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Copper(II) fluoride-catalyzed N-arylation of heterocycles with halothiophenes

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ABSTRACT

A novel, cheap copper(II) fluoride-mediated N-arylation of heterocycles with halothiophenes is described. The yield of the pyrazolylthiophene strongly depends on the nature of the initial thiophene. The molecular structure of 3,5-dimethyl-1-(5′-methyl-[2,2′]bithienyl-5-yl)-1*H*-pyrazole was studied by X-ray diffraction.

N-Aryl heterocycles are widely used fragments in the field of pharmaceutical chemistry.[1a] Arylation of heterocyclic nitrogen is a difficult problem.[1b] The first *ipso* substitution of an aryl halide by a nucleophile in the presence of copper(II) triflate, 1,10-phenanthroline, dibenzylideneacetone, and cesium carbonate was reported by Buchwald and co-workers.[2] Investigations in the field of copper-catalyzed arylation of *N*-heterocycles have gained attention, as reflected by the increasing number of reports in the literature. Various copper(I) and copper(II) salts and their complexes with N-, O-, and P-ligands were investigated as catalysts for the N-arylation of nitrogen-containing heterocycles. According to the literature, copper(I) iodide was the most promising source of copper in this type of reaction in the presence of potassium phosphate in toluene.[3] Recently, Lakshmi Kantam and co-workers reported that copper-exchanged fluoroapatite is an effective heterogeneous catalyst for the N-arylation of heterocycles with bromo- and iodoarenes in DMSO.[4]

Our experience with thiophene chemistry[5] inspired us to investigate the incorporation of five-membered *N*-heterocycles on thiophene and bithiophene cores in the presence of copper(II) fluoride with the purpose of optimizing the conditions for the coupling and to find a cheap and convenient method.

Typically, copper-mediated coupling of aryl halides with *N*-heterocycles is performed in aprotic solvents in the presence of a base and ligand. 4-Iodoanisole (**1**) and 3,5-dimethylpyrazole (**2**) were chosen as model compounds. Our investigation started with the reactions of **1** and **2** in DMF in the presence of potassium carbonate as base with the purpose of finding the best and the cheapest ligand (Table 1). It was found that the widely used DMEDA, TMEDA, and salicylaldoxime were ineffective in CuF_2-mediated coupling even after heating for 96 h. However, the use of 0.25 equiv of *o*-phenanthroline catalyzed the current reaction successfully and the desired product, 1-(4-methoxyphenyl)-3,5-dimethylpyrazole[6a] (**3**) was obtained in 81% yield. On performing the same reaction in DMSO, the yield of compound **3** was slightly lower (78%); no product was obtained in xylene. According to our experimental data, 2,2,6,6-tetramethyl-3,5-heptanedione was a good ligand for the CuF_2-mediated coupling (73% yield, entry 5), however, it is quite expensive. Finally, we chose 1,10-phenanthroline as the ligand and DMF as the solvent for further investigations.

Reactions of 4-iodoanisole (**1**) with various five-membered *N*-heterocycles are presented in Scheme 1. Using our new catalytic system, pyrazole was successfully N-arylated with **1** in almost quantitative yield (**4**,[6b] 98%). 1-(4-Methoxyphenyl)-4-bromo-3,5-dimethylpyrazole (**5**)[6c] and 1-(4-methoxyphenyl)imidazole (**6**)[6b] were obtained in good yields, however, our attempt to arylate benzimidazole was not impressive, the desired product **7**[6b] being obtained in only 16% yield. Notably, arylated indole **8**[6d] and ethyl 5-benzyloxyindol-2-ylcarboxylate **9**[6e] were prepared in good yields (72% and 60%, respectively).

