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Preparation of *N*-Aryl Anthranilic Acid Drugs by Modified Ullmann Coupling Reaction in Ionic Liquids

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Abstract—*N*-Aryl anthranilic acid drugs have been synthesized by a simple, environmentally friendly, low-cost, and high-yielding modified Ullmann coupling reaction protocol using potassium 2-bromobenzoate, substituted anilines, and copper acetate in tetrabutylphosphonium chloride ([TBP]Cl) ionic liquid. The optimal conditions have been found and applied to the synthesis of *N*-aryl anthranilic acid drugs at 170°C. Mass spectrometry, X-ray crystallography, and proton nuclear magnetic resonance were used to describe the structure of the products. Copper(I) complex catalyst was used as a starting catalyst for the Ullmann reaction because of the good fluidity and homogeneity in [TBP]Cl ionic liquid. Meclofenamic, mefenamic, clofenamic, and flufenamic acids were synthesized efficiently using the proposed general procedure. The distinct advantages of the described protocol are operational simplicity, cleaner reaction, high selectivity, excellent yield, rapid conversion, easy preparation, and the use of a low-cost catalyst.

Keywords: Ullmann coupling reaction, NSAIDs, N-aryl anthranilic acids, meclofenamic acid, ionic liquids

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INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most frequently used prescription drugs in the market. They exhibit anti-inflammatory, analgesic, and antipyretic properties and are widely used to relieve acute gout, postoperative pain, renal colic, intestinal obstruction, and metastatic bone pain [1–3]. There are various types of NSAIDs. *N*-Aryl anthranilic acid derivatives have been discovered in 1958, and they showed a strong effect in animal anti-erythema experiments. Since then, lunatic, codenamed, and mycophenolic acids have been discovered, and clinical trials have been carried out [4, 5]. Meclofenamic acid was first reported in 1977 and listed in 1981 by the American company Parke-Davis. It belongs to the *N*-aryl anthranilic acid family of NSAIDs and has anti-inflammatory, analgesic, and antipyretic effects. The key step in the synthesis of meclofenamic acid is the Ullmann coupling reaction [6–9]. However, the characteristics of the Ullmann reaction and the large number of functional groups on the benzene ring of the raw material lead to low yields [10]. Therefore, we tried using an ionic liquid as the reaction solvent to improve the yield. Researchers have tried using ionic liquids as solvents in organic reactions and found that they have a good promoting effect. Before that, either water or organic solvents were used as solvents in organic synthesis. However, most organic solvents have various shortcomings. They not only pollute the environment but also cause toxic effects on production personnel, and their flammable and explosive characteristics have also caused many painful accidents in the history of human chemical industry. As ionic compounds, ionic liquids have low vapor pressure, low toxicity, and high stability, which makes them more in line with the current concept of safe and green production [11–16]. This study explores the effects of different conditions of the Ullmann coupling reaction for different raw materials on the yield of *N*-aryl anthranilic acid drugs, tries to explain the reaction mechanism, and, finally, determines the best reaction conditions. The synthetic route is shown in Scheme 1.

We analyzed the conventional method for synthesizing *N*-aryl anthranilic acid drugs by consulting the

Scheme 1.

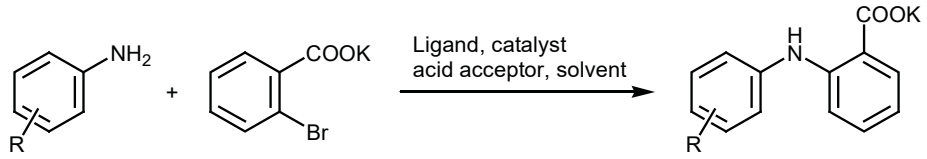
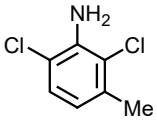
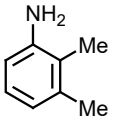
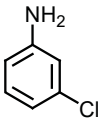
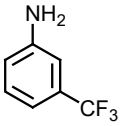


Table 1. Yields of conventional *N*-aryl anthranilic acid drugs **1**–**4** reported in the literature

