# An efficient heterogeneous catalytic method for the N-arylation of pyrrole and other N-heterocycles

János Németh $^1\cdot$ Nóra Debreczeni $^2\cdot$ Iván Gresits $^3\cdot$ Mária Bálint $^4\cdot$ Zoltán Hell $^2$ 

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Abstract 4 Å molecular sieve modified with copper(0) or copper(II) is an efficient heterogeneous catalyst for the arylation of pyrrole and some other heterocycles with iodoor bromoarenes,  $Cs_2CO_3$  base and pyrrole (or DMF) solvent. The catalysts can be easily prepared and are reusable. *Graphical Abstract* 



**Keywords** Heterogeneous catalysis · Heterocycles · Copper · Molecular sieve

Zoltán Hell zhell@mail.bme.hu

- <sup>1</sup> MTA-BME Organic Chemical Technology Research Group, Hungarian Academy of Sciences, Budapest 1111, Hungary
- <sup>2</sup> Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Műegyetemrkp. 3, Budapest 1111, Hungary
- <sup>3</sup> Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Budapest 1521, Hungary
- <sup>4</sup> Bálint Analitika Kft, Fehérvári út, 144, Budapest 1116, Hungary

## **1** Introduction

The N-substituted heterocycles (e.g. pyrrole) are important and common targets e.g. in the pharmaceutical industry [1]. A possible way for the synthesis of these compounds is the direct N-arylation of the unsubstituted heterocycle with aryl halides. There are numerous publications [2-14] about heterogeneous catalytic methods for this N-arylation using different copper catalysts e.g. Cu<sub>2</sub>O [9], CuI [3, 12], CuFAP [5], or Cu powder [10], and the desired arylated N-heterocycles are generally obtained with good (80-95 %) yields. But most of the publications report the examination of the arylation of imidazole, the solvents most commonly used in the reactions are DMF and DMSO, the reaction time is often 18-24 h, sometimes even with aryl iodides as arylating agent. Often, the best results were obtained using Cs<sub>2</sub>CO<sub>3</sub> as base. The main disadvantages of these processes are that the preparation of the catalyst is tedious [2, 4, 5, 7, 8], PTC is required [2, 6], sensitive Cu(I) salt is used [3, 9, 12], the reaction time is long [12], inert atmosphere is necessary [4, 8, 12], or there are problems with the reusability of the catalyst [9, 10, 13, 14].

Our research group works on the elaboration of new heterogeneous catalytic methods for the preparation of organic compounds using supported metal catalysts. During this work palladium(0) on Mg:La 3:1 mixed oxide was successfully used in the Heck [15], Sonogashira [16] and Suzuki [17] reactions, nickel(II) on the same support in the Kumada-coupling [18], while copper(II) on 4 Å molecular sieve (Cu<sup>2+</sup>/4A) in the A<sup>3</sup>-coupling [19], as well as in the selective transformation of oximes into nitriles [20] or nitriles into amides [21].

Continuing this work we examined the applicability of the supported copper catalysts in the arylation of pyrrole and other heterocycles. The support used was a commercial 4 Å molecular sieve, a crystalline, synthetic zeolite having sodalite structure. Its crystal grating is similar to a cage with numerous hollow spaces with volume  $0.3 \text{ cm}^3/\text{g}$ . The cavities are accessible from all sides by pores of exactly defined dimensions, 0.4 nm in diameter. This material is a very good adsorbent for molecules small enough to pass through the pores. The BET surface of 4A is 800 m<sup>2</sup>/g [22].

