

Synthesis of Diaryl Ethers by CuI-Catalyzed C-O Bond Formation via Ullman Coupling: Assessing the Reactivity of Aryl Halides

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Abstract: Using cuprous iodide as the catalyst, aryl halides reacted with phenols to form diaryl ethers. The reaction conditions were optimized: aryl halides (1 equiv) reacted with phenol (1 equiv) at 130 °C in DMF for 16 h with cuprous iodide (10 mol %), cesium carbonate (2.5 equiv) as the base, and tetramethylenediamine (5 mol %) as the ligand. Under the optimum conditions, reaction conversion with time was summarized. The structural parameters of four types of aryl halides and the ionization energy of various C-X bond lengths in all aryl halides-CuI π -complexes were calculated at the B3LYP/LANL2MB level by using the Gaussian 03 program and the corresponding Ullman reaction conversion was determined by HPLC. Results suggested that different relationships existed between reactivity and the energy of the lowest unoccupied molecular orbital E_{LUMO} , mean polarizability α and dipole moment μ . Both experimental and theoretical results, all displayed Ullman coupling reactivity order of the four aryl halides: fluorobenzene \ll chlorobenzene $<$ bromobenzene $<$ iodobenzene.

Keywords: Aryl halides, cuprous iodide, diaryl ethers, Gaussian computation, reactivity, Ullman coupling.

1. INTRODUCTION

Diaryl ethers are important organic compounds and play significant roles in chemical industry and medicine chemistry [1]. Many of them have shown special biological and pharmacological activities [2, 3]. Diaryl ethers are also widely used in material products, commercial dyes and so on [4]. Due to their wide distribution and important application, diaryl ethers and its derivatives have captured the interests of researchers for a long time. As a result, approaches to synthesize diaryl ethers have been investigated for over a century. Many papers reported new routes to carbon-oxygen bond formation, including many important review articles on the copper-mediated coupling reactions [5-7].

Traditional route to synthesize diaryl ethers is of Pd- or Cu-catalyzed Ullmann coupled with aryl halides and phenols to form C-O bond [8, 9]. Although Pd catalyzed C-O bond formations are successful to certain extent, copper-based catalysts are more attractive because of inexpensive raw materials, simple operations and low toxicity [10, 11]. The classical Cu-catalyzed Ullmann etherification is simple and useful but has many drawbacks such as harsh reaction conditions (high reaction temperature, high polarity solvent and the use of a strong base), limited scope of substrates, and great quantity of a copper salt which have severely limited the synthetic applications of this reaction [12-14].

At the present, lots of new ligands emerged and were introduced to promote the Cu-catalyzed Ullman coupling

reactions, and many efficient and simple synthetic methods for diaryl ethers have been developed. Buchwald [15] and Martina [16] groups reported that substituted diaryl ethers were synthesized using CuI as copper source and adding proper ligand; Niu [17] and co-workers proposed an efficient method to form C-O bond by the reaction of aliphatic alcohols with aryl halides with an air-stable copper (I) complex as the catalyst; Armelle [18] and co-workers found that the coupling of phenols and aryl bromides can be efficiently performed with catalytic amounts of cuprous iodide and the inexpensive ligand in a mild condition. Although previous studies focused on the Ullman coupling reactivity of aryl halides to synthesized diaryl ether, only few reports try to explain the phenomenon both in experimental and theoretical pattern. Hence, corresponding investigations need to be carried out.

In the present study, diaryl ethers were synthesized by the joining of ligands with aryl halides as the substrates, cuprous iodide as the catalyst, and the optimum Ullman coupling reaction conditions were obtained.

The reactivity (Ullman coupling reaction yield) of four types of aryl halides (fluorobenzene, chlorobenzene, bromobenzene and iodobenzene) was measured using high performance liquid chromatography (HPLC) under optimized conditions. The structural parameters of four aryl halides and ionization energies of four types of aryl halides with the influences of CuI were calculated on the B3LYP/LANL2MB level with the Gaussian 03 program [19]. With the combinations of the experimental data and the theoretical values, the Ullman coupling reactivity order of four aryl halides was proposed, and the corresponding explanations were tentatively given. In addition, the relationship between the structural parameters and reactivity was discussed.