Aniline	Solvent	Acid acceptor	Catalyst	Product	Yield, %
	DMF	*N*-Ethylmorpholine	$Cu(OAc)_2$	Meclofenamic acid (**1**)	55.6 [19]
	$MeO(CH_2)_2OH$	K_2CO_3	Cu/Cu_2O	Mefenamic acid (**2**)	53.3 [20]
	$EtO(CH_2)_2OH$	*N*-Ethylmorpholine	Cu/Cu_2O	Clofenamic acid (**3**)	53 [21]
	Dioxane	K_2CO_3	CuO	Flufenamic acid (**4**)	48.9 [22]

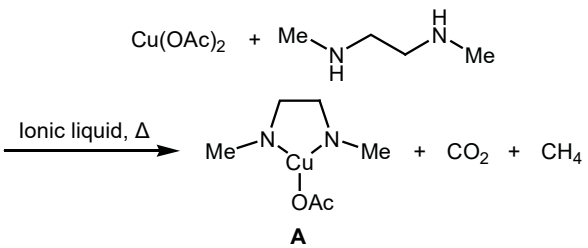
literature [17, 18] (Table 1). As shown in Table 1, the conventional Ullmann reaction has disadvantages such as low yield, complicated posttreatment process, and low atom economy. We speculate that it may be due to the poor compatibility of the valence state of the copper salt catalyst with the reaction solvent. According to the literature, some researchers used ionic liquids in the Ullmann reaction and achieved beneficial results. Therefore, we tried to synthesize *N*-aryl anthranilic acid drugs using ionic liquids. Ionic liquids have extremely low vapor pressure, good solvation properties, strong thermal stability, and easy-to-adjust chemical and physical properties [23, 24]. Therefore, as a reaction solvent, ionic liquids are suitable for the Ullmann reaction.

RESULTS AND DISCUSSION

Due to the large steric hindrance of 2,6-dichloro-3-methylaniline, it was the most difficult to synthesize the corresponding *N*-aryl anthranilic acid derivative (**1**). In addition, the Ullmann coupling reaction requires selection of suitable catalysts and ligands. Therefore, the process may be further optimized. The choice of reaction catalyst, acid-binding agent, and solvent was investigated. To explore the effect of reaction temperature on the yield of the Ullmann reaction, the synthesis of **1** was carried out at different temperatures using *N*,*N*′-Dimethylethylenediamine as acid acceptor, $Cu(OAc)_2$ as catalyst, and [TBP]Cl as solvent.

As shown in Fig. 1, the increase in temperature is useful for the progress of the Ullmann reaction. Additionally, the temperature of the reaction system has an important effect on the formation of cuprous acetate.

Scheme 2.



A

Finally, the best yield was reached at 170°C. According to Zhang's report [25], copper acetate decomposes into cuprous acetate under heating condition, and we proposed the reaction mechanism shown in Scheme 2.

Initially, with an increase in temperature, copper acetate ($Cu(OAc)_2$) slowly decomposes to produce cuprous acetate (CuOAc). Copper(I) complex catalyst **A** is formed very quickly with *N*,*N*′-dimethylethylenediamine at 170°C. Reactive intermediate **A** is highly soluble in ionic liquids, and a homogeneous phase is easily formed. Therefore, it is easier to collide with the amino group of 2,6-dichloro-3-methylaniline. However, as shown in Fig. 1, $Cu(OAc)_2$ easily decomposes above 170°C into cuprous oxide which is poorly soluble in ionic liquid, so that the catalytic effect and the yield are reduced. Although the steric hindrance of the amino group of 2,6-dichloro-3-methylaniline is relatively large, the reaction goes smoothly because of the good fluidity and homogeneity.