Copper(II) on 4 Å molecular sieve (Cu<sup>2+</sup>/4A) was prepared by impregnation of finely ground molecular sieve with copper(II) chloride in deionized water. The targeted copper content of this catalyst was 6.3 wt%, the experimental value was 5.8 wt% (determined by ICP-OES). The surface analysis by scanning electron microscope (SEM) showed cubic zeolite (sodalite) crystals, most of the particles were in the 2.5-5 µm range (Fig. 1). EDS showed that copper covered the support's surface evenly. The surface area of the original molecular sieve  $(800 \text{ m}^2/\text{g})$ dropped to 360 m<sup>2</sup>/g after the impregnation.  $Cu^{2+}/4A$  was reduced with hydrazine hydrate using the proven method described for the preparation of the supported Pd<sup>0</sup> catalysts earlier [15, 23]. Copper content of Cu<sup>0</sup>/4A catalyst dropped to 5.5 wt%. There were no remarkable changes in the surface area, the particle size distribution remained practically the same. Copper distribution on the surface was not modified during the reduction. The finely distributed copper made the catalyst slightly sensitive to the atmospheric oxygen [24].

## 2 Results and discussion

First the optimal reaction conditions were determined in the reaction of iodobenzene and pyrrole (Fig. 2). The effect of the solvent, the reaction time and the base added were examined. The results are summarized in Table 1.

Based on the GC–MS analysis of the filtered reaction mixture, good results were only obtained with cesium carbonate base. Potassium acetate, potassium carbonate and potassium hydroxide gave moderate or no conversion (entries 1–4). DMF and DMSO, the solvents often used in the published methods, gave poor or moderate yields (entries 10 and 11). We found, that the best solvent was the pyrrole itself. In case of  $Cu^{2+}/4A$ , after 15 h complete conversion was observed (entry 7), but an excellent conversion (86 %) could be reached already after 4 h (entry 9). Using  $Cu^{0}/4A$  the GC–MS spectra showed no starting materials in the reaction mixture after only 4 h (entry 8). This time is slightly shorter than the shortest found in literature (6 h) [5]. Without base or catalyst no reaction was observed.

The arylation of different aryl halides (Fig. 3.) were examined under the above mentioned conditions (Table 2).

The required products were generally obtained with good to excellent conversion and yield. In the reaction of 3-iodonitrobenzene (1g) instead of the desired (3-nitrophenyl)pyrrole (3g) (3-aminophenyl)pyrrole (3g') was the main product (entry 8). After changing the reaction time to 15 h, the amount of the amino compound accrued (entry 9). (3-Aminophenyl)pyrrole can be formed via the reduction of either the starting 3-iodonitrobenzene, or the product (3nitrophenyl)pyrrole. However, when the reaction temperature was decreased to 115 °C, the desired nitro compound became the main product (81 %, entry 10). The reduced product was also obtained when 4-iodonitrobenzene (1f) was the arylating agent, but in much lower amount (3f', 8 %, entry 7). Recently we observed a reduction of nitrobenzene derivatives via transfer hydrogenation in the presence of Pd/4A catalysts in ethanol [25], where ethanol



Fig. 2 Model reaction for the determination of the best reaction conditions



Fig. 1 SEM image of the Cu<sup>2+</sup>/4A catalyst (*left*  $\times$ 1000 magnification, *right*  $\times$ 20,000 magnification)

 Table 1
 Determination of the best reaction conditions

Entry	Catalyst	Base	Solvent	Reaction time	Yield (%) <sup>a</sup>
1	Cu <sup>0</sup> /4A	KOAc	DMF	24	_
2	Cu <sup>0</sup> /4A	K <sub>2</sub> CO <sub>3</sub>	DMF	20	38
3	Cu <sup>0</sup> /4A	K <sub>2</sub> CO <sub>3</sub>	Pyrrole	24	25
4	Cu <sup>0</sup> /4A	КОН	Pyrrole	24	40
5	Cu <sup>0</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	Pyrrole	24	100
6	Cu <sup>0</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	Pyrrole	15	100
7	Cu <sup>2+</sup> /4A	$Cs_2CO_3$	Pyrrole	15	100
8	Cu <sup>0</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	Pyrrole	4	100 (86 <sup>b</sup> )
9	Cu <sup>2+</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	Pyrrole	4	86
10	Cu <sup>0</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	DMF	4	19
11	Cu <sup>0</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	4	56
12	Cu <sup>0</sup> /4A	Cs <sub>2</sub> CO <sub>3</sub>	Acetonitrile	12	9
13	_	Cs <sub>2</sub> CO <sub>3</sub>	Pyrrole	24	0
14	Cu <sup>0</sup> /4A	_	Pyrrole	10	<1