Heteroarylthiophenes have attracted significant attention as useful building blocks in biologically active compounds and as materials showing conductive, semiconductive, non-linear, and liquid crystalline characteristics.[7] Thus, we investigated the introduction of a pyrazole ring at the α-position of thiophene via the reaction of 2-iodothiophene and 3,5-dimethylpyrazole. The desired product **10** was formed in moderate yield (65%) after heating for 72 h in DMF using copper(II) fluoride as the catalyst in the presence of 1,10-phenanthroline and potassium carbonate as the base (Table

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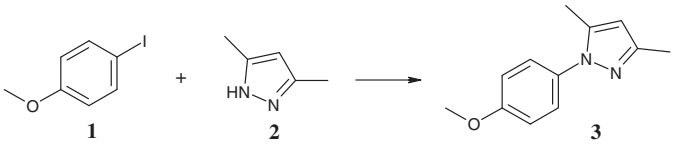
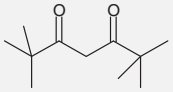
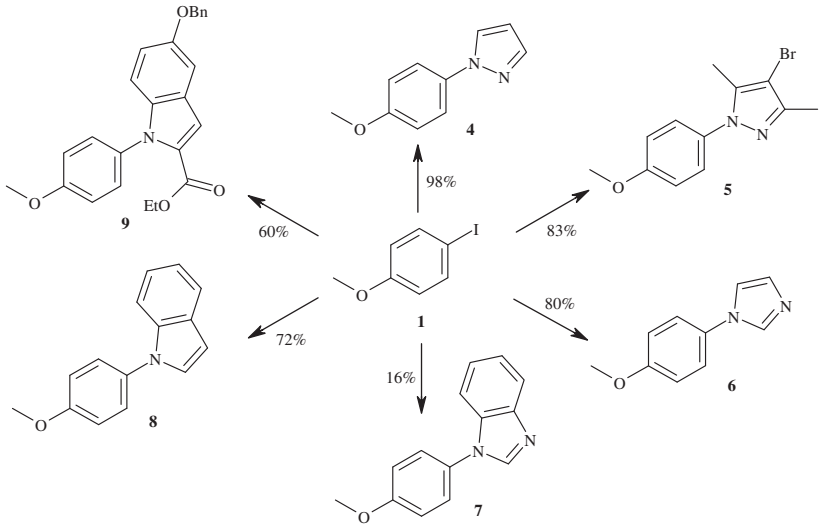
Table 1
CuF_2-catalyzed reaction of 4-iodoanisole with 3,5-dimethylpyrazole



Entry	Ligand	Catalyst equiv	Base	Solvent	Time (h)	Yield (%)
1	DMEDA	0.25	K_2CO_3	DMF	96	18
2	TMEDA	0.25	K_2CO_3	DMF	96	4
3	1,10-Phenanthroline	0.25	K_2CO_3	DMF	96	81
4	Salicyl aldoxime	0.25	K_2CO_3	DMF	96	10
5		0.25	K_2CO_3	DMF	96	73
6	—	—	K_2CO_3	DMF	96	6
7	1,10-Phenanthroline	0.25	K_2CO_3	DMSO	72	78
8	1,10-Phenanthroline	0.25	K_2CO_3	DMAC	72	36
9	1,10-Phenanthroline	0.25	K_2CO_3	xylene	72	0
10	1,10-Phenanthroline	0.25	K_2CO_3	DMF	22	~8
11	1,10-Phenanthroline	0.25	Cs_2CO_3	DMF	22	~10
12	1,10-Phenanthroline	0.2	K_2CO_3	DMF	48	20
13	1,10-Phenanthroline	0.4	K_2CO_3	DMF	48	52
14	1,10-Phenanthroline	0.6	K_2CO_3	DMF	48	50