We attempted to prepare compound **1** in four ionic liquids as solvents. *N*,*N*′-dimethylethylenediamine was used as both acid acceptor and ligand, and $Cu(OAc)_2$ was used as CuOAc source. The reaction was carried out at 170°C for 18 h in a nitrogen atmosphere. As shown in Table 2, the yield was improved by using suitable ionic liquids as a solvent. Ionic liquids well dissolve the catalyst and make the reaction to proceed more smoothly. Moreover, the reaction system can be safely held at 170°C to complete the reaction. It is also very convenient that no emulsion was formed when the target product was extracted during workup. Although

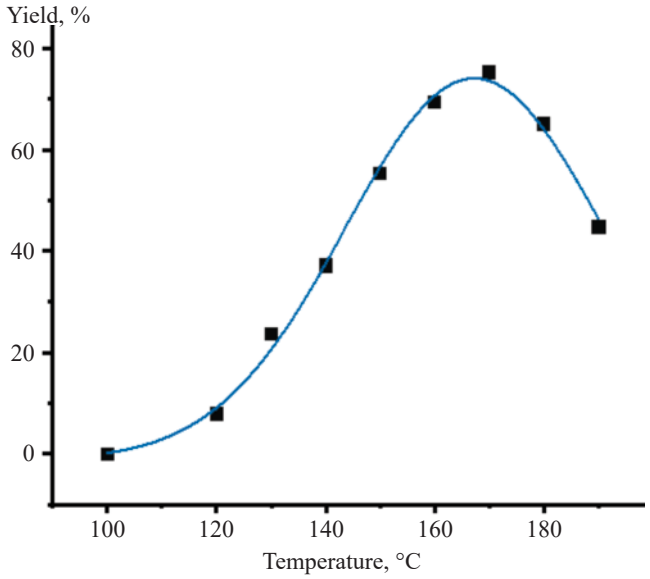


Fig. 1. Effects of temperature on the yield of **1**.

a higher yield can be achieved using CuI, $Cu(OAc)_2$ is more advantageous in terms of price. When [BMIM]OTf was used as a solvent, the reaction did not proceed smoothly, presumably due to formation of $Cu(OTF)_2$ with a more stable crystal structure which decomposes at 530°C.

Compared with acid **1**, the raw materials for *N*-aryl anthranilic acid derivatives **2**–**4** are less substituted on the benzene ring. Therefore, these three drugs were prepared more easily than **1**. The raw materials were also cheap and easily available. We have selected several reaction conditions with better performance to synthesize them.

Table 2. Effect of ionic liquids on the yield of meclofenamic acid (**1**)

Entry no.	Solvent[a]	Catalyst	Yield,[b] %
1	[EMIM][BF_4]	$Cu(OAc)_2$	68.1
2	[TBP]Cl	$Cu(OAc)_2$	75.2
3	[TBP]Cl	Cu_2O	67.9
4	[TBP]Cl	CuI	74.5
5	[TBP]Cl	Cu	46.3
6	[BMIM][BF_4]	$Cu(OAc)_2$	70.2
7	[BMIM]OTf	$Cu(OAc)_2$	0

[a] [EMIM][BF_4]: 1-ethyl-3-methylimidazolium tetrafluoroborate; [BMIM][BF_4]: 1-butyl-3-methylimidazolium tetrafluoroborate; [BMIM]OTf: 1-butyl-3-methylimidazolium trifluoromethanesulfonate.

[b] According to the LC analysis data without purification.

Table 3. Effects of ionic liquids and reaction time on the yields of *N*-aryl anthranilic acids **1**–**4**

Product	Solvent	Reaction time, h	Yield, %
2	[EMIM][BF_4]	18	75.6
	[TBP]Cl	18	81.1
	[TBP]Cl	12	68.2
	[TBP]Cl	6	35.7
	[BMIM][BF_4]	18	78.5
3	[EMIM][BF_4]	18	85.9
	[TBP]Cl	18	84.2
	[TBP]Cl	12	66.7
	[TBP]Cl	6	39.9
	[BMIM][BF_4]	18	83.3
4	[EMIM][BF_4]	18	73.7
	[TBP]Cl	18	79.5
	[TBP]Cl	12	62.1
	[TBP]Cl	6	32.3
	[BMIM][BF_4]	18	76.3

Scheme 3.