3 mmol 1a, 0.3 g catalyst, 6 mmol base, 3 ml solvent, 135 °C (or 80 °C in acetonitrile)

<sup>a</sup> Based on GC–MS examination of the reaction mixture

<sup>b</sup> Preparative yield



Fig. 3 N-Arylation of pyrrol with different aryl halides in the presence of copper on 4A

served as hydrogen donor. In the N-arylation reaction the mixture did not contain any obvious hydrogen donor. Perhaps, pyrrole itself induced this hydrogen transfer reaction.

In the cases of 2-iodophenol (1e), 3- and 4-iodonitrobenzene (1g, 1f) the reaction mixtures contained occasionally a little amount of phenol (2 %) or nitrobenzene, too, which can be formed via the dehalogenation of the starting materials (entries 6-8, 10).

 $Cu^{2+}/4A$  gave just slightly less conversion than  $Cu^{0}/4A$  in the reaction of iodobenzene (see Table 1). With iodoanisole (**1c**), after 4 h full conversion was observed (entry 3). Thus, in this case the electron donating group on the phenyl ring might have an activating effect. Therefore  $Cu^{2+}/4A$  (whose preparation is slightly shorter and simpler than  $Cu^{0}/4A$ ) can give a good alternative of  $Cu^{0}/4A$  for this reaction.

With bromoarenes, using  $Cu^{0}/4A$ , an increase in the reaction time was necessary for reaching good to excellent GC yields (entries 8, 9, 12–18). Better results were obtained when methoxy (**1i**) or ethyl group (**1j**) was attached to the aryl compound. In the reaction of aldehydes (**1m**, **1n**) a mixture of compounds was obtained, probably the products of a reaction between the carbonyl group and pyrrole. The desired aldehyde was not observed (entries 17, 18). With 4-bromoacetophenone (11) the desired arylpyrrole derivative was the main product, but a significant amount of other byproducts appeared, too (entry 16). From the GC-MS analysis of this mixture a similar reaction between the carbonyl group and pyrrole can be assumed as it was observed in the reaction of aldehydes. This means that our method is not suitable for the preparation of carbonyl derivatives from aryl bromides. 4-(1H-Pyrrol-1-yl)-benzoic acid (30) was isolated when 4-bromobenzonitrile (10) was the arylating agent (entry 19). This can be formed via the hydrolysis of the starting material under basic conditions. It is known that hydrocarbonates can disproportionate at higher temperature yielding carbonates and carbonic acid, the decomposition of which yield the water required for this hydrolytic side reaction.

4-Bromoanisole in the presence of  $Cu^{2+}/4A$  gave poor result even after 24 h (entry 13). Chlorobenzene (1p) failed to react even after 36 h (entry 20).

The recycling of the pyrrole is simple; after the workup it can be distilled from the mixture. In the small scale we applied, about 50 % of pyrrole could be recovered.

The reusability of both catalysts were examined in the reaction of iodobenzene and pyrrole (reaction time 4 h). After the reaction, the catalysts were filtered and washed with dichloromethane and water, and then preheated at ca. 150 °C for 1 h. In the first 3 use with Cu<sup>0</sup>/4A full conversion was reached, while in the 4th use the catalytic performance decreased, after 4 h ca. 75 % GC yield was obtained.

