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Effect of the Structural Factors on Reactivity of Aryl Halides in the Copper-Catalyzed Arylation of Aniline in Aqueous Medium

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Abstract—Arylation of aniline with substituted bromobenzenes in two-phase water–chlorobenzene system catalyzed by $Cu(OAc)_2$–*N*-phenyloxalyldihydrazide–hexane-2,5-dione system was found to be slightly sensitive to the polar effect of a substituent in the aryl halide. Value of the reaction parameter ρ was 0.55. However the presence of substituent in *ortho*-position of the benzene ring decreased significantly the reaction rate [k_{rel}(2-MeC_6H_4Br/4-MeC_6H_4Br) = 0.14].

Keywords: polar effect of substituents, steric effect of substituents, catalysis with copper complexes, arylation of anilines, aqueous medium

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Copper-catalyzed arylation of *N*-nucleophiles with aryl halides has been a known synthetic approach since 1903. It is potentially suitable for the preparation of important intermediates in pharmaceutical chemistry. Unfortunately, the conventional methods of C–N cross-coupling with the use of copper like the classical Ullmann reaction, in which amines are used as nucleophiles, and Goldberg reaction, where amides play the role of nucleophile, find only limited practical application first of all due to requirement of stoichiometric amount of copper, rigid reaction conditions (t > 200°C), and the use of high boiling polar organic solvent, usually nitrobenzene [1, 2]. Therefore the search for the catalytic systems for performing the modified Ullmann reaction, which would allow arylation of various NH-nucleophiles under relatively mild conditions attract close interest.

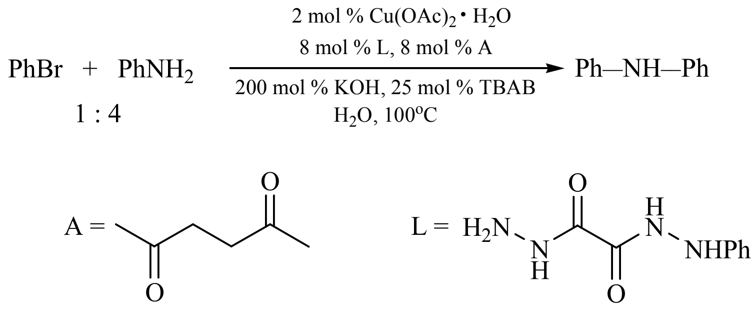
For the last 15 years a wide spectrum of such catalytic systems was elaborated [2–5]. The key role played selection of appropriate ligands, which increase the solubility and stability of copper complexes in the applied solvent. As a rule, the reaction is performed in organic solvents like DMSO, DMF, 2-propanol, toluene, *n*-decane. Examples of the copper-catalyzed C–N cross-coupling reactions in aqueous media are not numerous, but the described methods are of a great synthetic potential [6]. When the ligands based on oxalyldihydrazide [7, 8] and hydrazide of pyrrole-2-carboxylic acid [9] were used, the substrates and NH-nucleophiles of various structure participated in the C–N-cross-coupling reactions in aqueous medium, but the procedures required significant amount of copper (up to 10 mol %) and the ligand (up to 50 mol %).

Recently we discovered new effective catalytic system for the copper-catalyzed *N*-arylation of hydrazine [10], aliphatic amines [11], and anilines [12] with the use of water as a solvent. Arylation of anilines proceeded at 100°C in the presence of the catalytic system consisted of a copper(II) compound (1–2 mol %), *N*-phenyloxalyldihydrazide (L) (4–8 mol %), hexane-2,5-dione (A) (4–8 mol %), phase-transfer catalyst (tetrabutylammonium bromide, TBAB), and an inorganic base (Scheme 1).

Based on the catalytic system we developed simple and easily scaled-up preparative methods for the synthesis of diarylamines in 57–83% yield at 1–50 mmol of aryl bromide charge. However the described procedure consists of a number of empirical rules and its mechanism is not yet studied.

In this work we established regularities between the substrate structure (aryl halide) and its reactivity in the

Scheme 1.



discussed reaction of C–N cross-coupling. This would allow both determination of the potential substrate range together with optimization of the reaction conditions and therefore applicability of the method, and revealing of the mechanism details of the copper-catalyzed C–N cross-coupling.