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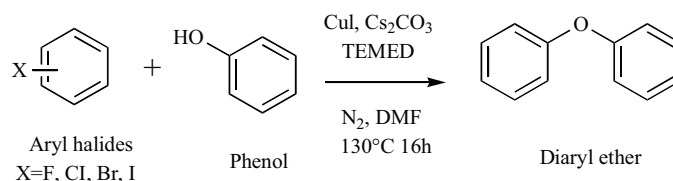


Fig. (1). CuI catalyzed C-O Ullman coupling of aryl halides with phenol.

2. MATERIALS AND METHODS

2.1. Materials

Fluorobenzene, chlorobenzene, bromobenzene, and iodobenzene (purity is greater than 99.0%) were purchased from Alfa Aesar, A Johnson Matthey Company; analysis grade cuprous iodide (CuI), TMEDA, 1,10-phenanthroline, trans-1,2-cyclohexanediamine, cesium carbonate (Cs_2CO_3), and anhydrous magnesium sulfate were all bought from J&K Scientific Ltd.; ethyl acetate and petroleum ether were provided by Sinopharm Chemical Reagent Co, Ltd.

Bruker Avance-500 MHz NMR spectrometer: experiments were carried out at room temperature with TMS as an internal standard in CDCl_3 ; Agilent 1200 HPLC, chromatographic column: Agilent ZORBAX SB-C18 5 μm , 4.6 \times 150 mm.

2.2. Methods

2.2.1. Experimental Method

Synthetic route: 5 mmol of each aryl halide was dissolved in 15 mL of DMF. Subsequently, 5 mmol of phenol and 12.5 mmol of cesium carbonate, together with 0.5 mmol of cuprous iodide (CuI), and 0.25 mmol of tetramethylethylenediamine (TMEDA)-a ligand were added into the mixture and the solution was heated to 130 $^\circ\text{C}$ for 16 hours under nitrogen. After cooling to room temperature, the solution was diluted with 100 mL of water and extracted at least 3 times with 60 mL of ethyl acetate. The extract was dried with anhydrous magnesium sulfate, filtered and concentrated. The crude product obtained was further eluted with petroleum ether and ethyl acetate (volume ratio ranged from 100:0 to 40:1) and then purified by silica gel column chromatography (300-400 mesh) to get the target product. The synthetic scheme is shown in Fig. (1).

HPLC conditions: the mobile phase was composed of methanol and water (methanol:water = 70 : 30), detect wavelength was 236 nm, flow rate was 1.0 mL/min and column temperature was set at 30 $^\circ\text{C}$.

2.2.2. Calculation Method

All the calculations were carried out using the density functional theory (DFT) method of the Gaussian 03 program at the B3LYP/ LANL2MB level. The structural parameters (mean polarizability α , dipole moment μ , energy of the lowest unoccupied molecular orbital E_{LUMO}) of four types of aryl halides were calculated with the DFT method by the Gaussian 03 program. The units of α , μ , and E_{LUMO} are 10^{-30} esu, debye and eV, respectively. The ionization energy of aryl halides-CuI π -complexes at different C-X bond length (including C-F, C-Cl, C-Br, C-I) was calculated.

3. RESULTS AND DISCUSSION

3.1. Optimization of the Reaction Conditions

In the current study, by using iodobenzene (5 mmol) and phenol (5 mmol) as the reaction substrates, TMEDA as the ligand, CuI as the catalyst, we observe and study the influences of different bases, different solvents, different catalyst amounts and temperatures on the reaction and finally obtain the optimum reaction conditions. The results are summarized in Table 1.

At first, DMSO was employed as solvent, Cs_2CO_3 as base, and the catalyst amount is 10%. The reaction conversion achieves 89% at 150 $^\circ\text{C}$ after 16h. And we found Cs_2CO_3 is a better base than K_2CO_3 . Using K_2CO_3 as the base, the highest reaction conversion is only 74%, but when replaced with Cs_2CO_3 , the lowest reaction conversion is more than 86%, except in the case of the solvent THF. The reason may be that though Cs_2CO_3 and K_2CO_3 are both Lewis alkali, the alkalinity of Cs_2CO_3 is bigger than that of K_2CO_3 , resulting in a stronger promoting effect on the reaction process.