Table 2 Reaction of pyrrole with aryl halides

Entry	Aryl halide	Reaction time (h)	Yield (%) <sup>a</sup>
1		4	<b>3a</b> 100 (86 <sup>b</sup> )
2		4	<b>→</b> N <b>3b</b> 100 (79 <sup>b</sup> )
3	le	4	→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→→
4		4	→→→→→ 3c 100 <sup>d</sup>
5	الله المعالم ال المعالم المعالم	4	<b>3d</b> 100 (86 <sup>b</sup> )
6	Ie	4	$\sim$ $^{OH}$ $_{3e}$ 77, phenol 2
7	0 <sub>2</sub> N	4	$ \begin{array}{c} & \swarrow_{N_{2}} \\ & & \swarrow_{N_{2}} \\ & & N_{2} \end{array} \begin{array}{c} & & \swarrow_{N_{2}} \\ & & & \swarrow_{N_{2}} \end{array} \begin{array}{c} & & & \swarrow_{N_{2}} \\ & & & & \swarrow_{N_{2}} \end{array} \begin{array}{c} & & & & & & \\ & & & & & & & \\ & & & & $
8	ر الم	4	$\bigvee_{NO_2}^{N} 3g 42, \qquad \qquad$
9	ر الم	15	$\bigvee_{NO_2}^{N} 3g 25, \qquad NH_2 3g' 69$
10	O <sub>2</sub> N 1g	4 <sup>d</sup>	$ \begin{array}{c}                                     $
11	Br 1h	24	3 <b>a</b> 71
12	o-Br 1i	24	Sc 100 (95 <sup>c</sup> )
13	b-Br 1i	24	<i>∕</i> o-√∕N → 3c 4 <sup>e</sup>

Table 2	continued
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Entry	Aryl halide	Reaction time (h)	Yield (%) <sup>a</sup>
14	o- Br 1j	24	√− 3j 100
15	Br 1k	24	<b>→</b> N <b>→</b> 3k 90
16	o Br	24	
17	OHC Br 1m	24	_f
18	OHC Br	24	_f
19	NC Br	24	ноос
20		36	n.r.

3 mmol 1, 0.3 g catalyst, 6 mmol Cs\_2CO\_3, 3 ml pyrrole, 135  $^{\circ}\text{C}$ 

- <sup>a</sup> Based on GC-MS examination of the reaction mixture
- <sup>b</sup> Isolated yield
- <sup>c</sup> Isolated yield after recrystallization from methanol
- <sup>d</sup> At 115 °C
- <sup>e</sup> Using Cu<sup>2+</sup>/4A
- <sup>f</sup> See text below

Contrarily,  $Cu^{2+}/4A$  gave significantly worse results after the first use. In the 2nd use moderate yield (67 %) was obtained, and in the 3rd use the yield dropped further (35 %). In the 4th use the conversion remained the same (36 %).

XRF examination showed that while in the products of the Cu<sup>0</sup>/4A experiments there was negligible amount of copper, in the case of Cu<sup>2+</sup>/4A high copper content (several %) of the products were observed. Thus, dissolution of Cu<sup>2+</sup> into the reaction mixture may explain the difference between the reusabilities of the two catalysts.

The arylation of other heterocycles with iodobenzene in the presence of our copper catalysts was also examined. As the applied N-heterocycles are solid at room temperature, DMF was used as a solvent. Both  $Cu^0/4A$  and  $Cu^{2+}/4A$  were efficient in the reactions. Although in case of pyrrole  $Cu^0/4A$  was more efficient, in case of indole (6)  $Cu^{2+}/4A$  gave slightly better result (Table 3).

In summary, copper(0) and copper(II) on 4 Å molecular sieve proved to be an efficient catalyst for the arylation of

pyrrole. The preparation of the catalysts is very simple and cheap. The best solvent was pyrrole itself. The nature of the halogen in the aryl halide had a crucial role to the conversion; iodobenzenes gave excellent yield after only 4 h, while aryl bromides required longer reaction time (24 h), chlorobenzene failed to react. Carbonyl and nitrile groups as substituents were not tolerated in the reaction. In case of aryl iodides  $Cu^{2+}/4A$  was also efficient, thus, as its preparation is simpler, it might give a good alternative.  $Cu^0/4A$  is reusable 3 times with full conversion of the aryl halide. The catalytic efficiency of  $Cu^{2+}/4A$  decreased significantly even after the first use, but still gave moderate yield in the second use. Imidazole, pyrazole and indole can also be arylated efficiently with both catalysts.

