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Copper-catalyzed C–N coupling reactions of aryl halides with α-amino acids under focused microwave irradiation

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ABSTRACT

We have developed an efficient method for the preparation of enantiopure *N*-aryl-α-amino acids via copper-catalyzed N-arylation of α-amino acids and aryl halides under microwave irradiation. This protocol only needs less than 30 min to obtain the products, which are far superior to those obtained under conventional heating.

1. Introduction

The formation of the carbon–nitrogen bond by the copper-catalyzed coupling of aryl halides with α-amino acids is one of the typical Ullmann condensation reactions.[1] The research on palladium- and copper-catalyzed arylations of amines was pioneered by Buchwald and Hartwig.[2,3] Nowadays, copper-catalyzed *N*-aryl bond formations rank among the most powerful methods in organic synthesis.[4,5] These copper-catalyzed N-arylations of amino acids offer many advantages,[6–9] but the reported transformations are in most cases both sluggish and time-consuming; normally these reactions suffer from problems such as harsh conditions, limited generality, and numerous synthetic steps.[4,6,10,11] Several Pd-catalyzed C–N formation methods have been introduced, which upon using some sterically hindered phosphine ligands,[11,12] carbocyclic carbene ligands[8] allowed many coupling reactions of aryl halides with N-containing compounds to proceed under relatively mild conditions and low temperature.[6] However, industrial use of these methods is hampered by the higher costs of Pd catalysts and the ligands, as well as by air and moisture sensitivity.[7] Although recent advances have made this route more attractive, a simpler, cost-effective development and a more efficient metal catalyst which can be suitable for the synthesis of chiral *N*-aryl-L-amino acids, are highly desirable.

Among numerous functionalized amines, α-amino acid is a key building block in organic synthesis because of its further conversions.[13,14] Furthermore, chiral *N*-aryl-α-amino acids are the common core structures for a number of synthetically challenging and medicinally important agents such as protein kinase C (PKC) activators, indolactam-V[15,16] and its analogue benzolactam-V8;[17] fibrinogen receptor antagonist SB 214857;[18] NMDA receptor antagonist L689560[19] and tricyclic quinoxalinedions;[20] ACE inhibitors;[21] and antiulcer agents.[22] In the past years, these structures were synthesized via several steps to get the desired enantiomerically pure form. The more direct and economical option, the coupling of an aryl halide with an amino acid derivative was achieved only when the aromatic ring was activated with an electron-withdrawing substituent.[23] An alternative method for N-arylation is the Cu-catalyzed reaction. This method is attractive from an economic standpoint because Cu is much cheaper than Pd and the removal of Pd residues from polar reaction products is difficult.[24–26] Some of the Cu-catalyzed C–N coupling reactions have been reported with 2-dimethylaminoethanol ligand,[26] *N*,*N*-diethylsalicylamide,[27] polymer-supported compounds (PS-PEG resin),[28] and Pd–Cu over TEBA.[6,29,30] Without Pd catalyst the CuI itself could catalyze the C–N coupling reaction under the reported procedure and a good yield can be obtained. The main drawbacks of the above reported methods among others are the bulkiness of ligands, the difficulty to remove the polymer support from the product, more reaction time, limited substrates and a low yield. Therefore, a general Cu-catalyzed C–N coupling reaction of aryl halides with α-amino acids appears attractive and is of great value.

However, the C–N coupling reaction requires longer reaction time and is performed in the presence of ligands, usually, at high temperature.[6] So, there is a need to decrease the reaction time as well as to simplify the purification procedure. Thus, high-density

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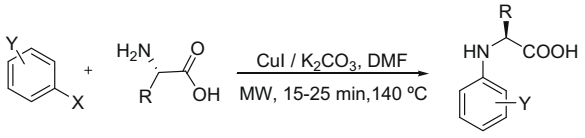
microwave heating has become an effective procedure because it allows rapid and convenient superheating to high temperatures in combination with excellent reaction control and low energy consumption. It has been proven recently that microwave heating improves the preparative efficiency and reduces the reaction time for several different types of organic transformations.[31–33] Although some of the microwave-enhanced palladium and palladium–copper reactions have been reported,[30,34] few references have shown the use of microwave heating with limited scope to the C–N and C–O cross-coupling reaction. Herein, we wish to report the development of a fast microwave-enhanced C–N coupling reaction for preparing chiral *N*-aryl-L-amino acids by copper-catalyzed coupling of L-amino acids with substituted aryl halides. In comparison with the current methods of the C–N bond formation, our approach displays specific advantages: (i) it proceeds faster and gives moderate to good yields; (ii) it requires only the inexpensive CuI; and (iii) it is applicable to a broader substrate scope (various amino acids and electron-rich and electron-deficient aryl halides).

