HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 595 - 602. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 12th April, 2013, Accepted, 27th May, 2013, Published online, 30th May, 2013
DOI: 10.3987/COM-13-S(S)4

COPPER-MEDIATED REGIOSELECTIVE HOMOCOUPLING OF THIOPHENES AND INDOLES VIA DIRECTED C–H CLEAVAGE

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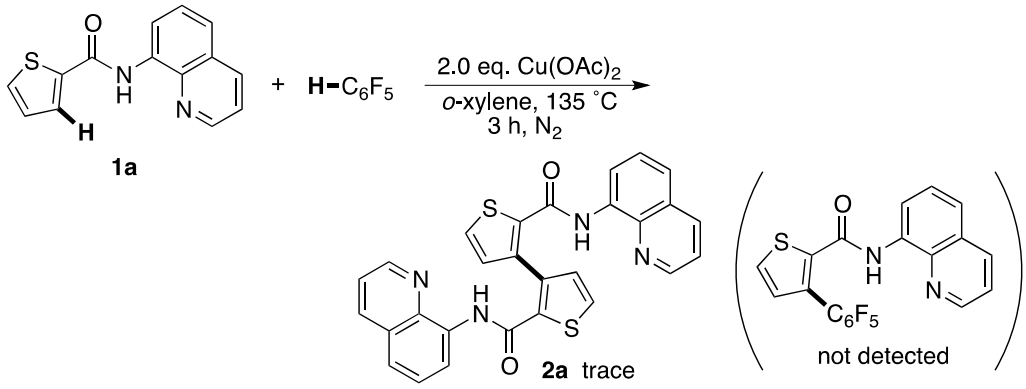
Abstract – We have developed a copper-mediated regioselective homocoupling reaction of thiophenes and indoles via functional-group-directed C–H cleavage to afford the corresponding bisthiophenes (bithiophenes) and bisindoles directly. The copper-based system can provide a concise and precious-metal-free access to the above heterocyclic cores of fundamental importance in material and pharmaceutical chemistry.

Bisthiophenes (bithiophenes) and bisindoles are frequently occurring heterocyclic structures in functional materials and pharmaceuticals. For example, the former is a key motif in many organic field effect transistors (OFETs), organic light-emitting diodes (OLEDs), and photovoltaic cells.[1] The latter is also found in many biologically active compounds and alkaloids.[2] Among numerous approaches to the above target structures, in addition to the conventional cross-coupling technologies with organic halides and organometallic reagents, metal-mediated direct C–H functionalization methodology has recently received significant attention.[3] In particular, dehydrogenative homocoupling reactions of thiophenes[4] and indoles[5] via two-fold C–H cleavage is of great interest. To date, a combination of precious palladium catalysts and a stoichiometric amount of copper- or silver-based oxidants is generally employed for such transformations. On the other hand, our group[6] and others[7] have focused on the potential and unique activity of less expensive and abundant copper salts and complexes, and succeeded in some types of copper-promoted C–H functionalization of (hetero)arenes. In this context, copper-mediated or copper-catalyzed regioselective direct homocoupling reactions also have been developed. However, in most cases, the substrate scope is still limited to relatively acidic arenes such as 1,3-azoles and polyfluoroarenes.[8] Thus, the application of copper-based protocols to nonacidic

The paper is dedicated to Prof. Victor Snieckus on the occasion of his 77th birthday.

thiophenes and indoles remains somewhat challenging and is strongly desired.[9] Here we report a copper-mediated regioselective homocoupling of thiophenes and indoles through functional-group-directed dual C–H cleavage, providing bisthiophenes and bisindoles directly.

Very recently, we reported a copper-mediated C–H/C–H biaryl cross-coupling of benzoic acid derivatives and 1,3-azoles[6p] with the aid of double coordination.[10] In the course of this study, we attempted the reaction of 2-thiophenecarboxamide **1a** with pentafluorobenzene. However, the desired cross-coupling product was not observed. Instead, a small but significant amount of homocoupling product, bisthiophene **2a**, was detected (Scheme 1).