Comparing with the published methods [2–14] the main advantages of our procedure are the simple preparation of the catalyst from commercially available, cheap starting materials, its reusability, no inert atmosphere is required, the workup is simple and easy, no chromatographic purification is required. The conversion is generally 100 %, Table 3 Reaction of N-heterocycles with iodobenzene

Entry	Catalyst	Compound	Product	Yield (%) <sup>a</sup>
1	Cu <sup>2+</sup> /4A	NH 4		~100
2	Cu <sup>2+</sup> /4A	NH 5		~100
3	Cu <sup>2+</sup> /4A		y g	96
4	Cu <sup>0</sup> /4A	€ €	9	90

6 mmol compound, 3 mmol iodobenzene, 0.3 g catalyst, 6 mmol Cs2CO3, 5 mL DMF, 150 °C, 24 h

<sup>a</sup> Based on GC-MS examination of the reaction mixture

the lower preparative yield can be originated from the loss during the workup. If pyrrole was used as solvent, too, it could be recovered and reused easily.

#### **3** Experimental

GC–MS was carried out on an Agilent 6890 N-GC-5973 N-MSD chromatograph, using a 30 m  $\times$  0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25  $\mu m$ . The initial temperature of column was 45 °C for 1 min, followed by programming at 10 °C/min up to 310 °C and a final period at 310 °C (isothermal) for 17 min. The temperature of the injector was 250 °C. The carrier gas was He and the operation mode was splitless.

<sup>1</sup>H NMR spectra were obtained in CDCl<sub>3</sub> solution on a Bruker AV-300 spectrometer operating at 300 or 500 MHz.

All chemicals are commercially available products, and were purchased from Meck Hungary Ltd.

## 3.1 Preparation of the catalysts

Finely ground 4A (5 g) was suspended in 500 mL of aqueous copper(II) chloride (0.6725 g, 5 mmol) solution and stirred at 25  $^{\circ}$ C for 12 h. The solid material was

filtered and washed thoroughly with 500 mL of deionized water yielding  $Cu^{2+}/4A$ .

 $Cu^{0}/4A$  was prepared by the reduction of  $Cu^{2+}/4A$ .  $Cu^{2+}/4A$  (5 g) was reduced with hydrazine hydrate (6.13 mL of 80 % aqueous solution) in ethanol (50 mL) for 3 h at room temperature, filtered, and washed with ethanol.

A mixture of pyrrole (3 ml),  $Cs_2CO_3$  (1.96 g, 6 mmol),  $Cu^0/4A$  or  $Cu^{2+}/4A$  (0.3 g) and the appropriate aryl halide (3 mmol) were stirred at 135 °C (bath temperature) for 4–36 h. Before adding to the mixture,  $Cu^{2+}/4A$  was preheated at ca. 150 °C for 1 h. The mixture was filtered, the solid was washed with dichloromethane. The filtrate was extracted with deionised water (2 × 40 ml). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated in vacuum. The residue was distilled and clarified. Certain products (**3c, 3f**) were purified by recrystallization from MeOH.

A mixture of the appropriate heterocycle (6 mmol),  $Cs_2CO_3$  (1.96 g, 6 mmol),  $Cu^0/4A$  or  $Cu^{2+}/4A$  (0.3 g), iodobenzene (334 µl, 3 mmol) and DMF (5 mL) were stirred at 150 °C (bath temperature) for 24 h. The mixture was filtered, the solid was washed with dichloromethane, and the filtrate was analyzed with GC–MS.

All products have satisfactory spectral data (<sup>1</sup>H NMR, MS). The spectral data of the known compounds were identical with those reported in the literature.

## 3.2 Representative spectroscopic data of compounds

# 3.2.1 1-Phenylpyrrole, 3a

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.34 (s, 2H), 7.08 (s, 2H), 7.22 (m, 1H), 7.37 (m, 4H).

GC: R<sub>t</sub>: 9.86 min; MS (m/z): M<sup>+</sup>: 143 (100), 115 (70), 104 (6), 89 (6), 77 (18).