C–N cross-coupling of aryl bromides with aniline was chosen as a model reaction. In the study the method of competing reactions was used. It was shown earlier [12] that the product of the aniline reaction with bromobenzene, diphenylamine, was not consumed under the reaction conditions therefore k_{rel} was determined from the accumulation of the reaction products. To fulfill this task a set of values of relative rate constants k_{rel} for two or more substrates with the same reagent, amine, should be obtained under comparable conditions.

The reactions were performed in two-phase chlorobenzene–water system at low conversions of the substrates with continuous stirring of the reaction mixture. Chlorobenzene (0.8 mL per 1 mmol of aryl bromides) was used as a solvent to ensure approximate constancy of the lipophilicity characteristics of the organic phase regardless of the applied aryl bromide. The test experiments demonstrated that chlorobenzene did not virtually react with aniline under the reaction conditions ($k_{\mathrm{PhCl}}/k_{\mathrm{PhBr}} = 0.007$). It was also showed that the values of observed relative rate constants did not depend on the substrate conversion.

For C–N cross-coupling reactions occurring in water the question arises: where the copper complex occurred to be and where the reaction takes place if the two-phase system is used. Although the detailed mechanism of C–N cross-coupling catalyzed with transition metals in two-phase systems was almost not studied, the available facts allowed to presume that the reaction proceeded not in the aqueous phase since the substrate concentration in water was too low, except for hydrophilic organic compounds like 2-halocarboxylic acids. Moreover, in the reactions of amines arylation performed in the presence of an excess of KOH or NaOH contribution of the side process of *O*-arylation did not generally exceed 5–10% (hydroxide ion played a role of nucleophile, whose concentration in aqueous phase was much larger than aniline concentration) [8–12].

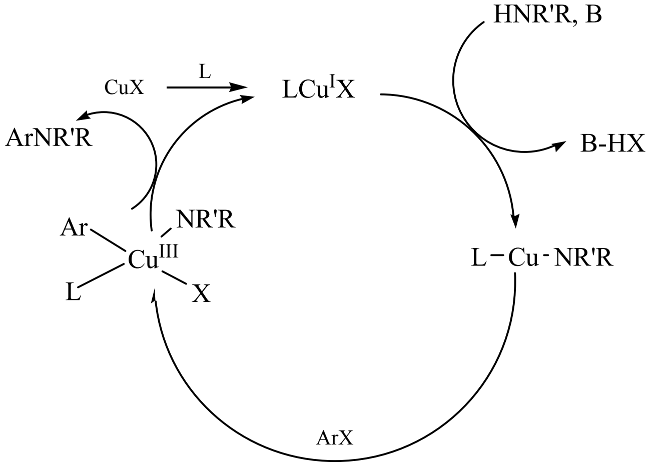
To check a possibility of the reaction occurrence on the phase boundary the procedure described in [13] was applied. Dependence of bromobenzene conversion on stirring intensity was determined and it was found that 5 times increase in the stirring rate (from 200 to 1000 rpm) had no effect on diphenylamine formation rate. The absence of micellar catalysis was also shown since the replacement of TBAB (25 mol %) with potassium stearate (25 mol %), which possesses a larger surface activity, led to 1.5-fold reduction in the diphenylamine yield. This fact allowed a conclusion that the location of catalytic cycle on the phase transfer boundary was unlikely and the discussed reactions of C–N cross-coupling proceeded in the organic phase.

The values of k_{rel} were determined at low conversion of the substrates (1–10%) with the use of gas-liquid chromatography for determination of relative concentrations of the reaction products. The relative coefficients of sensitivity of flame ionization detector to the analyzed compounds were determined by the analysis of calibration mixtures containing a precise charge of *N*-aryl amines obtained in analytically pure form according to our method [12].

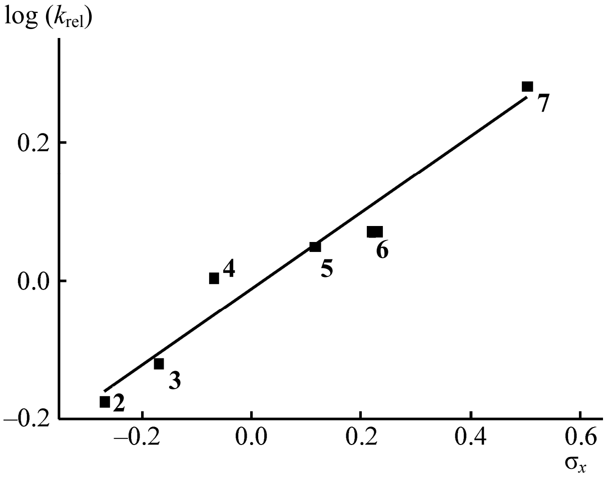
By this way the relative rate constants of aniline arylation with various aryl halides containing donor and acceptor substituents were determined (see the table, the figure).