Secondly, in order to examine the effect of the reaction temperature, the reaction was carried out at different temperatures, and it was found that the reaction conversion increased with the temperature, changing from 78% at 100 $^\circ\text{C}$ to 96% at 150 $^\circ\text{C}$, when DMF was used as the solvent. This phenomenon indicates that within a certain range increasing the reaction temperature is an effective means of improving the conversion.

As it is also shown in Table 1, when DMF is chosen as the solvent and other conditions are consistent, the reaction conversion rate reaches up to 97% at last. DMSO also demonstrated to be a good solvent and the reaction conversion rate can be achieved at 89%, but the post-processing of the reaction liquid, such as the separation, is more difficult. When the solvent is changed to THF, the highest reaction conversion rate is only 54%.

Thirdly, we also investigated the effect of different catalysts' (5 mol %, 10 mol %, 15 mol %) concentration on the reaction, and found that when catalyst concentration is higher than 10 mol %, there is no sharp difference in the reaction conversion.

Finally, we also examine the effect of different ligands (including TMEDA, 1,10-phenanthroline and trans-1,2-cyclohexanediamine) on the reaction conversion. Without ligands the reaction conversion was only 58%, when TMEDA, 1,10-phenanthroline and trans-1,2-cyclohexanediamine were added in the reaction system, the reaction conversion was 95%, 78% and 83%, respectively. Result suggested ligands largely promoted reaction conver-

Table 1. Different Reaction Conditions for CuI-Catalyzed Coupling of Iodobenzene with Phenol.

Entry	Catalyst (mol%)	Solvent	Ligand	Base	Temperature (°C)	Time (h)	Conversion (%) ^a
1	5%	DMSO	TMEDA	K ₂ CO ₃	100	6	47
2	5%	DMSO	TMEDA	K ₂ CO ₃	130	10	70
3	10%	DMSO	TMEDA	Cs ₂ CO ₃	130	10	86
4	10%	DMSO	TMEDA	Cs ₂ CO ₃	150	16	89
5	5%	DMF	TMEDA	K ₂ CO ₃	130	16	72
6	5%	DMF	TMEDA	Cs ₂ CO ₃	130	10	80
7	10%	DMF	TMEDA	K ₂ CO ₃	130	16	74
8	5%	THF	TMEDA	K ₂ CO ₃	100	10	43
9	10%	THF	TMEDA	Cs ₂ CO ₃	100	10	54
10	10%	THF	TMEDA	Cs ₂ CO ₃	85	16	49
11	10%	DMF	TMEDA	Cs ₂ CO ₃	100	12	78
12	10%	DMF	TMEDA	Cs ₂ CO ₃	110	12	83
13	10%	DMF	TMEDA	Cs ₂ CO ₃	150	12	94
14	5%	DMF	TMEDA	Cs ₂ CO ₃	130	16	91
15	10%	DMF	TMEDA	Cs ₂ CO ₃	130	16	95
16	15%	DMF	TMEDA	Cs ₂ CO ₃	130	20	97
17	10	DMF		Cs ₂ CO ₃	130	16	58
18	10	DMF	1,10-phenanthroline	Cs ₂ CO ₃	130	16	78
19	10	DMF	trans-1,2-cyclohexanediamine	Cs ₂ CO ₃	130	16	83

a. Determined by HPLC.