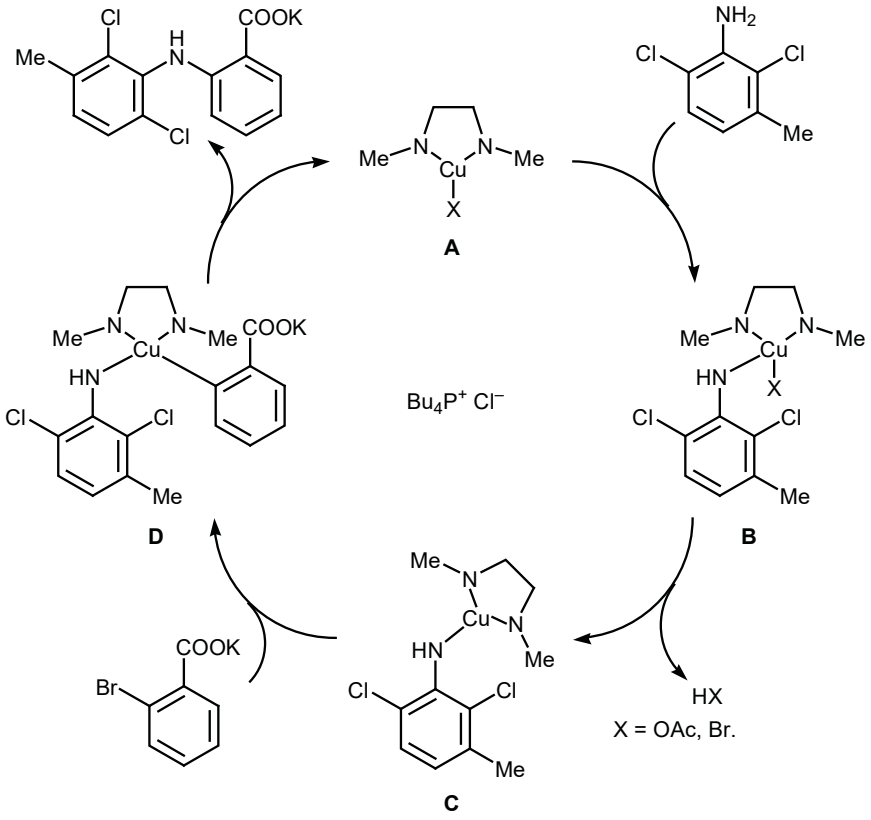


Table 3 shows that the yield trends of **2**, **3**, and **4** were roughly the same as for **1**. Due to the simple structure of the raw materials, their yields were also relatively high. The reaction time also has a greater impact on the yield of the reaction. Scheme 3 shows a plausible reaction mechanism with 2,6-dichloro-3-methylaniline as an example. Initially, $Cu(OAc)_2$ on heating in ionic liquid is converted to CuOAc which quickly forms copper(I) complex **A** with *N*,*N*′-dimethylethylenediamine. Then, the aryl nitrogen atom is attracted to participate in the coupling to form quaternary coupling state **B**. Next, elimination of hydrogen halide returns to ternary coupling state **C**. Subsequently, potassium 2-bromobenzoate participates in the coupling and forms stable coupling product **D**. Finally, *N*,*N*′-dimethylethylenediamine and copper ligands return to their original state and continue to participate in the catalytic coupling of the next molecule. The whole reaction is carried out in [TBP]Cl ionic liquid whose properties greatly promote the entire reaction progress.

EXPERIMENTAL

Ionic liquids were purchased from MonIonic Liquids Chem. Tech. Co., Ltd. (Shanghai). The other reagents and solvents were obtained from Aladdin or Macklin and were used as received without further purification. All reactions were monitored by thin-layer chromatography using commercial silica gel plates. Melting points were observed with a YRT-3 melting point tester and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker ACF-400 spectrometer at 400 MHz in DMSO-d_6 with tetramethylsilane as internal standard. High-resolution mass spectrometry was undertaken on an Agilent 7250 or JEOL-JMS-T100LP AccuTOF mass spectrometer.

Suitable single crystals of **1** were selected for lattice parameter determination and collection of intensity data on a Bruker SMART APEX CCD diffractometer with graphite-monochromated radiation (Mo K_α, λ = 0.071073 nm) using a φ–ω scan mode at 296(2) K. Multiscan absorption corrections were applied to all intensity data using SADABS. The structures were solved by direct methods and refined against F^2 by full-matrix least-squares procedures using SHELXTL software. All non-hydrogen atoms were refined in anisotropic approximation. All hydrogen atoms were fixed in the calculated positions and refined isotropically [26]. The molecular structure of **1** is shown in Fig. 2.