The value of the reaction parameter ρ was 0.55±0.06. The obtained value of ρ was in a good

Scheme 2.



L is bidental ligand.



Dependence of the relative rate constants of aniline arylation with substituted bromobenzenes on the σ-constants of substituents. log (k_{rel}) = (0.55±0.06)σ_x – (0.012±0.015), R = 0.979.

agreement with the known data for the copper-catalyzed single-phase processes of aryl iodides amination with ammonia (ρ = 0.49 at 25°C in liquid ammonia [14]) and aryl iodide amidation with 2-pyrrolidinone (ρ = 0.48 at 90°C in toluene [15]).

It was found that donor substituents in aryl bromide decelerated the reaction; however the effect was not strong that indicated a relatively small increase in the electron density on the *ipso*-carbon atom in the transition state (compared to the initial state) in the rate-determining step of the catalytic process.

Different mechanisms, which describe copper-catalyzed cross-coupling of aryl halides with various nucleophiles, have been suggested [2, 5]. In the present time most of the authors believe that the reaction proceedes through the formation of copper(III) complex $ArCuXLNR_2$ (Scheme 2) [2, 5, 18].

The stage of oxidative addition of aryl halide ArX to copper(I) complex LCuNHPh has been considered as the rate limiting step. In a number of the studies the key aspects connected with the oxidative state of active copper catalyst and the type of activation of aryl halide have been discussed [16–18]. The stage of oxidative addition can proceed as a concerted three-center process (OxIns) or through single electron transfer from the copper complex to aryl halide (SET). The last process can lead to the formation of aryl radical as a result of anion-radical fragmentation or halide-ion rupture from it with the copper complex (atom transfer, AT) (Scheme 3).

Most probably, the mechanism in each case depends on the type of nucleophilic reagent as well as on aryl halide used and on the reaction conditions [2, 5].

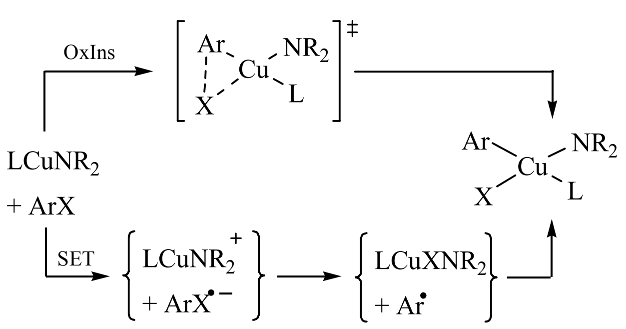
The data we obtained on the electronic effect of the substituents in substrate on the reaction rate was in accordance with the concept available in the literature on the catalytic cycle of the reactions of C–N cross-

Electronic effect of a substituent in the aromatic ring on the reactivity of substituted bromobenzenes in the C–N cross-coupling reaction with aniline in two-phase chlorobenzene–water system at 100°C[a]

Comp. no.	Substrate XC_6H_4Br	σ_x-Hammett constants	k_{rel}
1	PhBr	0	1
2	4-$MeOC_6H_4Br$	−0.268	0.67±0.11
3	4-MeC_6H_4Br	−0.170	0.76±0.07
4	3-MeC_6H_4Br	−0.069	1.01±0.26
5	3-$MeOC_6H_4Br$	0.115	1.12±0.17
6	4-ClC_6H_4Br	0.227	1.18±0.34
7	4-AcC_6H_4Br	0.502	1.91±0.64

[a] Reaction conditions: two aryl bromides (overall 1 mmol), aniline (4 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.02 mmol), L (0.08 mmol), A (0.08 mmol), TBAB (0.25 mmol), KOH (2 mmol), H_2O (0.8 mL), PhCl (0.8 mL), 100°C. Yield of diarylamines was determined with the help of gas-liquid chromatography using 1,2-diphenylethane as an internal reference.

Scheme 3.



coupling. Positive value of ρ evidenced the increase in the electron density at the *ispo*-carbon atom in the transition state (compared to the initial state) in the rate limiting step. However, the data obtained did not allow unambiguous choice between the ways of oxidative addition stage occurrence.