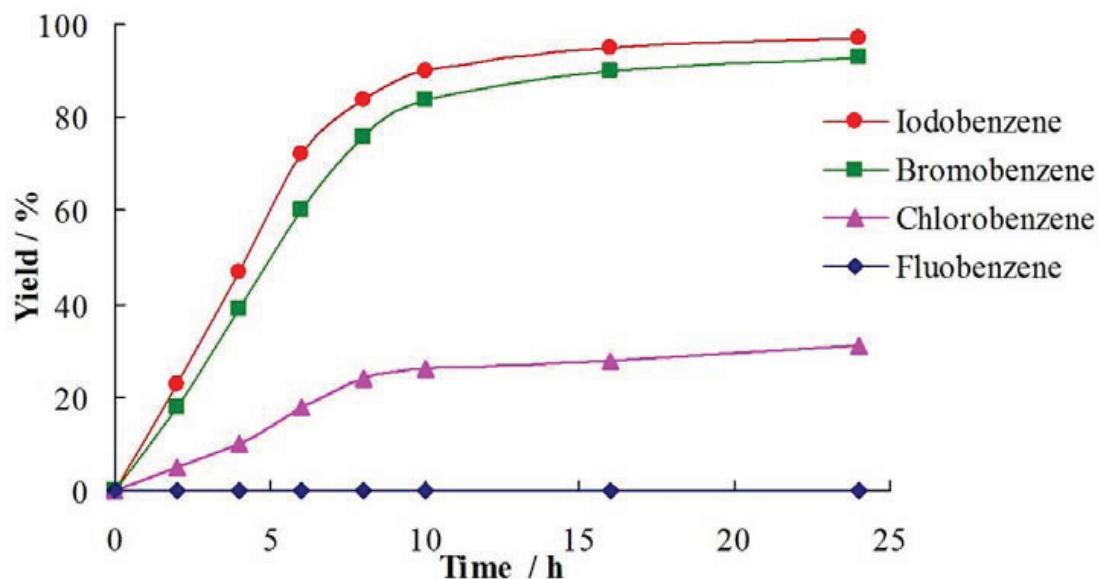


Fig. (2). Yields of the reaction of aryl halides with phenol at different reaction time.

sation and TMEDA was the most effective ligand for this reaction.

Thus, the optimum reaction conditions were acquired: with CuI (10 mol %), Cs₂CO₃ (2.5equiv, 12.5 mmol), TMEDA (5 mol %) in DMF (15 mL), iodobenzene (1equiv, 5 mmol) and phenol (1equiv, 5.0 mmol) react to afford the diphenyl ether, achieve a 95% conversion after a reaction time of 16 h at 130 °C.

3.2. Effects of Reaction Time on the Ullman Reaction Conversion

The effect of reaction time by using phenol and four kinds of aryl halides was also examined. All of the reactions were carried out under the optimum conditions, and the only difference was the reaction time. The relationships between the reaction time and the reaction conversion are illustrated in Fig. (2).

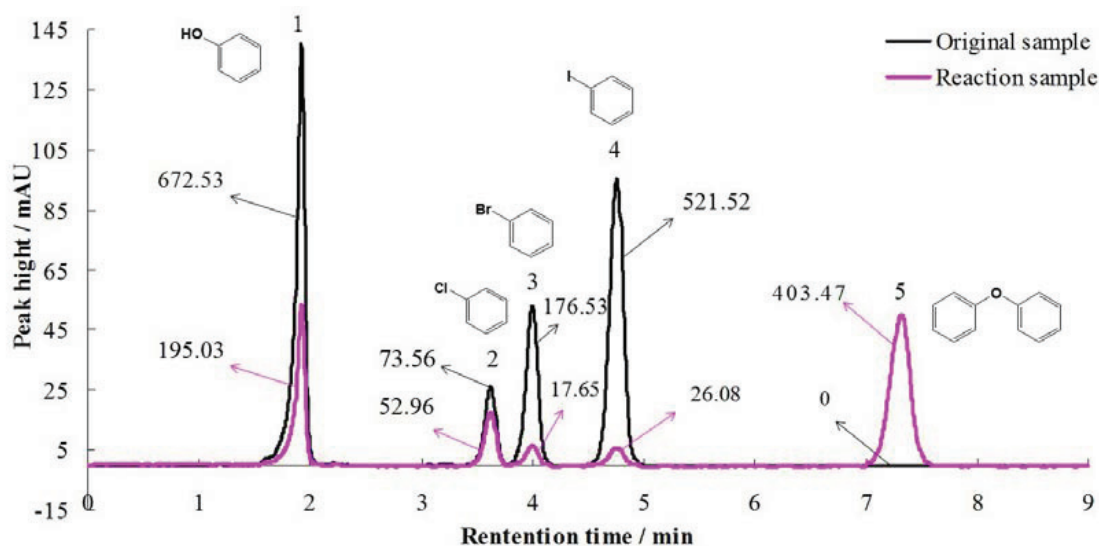


Fig. (3). The HPLC peak areas of the original samples and the reaction samples (after 16h).

Table 2. Quantum Chemistry Structural Parameters of Four Types of aryl Halides.