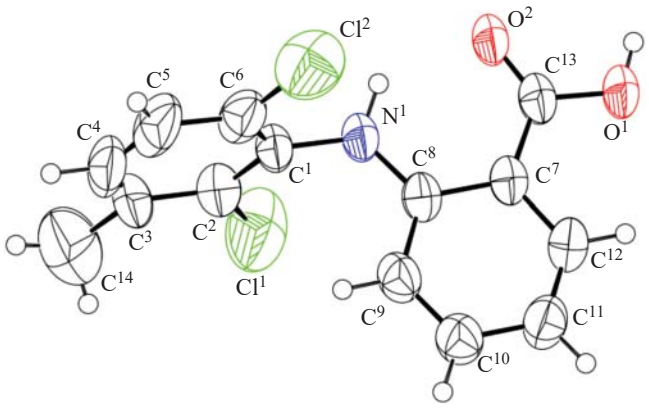


Fig. 2. Structure of the molecule of meclofenamic acid (**1**) according to the X-ray diffraction data.

General procedure for the synthesis of *N*-aryl anthranilic acid derivatives 1–4. The corresponding substituted aniline (46 mmol), potassium 2-bromobenzoate (57 mmol), copper-based catalyst (4.7 mmol), and acid acceptor (0.096 mol) were added to an appropriate ionic liquid (30 mL). The mixture was heated at 170°C for 18 h in a nitrogen atmosphere [27, 28]. After acidification, extraction, suction filtration, rotary evaporation, and recrystallization, white crystals were obtained.

Meclofenamic acid (1). mp 257°C. ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 6.78–7.91 m (6H, H_{arom}), 9.93 s (1H, NH), 13.19 s (1H, COOH).. Mass spectrum (ESI): *m*/*z* 294.0082 [M – 1]$^+$; calculated for $C_{14}H_{10}Cl_2NO_2$: 294.1322. Monoclinic crystal system, space group $P2_1/c$; unit cell parameters: a = 8.608(4), b = 8.951(2), c = 9.479(3) Å; α = 102.794(5), β = 99.576(5), γ = 92.360 (5)°; V = 688.3(5) Å^3; Z = 2; R = 0.0874.

Mefenamic acid (2). mp 230°C. ^{1}H NMR spectrum, δ, ppm: 2.08 s (3H, CH_3), 2.29 s (3H, CH_3), 6.68–7.88 m (7H, H_{arom}), 9.46 s (1H, NH). Mass spectrum (ESI): *m*/*z* 240.1022 [M – 1]$^+$; calculated for $C_{15}H_{15}NO_2$: 240.2772.

Clofenamic acid (3). mp 171°C. ^{1}H NMR spectrum, δ, ppm: 6.87–7.92 m (8H, H_{arom}), 9.63 s (1H, NH). Mass spectrum (ESI): *m*/*z* 246.0323 [M – 1]$^+$; calculated for $C_{13}H_{10}ClNO_2$: 246.6688.

Flufenamic acid (4). mp 133°C. ^{1}H NMR spectrum, δ, ppm: 6.90–8.02 m (8H, H_{arom}), 9.68 s (1H, NH). Mass spectrum (ESI): *m*/*z* 282.0612 [M + 1]$^+$; calculated for $C_{14}H_{10}F_3NO_2$: 280.2379.

CONCLUSIONS

The influence of different reaction conditions on the synthesis of meclofenamic acid by the Ullmann coupling reaction has been studied, and suitable catalysts, acid-binding agents, and solvents have been proposed for this reaction. In particular, the application of ionic liquids in the synthesis of *N*-aryl anthranilic acid drugs largely improves the reaction yield. After optimization of the conditions, the yield of meclofenamic acid finally increases to 75.2%. The yield is particularly improved by using ionic liquids. Moreover, the reaction time and postprocessing difficulty are reduced, thus reducing the cost of industrial production. The results of this study can be used to increase the yield of meclofenamic acid and other *N*-aryl anthranilic acid drugs.

ACKNOWLEDGEMENTS

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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