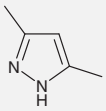
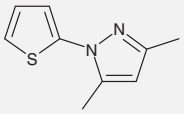
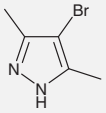
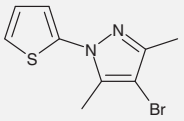
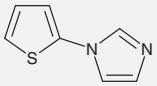
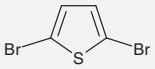
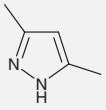
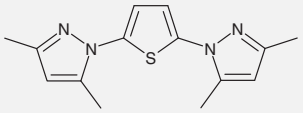
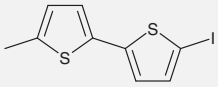
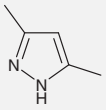
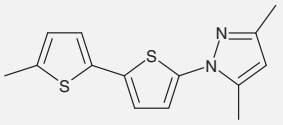
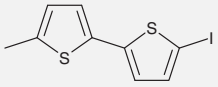
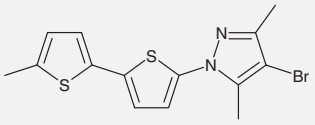
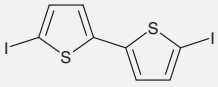
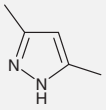
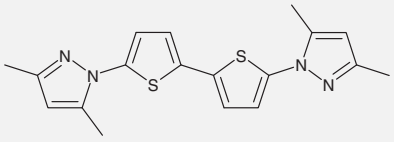
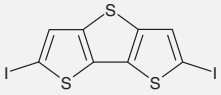
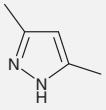
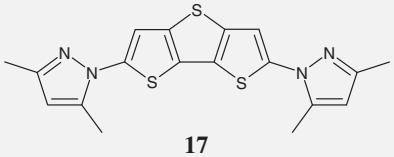
Scheme 1. Reagents and conditions: 4-iodoanisole (1 equiv), *N*-heterocycle (1.2 equiv), copper(II) fluoride (0.5 equiv), 1,10-phenanthroline (0.5 equiv), K_2CO_3 (3 equiv), DMF, 140 °C, 72 h.

2). It was found that 4-bromo-3,5-dimethylpyrazole reacted with 2-iodothiophene in lower yield to afford the corresponding 4-bromo-3,5-dimethyl-1-(thien-2-yl)-1*H*-pyrazole (**11**),[6f] however, a more promising result was obtained in the reaction with imidazole (**12**,[6g] 59%). 2,5-Di(3,5-dimethylpyrazolyl)thiophene (**13**)[6h] was synthesized in moderate yield from 2,5-dibromothiophene (bromo substituents are not as convenient leaving groups under the current reaction conditions). 5-Iodo-5′-methyl-2,2′-bithiophene was successfully converted into the corresponding 3,5-dimethyl-1-(5′-methyl-[2,2′]bithienyl-5-yl)-1*H*-pyrazole (**14**)[6i] and 4-bromo-3,5-dimethyl-1-(5′-methyl-[2,2′]bithienyl-5-yl)-1*H*-pyrazole (**15**)[6j] in good yields. The structure of **14** was confirmed unambiguously by X-ray diffraction (Fig. 1).[8] Crystals of **14** suitable for X-ray analysis were obtained by slow crystallization from a mixture of petroleum ether/dichloromethane. The bithiophene fragment is characterized by a transoid conformation. The N(1)–C(2A) and C(5A)–C(5B) bond lengths [1.408(4) and 1.445(4) Å] indicate that a conjugated system is present over the whole molecule. There is a weak shortened intermolecular contact N(2)···H(C6B) (2.65(5) Å) in the crystal structure. It should be noted that there are no asymmetric atoms in the structure and the molecules coincide with their mirror antipodes due to the planar conformation, nevertheless, the crystal structure is chiral (the space group is $P2_12_12_1$).

The useful oligomer **16**[6k] was prepared by treatment of 5,5′-diiodo-2,2′-bithiophene with 2 equiv of 3,5-dimethylpyrazole in good yield (87%). Also 2,6-diiodo-dithieno[3,2-*b*;2′,3′-*d*]thiophene was converted into 2,6-(3,5-dimethylpyrazolyl)-dithieno[3,2-*b*;2′,3′-*d*]thiophene (**17**)[6l] in a poor 20% yield.

In summary, a mild and inexpensive method for the arylation of five-membered *N*-heterocycles was developed. Introduction of pyrazole moieties to an α-thiophene chain opens an easy route to prepare more complicated oligomers.