Name	E_{LUMO} / eV	μ / debye	α / 10^{-30} esu,
Fluorobenzene	0.0855	0.3610	35.9270
Chlorobenzene	0.0508	3.7097	41.9933
Bromobenzene	0.0248	3.7490	45.3717
Iodobenzene	0.0020	3.7763	49.7517

As it is shown in Fig. (1), the conversion changed with the reaction time. The reaction process of fluorobenzene did not occur at all times. Fig. (2) also reveals that there exist distinct differences among the reaction conversions of the other three kinds of aryl halides. At different reaction time, the general trend is: the reaction conversion of chlorobenzene is the minimum, bromobenzene takes the second place, and iodobenzene is the maximum. When the reaction time was increased to 24 h, 26%, 93% and 97% conversions were obtained under the same reaction conditions, respectively.

Because the reaction of fluorobenzene totally does not occur under the experimental conditions, we only discussed the Ullman reaction reactivity of the other three kinds of aryl halides in the following contents. The order of the relative reaction conversion was ascertained by the HPLC analysis (Fig. 3).

In this experiment, 3 mmol chlorobenzene, bromobenzene and iodobenzene reacted with 12 mmol phenol in the optimized conditions. The samples were taken at the reaction time 0 h and 16 h, and after filtrated by 0.22 μm filter, RP-HPLC was used to determine the reaction conversions. And all the peak areas (mAU*S) were shown in Fig. (3).

3.3. Relationship Between Structural Parameters and Reactivity of Aryl Halides

As only few publications focused on the relationship between structural parameters and reactivity of four types of aryl halides, we carried out this investigation. As it is shown in Table 2 that relations clearly existed between reactivity and E_{LUMO} , α and μ .

With the decreasing of E_{LUMO} , the reactivity of aryl halides showed an increase trend, for instance, E_{LUMO} of iodobenzene is the smallest while fluorobenzene is the biggest. The E_{LUMO} is related to the electronic-accept ability of molecule, the smaller E_{LUMO} is, the bigger electronic-accept ability of molecule is. And it is speculated that CuI may act as an electron donor in the Ullman coupling reactions. Among four types of aryl halide, iodobenzene possesses the biggest electronic-accept ability and results in the highest Ullman reactivity, then is bromobenzene and chlorobenzene. By contrast, no Ullman coupling reaction occurred for fluorobenzene.

It was found that the bigger μ is, the higher reactivity of aryl halide is observed. Mean polarizability values μ of iodobenzene, bromobenzene and chlorobenzene are 3.7097, 3.7490 and 3.7763, respectively, all are far more than that of fluorobenzene's (only 0.3610). Similarly, when α is increased, higher Ullman coupling reactivity is present. A higher α represented a bigger molecule deformation ability, indicating the reaction was easy to be affected by other molecule and resulted in higher reactivity.

3.4. Comparative Study on the Reactivity of the Four Types of Aryl Halides

Previous researches showed that the catalyst Cu (I) could combine with aryl halides and form a π -complex [19-22]. In order to clarify the mechanism of the diversity of the Ullman reaction reactivity of different aryl halides thoroughly, the corresponding theoretical calculations have been carried out using the Gaussian 03 program. We considered the impacts of the catalyst CuI during the calculation process. According