# 3.2.2 1-(4-Methylphenyl)pyrrole, 3b

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 2.37 (s, 3H), 6.33 (s, 2H), 7.05 (s, 2H), 7.2 (d, 2H), 7.28 (d, 2H).

GC: R<sub>t</sub>: 12.37 min; MS (m/z): M<sup>+</sup>: 157 (100), 142 (6), 129 (20), 115 (19), 91 (7), 77 (6).

# 3.2.3 1-(4-Nitrophenyl)pyrrole, 3f

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.43 (m, 2H), 7.17 (m, 2H), 7.51 (d, 2H), 8.31 (d, 2H).

GC: R<sub>t</sub>: 16.77 min; MS (m/z): M<sup>+</sup>: 188 (100), 158 (8), 141 (31), 115 (30), 103 (4), 89 (7), 76 (7).

3.2.4 1-(3-Aminophenyl)pyrrole, 3 h

GC: R<sub>t</sub>: 14.99 min; MS (m/z): M<sup>+</sup>: 158 (100), 142 (2), 130 (44), 118 (4), 103 (5), 91 (3), 76 (4).

# References

 Cozzi P, Carganico G, Fusar D, Grossoni M, Menichincheri M, Pinciroli V, Tonani R, Vaghi F, Salvati P (1993) J Med Chem 36:2964

- 2. Yang Q, Wang Y, Lin D, Zhang M (2013) Tetrahedron Lett 54:1994
- Sreedhar B, Arundhathi R, Reddy PL, Kantam ML (2009) J Org Chem 74:7951
- 4. Panda N, Jena AK, Mohapatra S, Rout SR (2011) Tetrahedron Lett 52:1924
- 5. Kantam ML, Venkanna GT, Sridhar Ch, Kumar KBS (2006) Tetrahedron Lett 47:3897
- Yong FF, Teo YC, Tay SH, Tan BYH, Lim KH (2011) Tetrahedron Lett 52:1161–1164
- Kim AY, Lee HJ, Park JC, Kang H, Yang H, Song H, Park KH (2009) Molecules 14:5169
- Islam M, Mondal S, Mondal P, Roy AS, Tuhina K, Mobarok M, Paul S, Salam N, Hossain D (2011) Catal Lett 141:1171
- 9. Correa A, Bolm C (2007) Adv Synth Catal 349:2673
- Zhu R, Xing L, Wang X, Cheng C, Su D, Hua Y (2008) Adv Synth Catal 350:1253
- 11. Rout L, Jammi S, Punniyamurthy T (2007) Org Lett 9:3397-3399
- 12. Zhu L, Guo P, Li G, Lan J, Xie R, You J (2007) J Org Chem 72:8535
- Kantam ML, Yadav J, Laha S, Sreedhar B, Jha S (2007) Adv Synth Catal 349:1938
- 14. Taillefer M, Xia N, Ouali A (2007) Angew Chem Int Ed 46:934
- 15. Cwik A, Hell Z, Figueras F (2006) Adv Synth Catal 348:523
- 16. Cwik A, Hell Z, Figueras F (2006) Tetrahedron Lett 47:3023
- 17. Cwik A, Hell Z, Figueras F (2005) Org Biomol Chem 3:4307
- 18. Kiss A, Hell Z, Balint M (2010) Org Biomol Chem 8:331
- Fodor A, Kiss A, Debreczeni N, Hell Z, Gresits I (2010) Org Biomol Chem 8:4575
- 20. Kiss A, Hell Z (2013) Synth Commun 43:1778
- 21. Kiss A, Hell Z (2011) Tetrahedron Lett 52:6021
- 22. Drying Agents Brochure, Merck KGaA, Germany. http://www. merckmillipore.com/reagents-chemicals-labware/literature-inorg anics
- 23. Choudary BM, Madhi S, Chowdari NS, Kantam ML, Sreedhar B (2002) J Am Chem Soc 124:14127
- 24. Debreczeni N, Fodor A, Hell Z (2014) Catal Lett 144:1547-1551
- 25. Németh J, Hell Z (2013) React Kinet Mech Catal 111:115-121