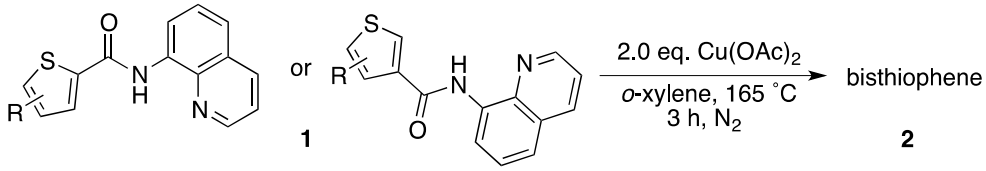


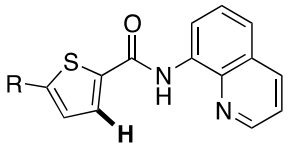
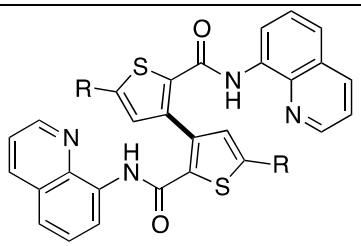
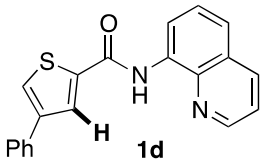
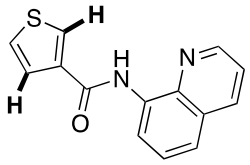
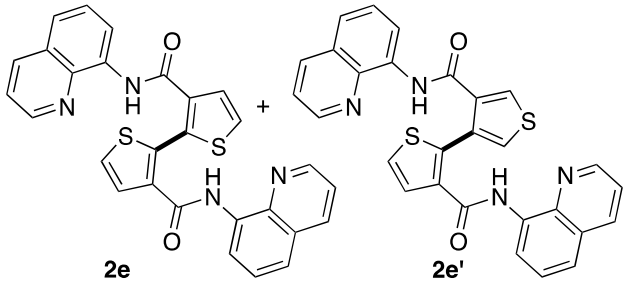
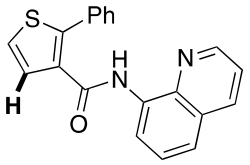
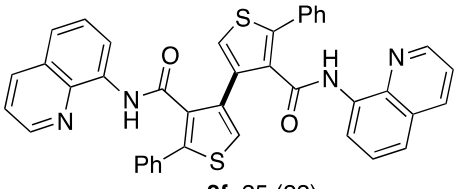
Scheme 1. Initial finding of copper-mediated regioselective homocoupling of thiophene **1a**

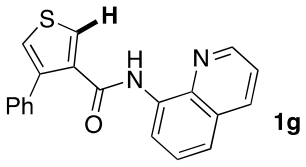
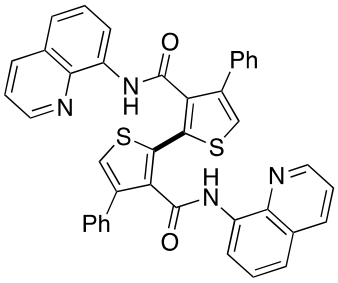
The serendipity prompted us to optimize conditions for the regioselective homocoupling of **1a**. After investigation of various reaction parameters, we identified higher reaction temperature (165 °C) to be essential for the satisfactory yield of **2a** (Table 1, entry 1). Under the same conditions, we next performed the reaction of an array of substituted thiophenecarboxamides **1**. The installation of any substituents at the C5 position gave negative impacts on yield; methyl and chloro-substituted bisthiophenes **2b** and **2c** were obtained in lower yields (entries 2 and 3). On the other hand, 4-substituted 2-thiophenecarboxamide **1d** was completely inert probably due to steric factors (entry 4). 3-Thiophenecarboxamide **1e** showed good reactivity, and a regioisomeric mixture of 2,2'- and 2,4'-bisthiophenes was obtained in a ratio of 78:22 (entry 5). Some substituted 3-thiophenecarboxamides were also tested. Although moderate, the corresponding phenyl-substituted bisthiophenes **2f**, **2g**, and **2h** were formed directly (entries 6–8). In the case of 5-phenyl-3-thiophenecarboxamide **1h**, the C–C bond formation occurred regioselectively at the less congested C2 position (entry 8). Moreover, methoxyphenyl and thienyl groups were tolerated, and functionalized π-extended bisthiophene cores **2i** and **2j** were readily accessible (entries 9 and 10). The resultant amide moiety can be easily transformed to the ethyl ester, which is useful synthetic handle for further manipulations.[6p] Unfortunately, attempts to apply other arenecarboxamides involving benzene,