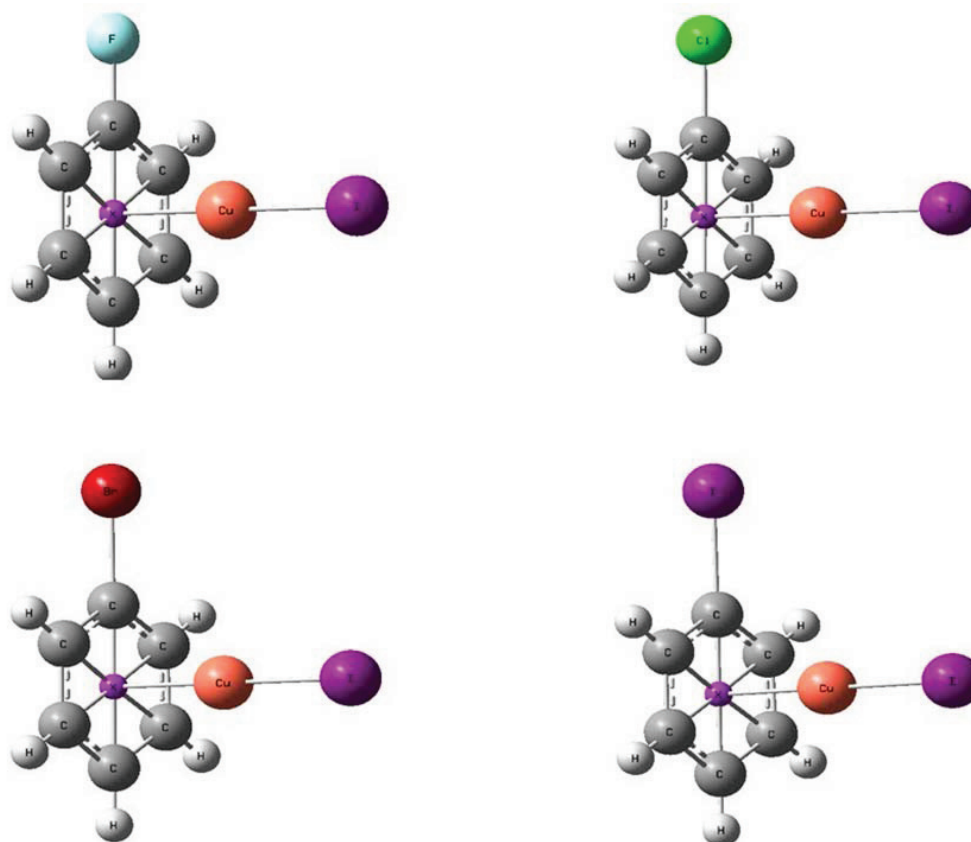


Fig. (4). The structures of the aryl halides-CuI π -complexes. The atoms X in the center of benzene ring are the dummy atoms that set to determine the configuration of aryl halides-CuI π -complexes.

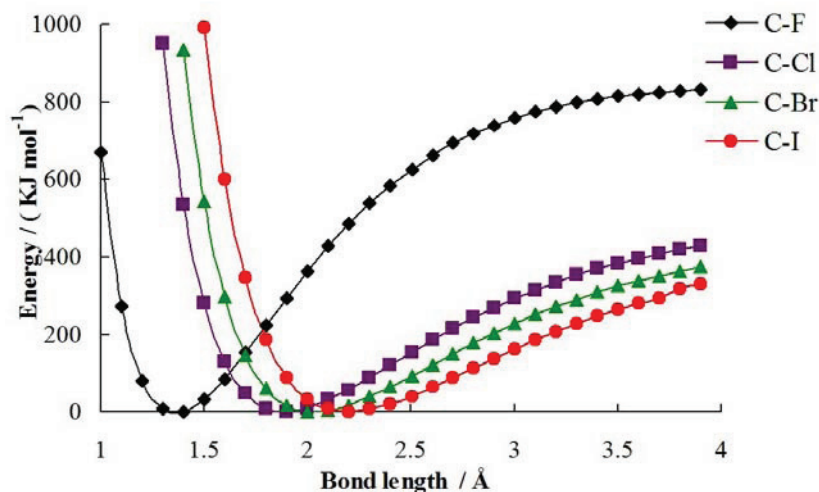


Fig. (5). The Relationships between bond length and reaction energies of the four kinds of aryl halides.

to the reference [17], the structures of all the π -complexes were optimized and calculated. Fig. (4) displays the structures of the four kinds of aryl halides-CuI π -complexes.

By limiting the length of C-X bond (1.0 - 4.0 Å), the total energies of the four kinds of aryl halides at various bond lengths were calculated. With the most stable π -complexes as a reference point, the relationship of the ionization energy and C-X bond length was obtained (See Fig. 5). Moreover, Fig. (5) also shows the bond length with the minimum energy of all the four kinds of aryl halides: C-F (1.40 Å) < C-Cl (1.90 Å) < C-Br (2.00 Å) < C-I (2.20 Å).

3.5. Synthesis of 4-methoxy Diaryl Ether and 2-methoxy Diaryl Ether

Encouraged by the efficiency of the cross-coupling protocol described above, the scope of the substrate was expanded to substituted phenols. 2-methoxy phenol and 4-methoxy phenol were tested under the optimized reaction conditions using iodobenzene as the arylating agent, and the two reactions both generated the corresponding diaryl ethers (**2a** and **2b**) in good yields. It means that the optimum reaction conditions we obtained have certain applicability.

