bromobenzoic acids with anilines in the presence of anhydrous potassium carbonate as base.

1. Experimental

Melting points were determined on electro thermal apparatus and are uncorrected. All ^{1}H NMR spectra were recorded on Bruker 500 MHz spectrometer instrument. IR spectra were determined on SP-1100, P-UV-Com instrument. Microwave experiments were carried out in a domestic oven.

Typical procedure for copper-catalyzed N-arylation of o-chloro and o-bromobenzoic acids: In a 10 mL glass tube was placed 2-chloro or 2-bromo benzoic acid (5 mmol), aryl amine (10 mmol), $Cu(OAc)_2$ (0.7 mmol) and anhydrous K_2CO_3 (5 mmol). The mixture was stirred then the vessel was sealed with a septum and was placed in the microwave cavity. On completion of the reaction as monitored by TLC (ethyl acetate:*n*-hexan = 4:1, v/v). The cooled reaction mixture was poured into 3 × 20 mL of diethyl ether. The reaction mixture was filtered and the filtrate was evaporated. The residue was dissolved in 50 mL of 15% aqueous Na_2CO_3 solution and was filtered. The final product was isolated by precipitation upon acidification to pH 5 of the filtrate with dilute HCl.

Spectroscopic data for representative products:

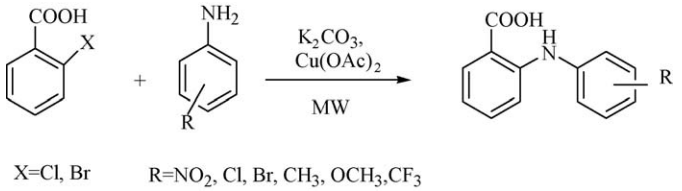
- Flufenamic acid (17): mp 124–125 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 6.88–7.93 (m, 8H, ArH), 9.69 (s, 1H, NH), 13.15(s, 1H, COOH).
- Tolfenamic acid (3): mp 205–207 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.24 (s, 3H, CH_3), 6.75–7.89 (m, 7H, ArH), 9.57 (s, 1H, NH), 13.14 (s, 1H, COOH).
- Mefenamic acid (7): mp 224–225 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.08 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.66–7.88 (m, 7H, ArH), 9.45 (s, 1H, NH), 12.98 (s, 1H, COOH).

2-[(2, 4-Dimethylphenyl) amino] benzoic acid (13): mp 185–187 °C; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 2.13 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.65-7.87 (m, 7H, ArH), 9.37 (s, 1H, NH), 12.95 (s, 1H, COOH).

2. Results and discussion

Herein we report a chemoselective 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. In order to decrease the reaction times and improve the yields, we examined the effect of microwave irradiation on the Ulmann condensation in dry media taking as a model the reaction of 2-chlorobenzoic acid with aniline and copper acetate as a catalyst (Scheme 1).

The condensation goes well with good yield in shorter duration by using *o*-chloro or *o*-bromobenzoic acids with 2.0 equiv. of aryl amines by using 1.0 equiv. of anhydrous potassium carbonate and 0.14 equiv. of copper acetate.



Scheme 1. Synthesis *N*-aryl anthranilic acids using Cu-catalyzed amination of 2-halobenzoic acids.

Table 1
Aromatic animation of *o*-chloro and *o*-bromobenzoic acids using $Cu(OAc)_2$ under microwave irradiation.