Table 2
CuF_2-catalyzed N-arylation of heterocycles with halothiophenes

Entry	Ar-Hal	Het-NH	Product	Yield (%)
1			 **10**	65
2			 **11**	37
3			 **12**	59
5			 **13**	36
6			 **14**	67
7			 **15**	71
8			 **16**	87
10			 **17**	20

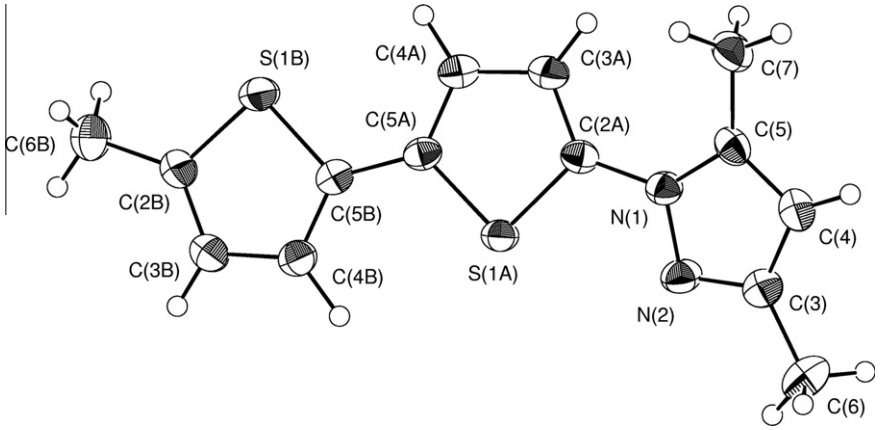


Figure 1. ORTEP molecular structure of 3,5-dimethyl-1-(5′-methyl-[2,2′]bithienyl-5-yl)-1*H*-pyrazole (**14**).