2-methoxy diaryl ether (**2a**):

Yield 78%; ¹H NMR (CDCl₃, 500MHz) δ (ppm) 3.91(s, 3H), 6.97-7.19(m, 6H), 7.16(t, 1H, *J* 10.5 Hz), 7.33(t, 2H, *J* 11.0 Hz).

4-methoxy diaryl ether (**2b**):

Yield 74%; ¹H NMR (CDCl₃, 500MHz) δ (ppm) 3.84(s, 3H), 6.92(dd, 2H, *J*₁ 3.5 and *J*₂ 8.5 Hz), 6.98(dd, 2H, *J*₁ 2.0 and *J*₂ 10.5 Hz), 7.03(dd, 2H, *J*₁ 4.0 and *J*₂ 8.5 Hz), 7.09(t, 1H, *J* 10.5 Hz), 7.32(dd, 2H, *J*₁ 3.5 and *J*₂ 12.0 Hz).

4. CONCLUSION

In the present study, we obtained an efficient and simple route to synthesis of diaryl ethers. Meanwhile, the structural parameters of four types of aryl halides and ionization energy of four types of aryl halides were calculated by Gaussian 03 program. Relationship between structural parameters and reactivity of four types of aryl halides was discussed. In addition, the ionization energy order of the four kinds of aryl halides is: fluorobenzene >> chlorobenzene > bromobenzene > iodobenzene, which indicates that the Ullman reactivity of iodobenzene is the biggest, and Ullman reactivity of fluorobenzene is the lowest. This result corresponds to Ullman reaction conversions that were determined by HPLC. Theoretical investigations of the reactivity of aryl halides would provide useful working guidelines for the design of reaction system. Besides, under the optimum reaction condition two kinds of methoxy substituted diaryl ethers were synthesized, which means the optimum reaction conditions obtained have certain applicability.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