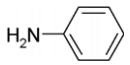
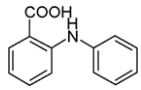
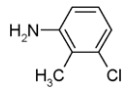
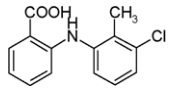
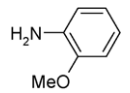
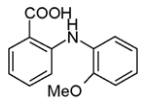
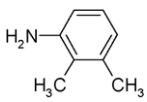
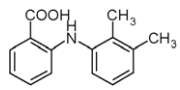
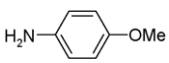
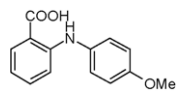
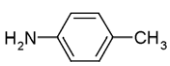
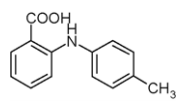
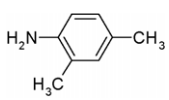
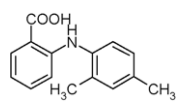
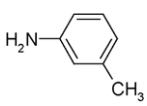
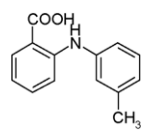
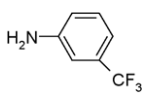
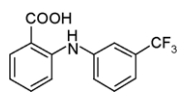
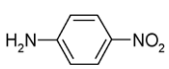
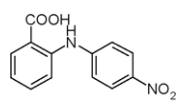
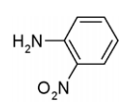
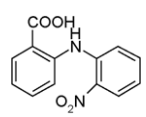
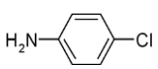
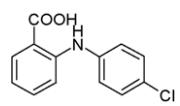
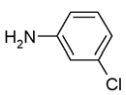
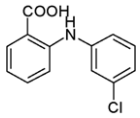
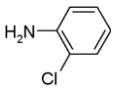
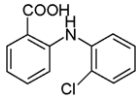
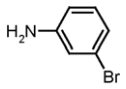
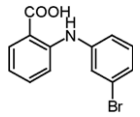
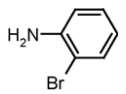
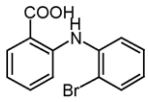
Entry	Aryl amine	*o*-Halobenzoic acid	Irradiation time (min)[a]	Product[b]	Yield[c] (%)
1		2-Cl	6		87
2		2-Br	6		93
3		2-Cl	14		75
4		2-Br	12.5		84
5		2-Cl	8		83
6		2-Br	6		91
7		2-Cl	8.7		83
8		2-Br	6.8		90
9		2-Cl	6.5		88
10		2-Br	6.0		97
11		2-Cl	6.6		85
12		2-Br	6.3		94
13		2-Cl	7		86
14		2-Br	6.5		91
15		2-Cl	7.5		87
16		2-Br	6.6		95
17		2-Cl	14.5		72
18		2-Br	13		76
19		2-Cl	11		75
20		2-Br	10		81
21		2-Cl	14		70
22		2-Br	13		78
23		2-Cl	13		78
24		2-Br	10		86

Table 1 (*Continued*)

Entry	Aryl amine	*o*-Halobenzoic acid	Irradiation time (min)[a]	Product[b]	Yield[c] (%)
25		2-Cl	14		73
26		2-Br	12.5		81
27		2-Cl	15		69
28		2-Br	14.5		75
29		2-Cl	11		74
30		2-Br	9		80
31		2-Cl	12		65
32		2-Br	11		69

[a] Entries 1–28 and 29–32 were carried out in 700 and 900 W, respectively.
[b] Products were confirmed by comparison with authentic samples (IR, ^{1}H NMR, TLC).
[c] Yield of isolated pure *N*-aryl anthranilic acid compounds.

Completion of the reaction was checked by TLC until the disappearance of starting material (*n*-Hexane:Ethyl acetate = 4:1). The optimized amination procedure was then applied to a variety of aryl amines and *o*-chloro or *o*-bromobenzoic acids to evaluate synthetic potential of this method (Table 1). All products are known compounds and were characterized by comparison of their physical and spectroscopic data with those reported in literatures. The infrared spectra of all products showed a singlet band in 3300–3350 cm^{-1} region, indicating a secondary amine. Melting point and ^{1}H NMR of the representative compounds are reported in Section 1.

The copper-catalyzed amination was found to proceed with high chemoselectivity. In all cases, the coupling reaction only occurred between aniline with *ortho* position of *o*-halobenzoic acid to produce variety of *N*-aryl anthracitic acids without formation of any amide by products. Aryl halide bonds located in the aniline moiety are also not affected (entries 23–32 and 3–4). As shown in Table 1, the microwave conditions worked well for a variety of anilines with electron-donating groups (entries 5–16). The presence of electron withdrawing groups like chloro, bromo, nitro and triflouro methyl groups in anilines slow down the reaction (entries 17–32). It can be seen that *o*-substituted compounds give comparatively low yield as compared to *p*-substituted compounds, which may be attributed to steric hindrance. *o*-Bromobenzoic acid substrate gave appreciably the lower reaction time than that of the corresponding *o*-chlorobenzoic acid substrate. However, when we used microwave-assisted protocol, the reaction times were dramatically decreased and in some cases higher yields than the traditional chemical methods were obtained.

3. Conclusion

In conclusion, we have developed a convenient, easy operation, environmental friendly, high yield procedure with high chemoselectivity and short reaction times for the synthesis of *N*-aryl anthranilic acid derivatives, which are the key intermediates in the synthesis of pharmaceutically molecules.

Acknowledgments

We gratefully acknowledge the financial support of this work by the Research Council of Mazandaran University.

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