References and notes

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6. *General procedure*: A mixture of 4-iodoanisole (0.2 mmol), *N*-heterocycle (0.22 mmol), copper(II) fluoride (0.1 mmol), 1,10-phenanthroline (0.1 mmol), and K_2CO_3 (0.6 mmol) in dry DMF was heated at 140 °C for 72 h. The reaction mixture was poured into EtOAc, washed with brine, and dried over $MgSO_4$. Pure product was isolated by column chromatography on silica gel using petroleum ether/EtOAc as eluent. The structures of all the compounds were confirmed by ^{1}H (400 MHz, $CDCl_3$) and ^{13}C (100.6 MHz, $CDCl_3$) NMR (a) Alberola, A.; Bleye, L. C.; Gonzalez-Ortega, A.; Sadaba, M. L.; Sanudo, M. C. *Heterocycles* **2001**, *55*, 331–352; (b) Zhu, L.; Li, G.; Luo, L.; Guo, P.; Lan, J.; You, J. *J. Org. Chem.* **2009**, *74*, 2200–2202; (c) 1-(4-methoxyphenyl)-4-bromo-3,5-dimethylpyrazole (**5**) Oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.23 (3H, s, CH_3); 2.27 (3H, s, CH_3); 3.83 (3H, s, CH_3); 6.92–6.97 (2H, m, 2 × ArH); 7.24–7.30 (2H, m, 2 × ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 11.5, 12.3, 55.5, 95.6, 114.2, 126.3, 132.9, 137.6, 147.1, 159.1.; (d) Tang, B.-X.; Guo, S.-M.; Zhang, M.-B.; Li, J.-H. *Synthesis* **2008**, 1707–1716; (e) ethyl 5-benzyloxy-1-(4-methoxyphenyl)indol-2-ylcarboxylate (**9**)[1] H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 1.26 (3H, t, CH_3, J = 7.4 Hz); 3.89 (3H, s, CH_3); 4.23 (2H, q, CH_2, J = 7.4 Hz); 5.12 (2H, s, CH_2); 6.98–7.07 (4H, m, 4(ArH); 7.18–7.21 (1H, m, ArH); 7.22–7.28 (2H, m, 2(ArH); 7.31–7.44 (4H, m, 4(ArH); 7.45–7.51 (2H, m, 2(ArH).[13] C NMR (100.6 MHz, $CDCl_3$/TMS) (ppm): 14.2, 55.4, 60.4, 70.7, 103.9, 110.5, 112.5, 114.1, 117.3, 126.1, 127.5, 127.8, 128.5, 129.0, 129.4, 131.3, 136.6, 137.3, 154.1, 159.1, 161.2.; f 4-bromo-3,5-dimethyl-1-(thien-2-yl)-1*H*-pyrazole (**11**) Oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.28 (3H, s, CH_3); 2.34 (3H, s, CH_3); 6.95–7.00 (2H, m, 2 × ArH); 7.18 (1H, dd, ArH, J = 2.2 Hz, J = 5.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 11.6, 12.4, 96.6, 120.3, 122.9, 125.6, 138.7, 141.7, 148.3.; (g) Chen, W.; Zhang, Y.; Zhu, L.; Lan, J.; Xie, R.; You, J. *J. Am. Chem. Soc* **2007**, *129*, 13879–13886; (h) 2,5-di(3,5-dimethylpyrazol-1-yl)thiophene (**13**) Oil. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.27 (6H, s, 2 × CH_3); 2.34 (6H, s, 2 × CH_3); 5.97 (2H, s, 2 × ArH); 6.83 (2H, s, 2 × ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 12.2, 13.5, 107.4, 118.3, 138.5, 140.9, 150.0.; (i) 3,5-dimethyl-1-(5′-methyl-[2,2′]bithienyl-5-yl)-1*H*-pyrazole (**14**) ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.28 (3H, s, CH_3); 2.37 (3H, s, CH_3); 2.48 (3H, d, CH_3, J = 1.2 Hz); 5.97 (1H, s, ArH); 6.64–6.68 (1H, m, ArH); 6.80 (1H, d, ArH, J = 4.0 Hz); 6.92 (1H, d, ArH, J = 3.4 Hz); 6.94 (1H, d, ArH, J = 3.4 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 12.4, 13.5, 15.3, 107.5, 118.9, 121.1, 123.6, 125.9, 134.2, 134.5, 139.4, 140.1, 140.4, 149.8.; (j) 4-bromo-3,5-dimethyl-1-(5′-methyl-[2,2′]bithienyl-5-yl)-1*H*-pyrazole (**15**) ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.21 (3H, s, CH_3); 2.30 (3H, s, CH_3); 2.41 (3H, s, CH_3); 6.57–6.61 (1H, m, ArH); 6.76 (1H, d, ArH, J = 4.0 Hz); 6.85 (1H, d, ArH, J = 4.0 Hz); 6.88 (1H, d, ArH, J = 3.6 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 11.7, 12.4, 15.4, 96.9, 120.1, 121.1, 123.9, 126.0, 134.2, 135.1, 138.5, 139.4, 139.8, 148.4.; (k) 5,5′-(3,5-dimethylpyrazol-1-yl)-2,2′-bithiophene (**16**) mp = 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.28 (6H, s, 2 × CH_3); 2.38 (6H, s, 2 × CH_3), 5.98 (2H, s, 2 × ArH); 6.82 (2H, d, 2 × ArH, J = 4.0 Hz); 6.99 (2H, d, 2 × ArH, J = 4.0 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 12.5, 13.5, 107.7, 118.6, 121.9, 133.0, 140.4, 141.0, 150.0.; (l) 2,6-(3,5-dimethylpyrazol-1-yl)-dithieno[3,2-*b*;2′,3′-*d*]thiophene (**17**) ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ (ppm): 2.22 (6H, s, 2 × CH_3); 2.34 (6H, s, 2 × CH_3); 5.94 (2H, s, 2 × ArH); 7.11 (2H, s, 2 × ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$/TMS) δ (ppm): 12.4, 13.5, 107.9, 112.6, 127.0, 137.6, 140.7, 141.9, 150.2.
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8. Diffraction data were collected at −20 °C on a Nonius KappaCCD diffractometer using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). The crystal structure of **14** was solved by direct methods[9a] and refined by full-matrix least squares.[9b] All non-hydrogen atoms were refined in anisotropic approximation; all H atoms were refined isotropically. Crystal data for **14**: orthorhombic; a = 5.8002(1), b = 14.6023(4), c = 15.8278(5) Å; V = 1340.56(6) Å^3, Z = 4, μ = 0.38 mm^{-1}, D_{calcd} = 1.360 g cm^{-3}; space group is $P2_12_12_1$. A total of 2234 reflection intensities were collected; for structure refinement, 1934 independent reflections with $I > 3\sigma(I)$ were used. The final R-factor is 0.042. For further details, see the crystallographic data for **14** deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Number CCDC 760725. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.
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