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REFERENCES

- [1] Sawyer, J.S. Recent advances in diaryl ether synthesis. *Tetrahedron*, **2000**, *56*, 5045-5065.
- [2] Nicolaou, K.C.; Boddy, C.N.C.; Brase, S.; Winssinger, N. Chemistry, biology, and medicine of the glycopeptide antibiotics. *Angew. Chem. Int. Ed.*, **1999**, *38*, 2096-2152.
- [3] Nicolaou, K.C.; Natarajan, S.; Li, H.; Jain, N.F.; Huges, R.; Solomon, M.E.; Ramanujulu, J.M.; Boddy, C.N.C.; Takayanagi, M. Total synthesis of vancomycin aglycon—part I: Synthesis of amino acids 4–7 and construction of the AB-COD ring skeleton. *Angew. Chem. Int. Ed.*, **1998**, *37*, 2708-2714.
- [4] Zhang, Q.; Wang, D.P.; Wang, X.Y.; Ding, K. (2-Pyridyl)acetone-Promoted Cu-Catalyzed O-Arylation of phenols with aryl iodides, bromides, and chlorides. *J. Org. Chem.*, **2009**, *74*, 7187-7190.
- [5] Evano, G.; Blanchard, N.; Toumi, M. Copper-mediated coupling reactions and their applications in natural products and designed biomolecules synthesis. *Chem. Rev.*, **2008**, *108*, 3054-3131.
- [6] Kunz, K.; Scholz, U.; Ganzer, D. Copper-mediated C(aryl)–O, C(aryl)–N, and C(aryl)–S bond formation. *Synlett.*, **2003**, *15*, 2428-2439.
- [7] Monnier, F.; Taillefer, M. Catalytic C–C, C–N, and C–O Ullmann-type coupling reactions. *Angew. Chem. Int. Ed.*, **2009**, *48*, 6954-6971.
- [8] Lindley, J. Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron*, **1984**, *40*, 1433-1456.
- [9] Henrion, J.C.; Pascal, P.C.; Samy, H.; Jean, F.S.; Marc, T. A general and mild Ullmann-type synthesis of diaryl ethers. *Org. Lett.*, **2004**, *6*, 913-916.
- [10] Huang, J.K.; Chen, Y.; Chan, J.H.; Mike, L.R.; Robert, D.L.; Margaret, M.F. An efficient copper-catalyzed etherification of aryl halides. *Synlett.*, **2011**, *10*, 1419.
- [11] Wolter, M.; Nordmann, G.; Job, G.E.; Buchwald, S.L. Copper-catalyzed coupling of aryl iodides with aliphatic alcohols. *Org. Lett.*, **2002**, *4*, 973-976; Shafir, A.; Lichtor, P.A.; Buchwald, S.L. N- versus O-Arylation of aminoalcohols: orthogonal selectivity in copper-based catalysts. *J. Am. Chem. Soc.*, **2007**, *129*, 3490-3491; Liu, Y.H.; Li, G.; Yang, L.M. Glyoxal bis(phenylhydrazone) as promoter for CuI-catalyzed O-arylation of phenols with bromoarenes. *Tetrahedron Lett.*, **2009**, *50*, 343-346; Naidu, A.B.; Sekar, G. An efficient intermolecular BINAM–copper(I) catalyzed Ullmann-type coupling of aryl iodides/bromides with aliphatic alcohols. *Tetrahedron Lett.*, **2008**, *49*, 3147-3151; Marcoux, J.F.; Doye, S.; Buchwald, S.L. A general copper-catalyzed synthesis of diaryl ethers. *J. Am. Chem. Soc.*, **1997**, *119*, 10539-10540.
- [12] Benyahya, S.; Monnier, F.; Taillefer, M.; Man, W.C.M.; Bied, C.; Ouazzani, F. Efficient and versatile Sol-Gel immobilized copper catalyst for Ullmann arylation of phenols. *Adv. Synth. Catal.*, **2008**, *350*, 2205-2208.
- [13] Sreedhar, B.; Arundhati, R.; Reddy, M.A.; Kantam, M.L. Efficient catalytic activity of copper/aluminum hydrotalcite in diaryl ether synthesis. *Synthesis*, **2009**, *3*, 483-487.
- [14] Li, F.; Wang, Q.R.; Ding, Z.B.; Tao, F.G. Microwave-assisted synthesis of diaryl ethers without catalyst. *Org. Lett.*, **2003**, *5*, 2169-2171.
- [15] Strieter, E.R.; Blackmond, D.G.; Buchwald, S.L. The role of chelating diamine ligands in the Goldberg reaction: A kinetic study on the copper-catalyzed amidation of aryl iodides. *J. Am. Chem. Soc.*, **2005**, *127*, 4120-4121; Strieter, E. R.; Bhayana, B.; Buchwald, S. L. Mechanistic studies on the copper-catalyzed N-arylation of amides. *J. Am. Chem. Soc.*, **2009**, *131*, 78-88.
- [16] Martina, W.; Gero, N.; Gabriel, E.J.; Stephen, L.B. Copper-catalyzed coupling of aryl iodides with aliphatic alcohols. *Org. Lett.*, **2002**, *4*, 973-976.
- [17] Niu, J.J.; Zhou, H.; Li, Z.G.; Xu, J.W.; Hu, S.J. An efficient Ullmann-Type C–O bond formation catalyzed by an air-stable copper(I)–bipyridyl complex. *J. Org. Chem.*, **2008**, *73*, 7814-7817.
- [18] Armelle, O.; Jean, F.S.; Henri, J.C.; Marc, T. Mild conditions for copper-catalyzed coupling reaction of phenols and aryl iodides and bromides. *Adv. Synth. Catal.*, **2006**, *348*, 499-505.
- [19] Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Zakrzewski, V.G.; Montgomery, J.A.; Stratmann, R.E.; Burant, J.C.; Dapprich, S.; Millam, J.M.; Daniels, A.D.; Kudin, K.N.; Strain, M.C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G.A.; Ayala, P.Y.; Cui, Q.; Morokuma, K.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Cioslowski, J.; Ortiz, J.V.; Baboul, A.G.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E.S.; Pople, J.A. Gaussian 03, Revision A.1, Gaussian, Inc, Pittsburgh, PA. **2003**.
- [20] Weingarten, H. Mechanism of the Ullmann Condensation. *J. Org. Chem.*, **1964**, *29*, 3624-3626.
- [21] Zhang, H.; Cai, Q.; Ma, D.W. Amino acid promoted CuI-catalyzed C–N bond formation between aryl halides and amines or N-containing heterocycles. *J. Org. Chem.*, **2005**, *70*, 5164-517.
- [22] Elena, S.; Gerard, P.M. van K.; Gerard, van K.; Johannes, G. de V. The mechanism of the modified Ullmann reaction. *Dalton Trans.*, **2010**, *39*, 10338-10351.