2. Results and discussion

Initially, the coupling reaction of bromobenzene (1 mmol) with L-valine (1 mmol) was tried by using copper acetate (10 mol %) and K_2CO_3 (1 mmol) in DMF (3 mL) which gave only 45% yield of the C–N coupled product. After that we increased the loading of K_2CO_3 from 1 mmol to 1.5 mmol, which yielded 78% of the product. Further increasing to 2 mmol did not result in any improvement of yield. All the reactions were done under conventional heating in an oil bath at 140 °C in 6 h. Here it is worth mentioning that when the same reaction was done at 90 °C under conventional heating it took 48 h for completion. To compare the efficacy of microwave irradiation with that of conventional heating, the reaction was repeated in focused microwave (Biotage) oven in a sealed vessel under the same conditions for 15 min (140 °C) which gave almost the same yield to that of conventional heating (see Scheme 1). This was followed by another coupling reaction of bromobenzene with glycine with identical condition, but no desired product was observed. This could be attributed to the lack of reactivity due to the zwitterionic nature of the amino acids. Thus, the function of K_2CO_3 in this reaction is to enhance the nucleophilicity of amino acid especially, the amine group. Good yields (60–90%) of the N-arylated amino acids were produced under microwave irradiation at 140 °C in 10–25 min.[35] The results obtained are summarized in Table 1.

The C–N coupling reaction was also tested for a number of different amino acids and *ortho*- and *para*-substituted aryl halides. The reactivity of aryl halides was greatly improved by electron-withdrawing groups such as NO_2, $COCH_3$, either *ortho* or *para* to the aryl halides. 1-Bromo-2-nitrobenzene gave 90% of the C–N coupled yield where as 4-bromotoluene gave only 64% of the C–N coupled yield. From this we found that electron-rich aryl halides gave lower yields than electron-deficient aryl halides. However, aryl chlorides were poor coupling reagents. Both CuI and $Cu(OAc)_2$ catalyzed this reaction but CuI is more efficient than copper acetate. Both electron-deficient and electron-rich aryl bromides and iodides underwent the coupling reactions (entry 9–14).



Scheme 1. Copper-catalyzed C–N coupling reaction of aryl halides with α-amino acids.

Table 1
Copper-catalyzed coupling reaction of aryl halides and α-amino acids[a]

Entry	ArX		Amino acid	Catalyst	Time (min)	Yield[b] (%)
	X	Y				
1	Br	H	L-Valine	$Cu(OAc)_2$	15	78
2	B	H	L-Valine	CuI	15	80
3	Br	H	L-Proline	CuI	20	75
4	Br	H	L-Phenylalanine	CuI	20	65
5	Br	H	Glycine	CuI	20	0
6	4-I	$COCH_3$	L-Valine	CuI	18	89
7	4-I	$COCH_3$	L-Proline	CuI	20	83
8	4-Br	$COCH_3$	L-Valine	CuI	20	82
9	4-Br	$COCH_3$	L-Proline	CuI	18	80
10	4-Br	CH_3	L-Proline	CuI	22	65
11	4-Br	CH_3	L-Valine	$Cu(OAc)_2$	25	64
12	1-Br	$COCH_3$	L-Valine	CuI	20	78
13	1-Br	$COCH_3$	L-Proline	CuI	20	80
14	1-Br	2-NO_2	L-Proline	CuI	15	90
15	1-Br	2-NO_2	L-Valine	CuI	16	89

[a] Reaction conditions: 10 mol % CuI, 1.5 mmol K_2CO_3, ArX (1 mmol), amino acid (1 mmol), DMF (3 mL), under microwave irradiation (140 °C).
[b] Isolated yield.

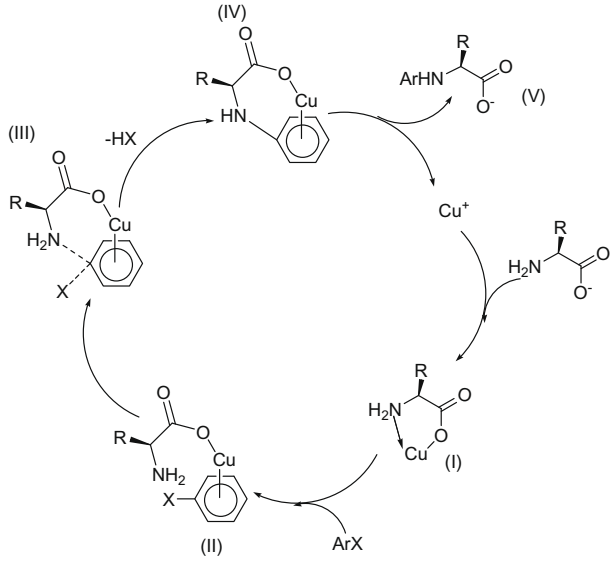
These results are consistent with the literature and the microwave heating gave the same results as conventional heating but in a very short time. 4-Iodoacetophenone gave higher yield (89%) than 4-bromoacetophenone (78%), that is, the iodobenzene reacts more quickly than bromobenzene and chlorobenzene. The displacement of halogen from the aromatic ring is in the following order:

$$I > Br > Cl$$

The synthetic utility of the present reaction methodology can be illustrated by some reaction products. For instance *N*-phenyl-L-valine, the direct coupling product of L-valine with bromobenzene, is a key precursor for synthesizing antiulcer agents,[22] while the original synthesis for this compound took several steps to yield the racemic product. However, the optical rotation of the product revealed that no racemizations had occurred. Optical rotation of the coupling product was obtained on a Rudolph Autopol IV polarimeter at a wavelength of 50 nm. Thus the present method provides a very efficient protocol to synthesize compounds with therapeutic value.

3. Mechanism studies

On the basis of the proposed D. Ma and co-workers' mechanism of the Cu(I)-catalyzed coupling reaction of aryl halides with α-amino acid,[6] we present the following mechanism for the reaction. In the first 10 min of the bromobenzene and L-valine reaction we found that a blue-colored complex was formed and, further, we increased the time to 15 min, after which the blue-colored complex disappeared and formed the final product. It is a well known fact that copper ions can form chelates with amino acids through amino and carboxyl groups. This blue-colored complex was Cu(I)–L-valine chelate (Scheme 2). First the cuprous ion reacts with α-amino acid to form the chelate (I), which was coordinated with a suitable aryl halide to provide the π-complex (II). After that, intramolecular nucleophilic substitution occurs at the aromatic ring to give the intermediate (III). This step might be the rate-determining step, and the intramolecular attack lowers the activation energy. The distance between amino and carboxylate groups is increased, the size of the ring in the transition state (III) becomes larger, therefore (III) would be more unstable. This might be the accelerating effect induced by the structure of different amino acids which decreases in the following order: α-amino acid > β-amino acid > γ-amino acid. Finally, HX is removed from (III) by using K_2CO_3 to produce another



Scheme 2. Catalytic cycle.

π-complex (IV), which decomposes to produce the *N*-aryl-α-amino acid (V) and regenerates the cuprous ion.

4. Conclusion

In brief, we have successfully developed a general method for the microwave-assisted N-arylation of amino acids in DMF providing moderate to high yields, high catalytic activity, and selectivity. The catalyst system is inexpensive, safe, and encounters fewer environmental problems. CuI is an effective catalyst for this C–N coupling reaction. We have reported a convenient microwave-enhanced, high speed, short, and economic way for the synthesis of *N*-aryl-α-amino acids, which are common core structures for a number of biologically active compounds. Though the present protocol uses DMF as a solvent further research is under progress with alternative reaction conditions.

Acknowledgments

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35. *General procedure for reaction of amino acid and aryl halides:* Typically, a mixture of L-valine (1 mmol), 4-iodoacetophenone (1 mmol), CuI or $Cu(OAc)_2$ (10 mol %), K_2CO_3 (1.5 mmol), and DMF (3 mL) was heated for 18 min in a 10 mL vessel. The vessel was sealed with a septum and placed inside the microwave cavity in the Biotage microwave reactor and subjected to microwave irradiation. The temperature was fixed at 140 °C. Initial microwave irradiation of 150 W was used, with the temperature being ramped from room temperature to the desired temperature of 140 °C (measured using the built-in IR temperature device). Once this was reached, the reaction mixture was held at this temperature until a total time of 15 min had elapsed. During this time, the power was modulated automatically to hold the reaction mixture at 140 °C. The mixture was not stirred during the reaction. In order to cool the reaction mixture vessel, nitrogen gas was passed to the surroundings of the vessel in microwave cavity, and after being cooled to room temperature the reaction mixture was diluted with 10 mL of ethyl acetate and 10 mL of water. Under cooling with ice/water, concentrated HCl was added to adjust the pH to 2–3. Then the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to dryness by rotovapor. The resulting residual oil was loaded on a silica gel column and eluted with ethyl acetate/petroleum ether (5:95) to afford the desired pure coupling product. ^1H NMR spectra were recorded with TMS as an internal standard on a Brucker AM-400 spectrometer. Spectral data for *N*-(acetylphenyl)-L-valine: ^1H NMR (400 MHz, $CDCl_3$) δ ppm, 7.8 (m, 2H), 6.5–6.6 (m, 2H), 4.0 (d, 1H), 2.5 (d, 1H), 2.1 (s, 3H), 1.05–1.1 (m, 6H).
Optical rotation $[\alpha]^{50} = -222.00$ (*c* 0.2, EtOH).