To gain a greater insight into why the depicted on Fig. 3 routes of oxidative addition proceeds, the steric effect of the methyl group in the *ortho*-position with respect to the reaction site was investigated. In the case of anion-radical mechanism of aryl halide activation, an accelerating *ortho*-effect of alkyl groups is known to be observed [19, 20]. At the same time the three-center mechanism OxIns is characterized with the "normal" steric effect of alkyl substituents, which inhibit the oxidative addition.

We compared the reactivity of 2- and 4-bromotoluenes in the reaction of aniline arylation. It was found that *ortho*-bromotoluene occurred to be significantly less reactive than the *para*-isomer (k_{rel} = 0.14). Taking into account that the electronic effect of methyl group in *ortho*- and *para*-positions is nearly the same, the obtained result showed a marked inhibitory steric effect, i. e. in this case the oxidative addition happened through the three-center transition sate, but not by the anion-radial mechanism (Scheme 3, OxIns).

In summary, we showed that the copper-catalyzed reaction of aniline arylation with substituted bromobenzenes in two-phase water–chlorobenzene system occurred to be slightly sensitive to the polar effect of the substituent in aryl halide (ρ equaled 0.55±0.06). Low sensitivity of the rate of the discussed reaction to the electronic effect of substituents in aromatic ring of the substrate allowed expecting that the optimal reaction conditions we formerly developed [12] occurred to be suitable for the reactions with a wide range of substituted aryl bromides. It was confirmed that the reaction rate was significantly decreased when using the *ortho*-substituted substrate [k_{rel}(2-MeC$_6$H$_4$Br/4-MeC$_6$H$_4$Br) = 0.14]. The key stage of the process, oxidative addition, apparently proceeded through the three-center transition state, but not via electron transfer.

EXPERIMENTAL

Commercially available inorganic reagents of analytically pure grade were used without preliminary purification; KOH by Reakhim contained 85% of the target compound. Aryl bromides, aniline, and the solvents of analytically pure grade were used without preliminary purification as well as hexane-2,5-dione (by Acros Organics, 97%). Purity of all the compounds was monitored by ^{1}H NMR spectroscopy and gas-liquid chromatography.

^{1}H NMR spectra were registered on a Bruker Avance II+ (400.13 MHz) and a Bruker DPX-300 (300.13 MHz) spectrometers at room temperature.

Analysis by gas-liquid chromatography was accomplished on a Chromatek Kristall 5000.2 instrument equipped with a flame ionization detector, capillary column VRCh-1 (10 m × 0.53 mm × 2.65 μm), and on a Tsvet-104 instrument with flame ionization detector and packed glass columns of 3 mm diameter and 3000 mm of length of two types: with stationary phase SE-30 (5%) and OV-225 (5%); Chromaton N-Super 80–100 mesh was used as a carrier in both cases.

Synthesis of *N'*-phenyloxalyldihydrazide L was done according to the method we described earlier [10].

***N*-Arylation of amines with aryl halides (method for determination of the relative rate constants)**. The starting mixture contained precisely measured amounts of bromobenzene, substituted bromobenzene, 1,2-diphenylethane (internal reference), and aniline. The starting mixture contained overall approximately 1 mmol of aryl bromides and 4 mmol of aniline, KOH (230 mol % relative to the sum of two aryl bromides), tetrabutylammonium bromide (25 mol%), ligand L (8 mol %), hexane-2,5-dione (8 mol %), 170 mg of aqueous solution of copper acetate (2 mol%), and the solvents, chlorobenzene (0.8 mL per 1 mmol of aryl bromides mixture), and water (0.8 mL). It was placed into a glass vial of 5–6 mL capacity. The Teflon-coated stirring bar was placed into the vial and the mixture was stirred for 1 min, then argon was bubbled through the mixture for 4–5 min at a rate of 6–8 mL per min. The vial was sealed and placed into the preliminarily temperature-controlled oil bath on a magnetic stirrer. The conversion was regulated by the reaction time. In a definite time interval the vial was cooled to room temperature, and opened. Then ethyl acetate (2–3 mL) was added, the mixture was stirred for 1 min, the organic phase was separated, washed with water (2 × 2 mL), dried over anhydrous sodium sulfate, and analyzed by gas-liquid chromatography. The values of relative rate constant were calculated as an average by the data of 4–5 independent experiments.

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