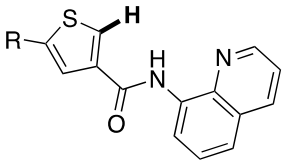
furan, and pyrrole remained unsuccessful, and the homocoupling reaction was unique to the thiophene ring.

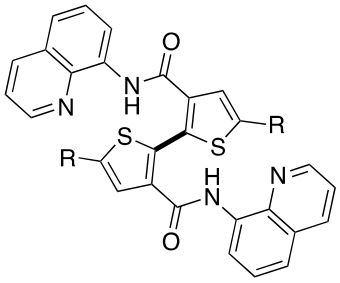
Table 1. Copper-mediated direct homocoupling of thiophenecarboxamides **1**[a]



entry	**1**	**2**, yield (%)[b]
		
1	R = H: **1a**	R = H: **2a** 68 (67)
2	R = Me: **1b**	R = Me: **2b** 18
3	R = Cl: **1c**	R = Cl: **2c** 33 (30)
4	 **1d**	no reaction
5	 **1e**	 **2e** **2e'** (60), **2e/2e'** = 78:22
6	 **1f**	 **2f** 25 (22)

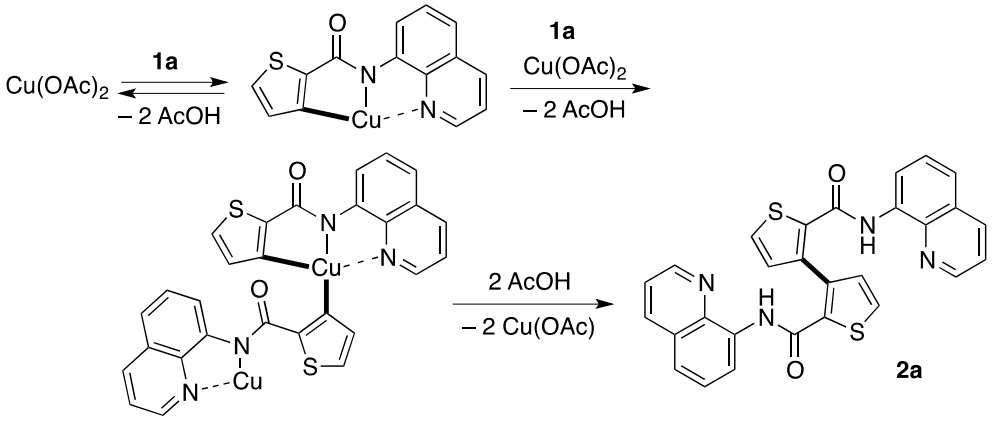
7	 **1g**	 **2g** 18 (16)
8	R = Ph: **1h**	R = Ph: **2h** (38)
9	R = 4-MeOC$_6$H$_4$: **1i**	R = 4-MeOC$_6$H$_4$: **2i** (26)
10	R = 3-thienyl: **1j**	R = 3-thienyl: **2j** (39)



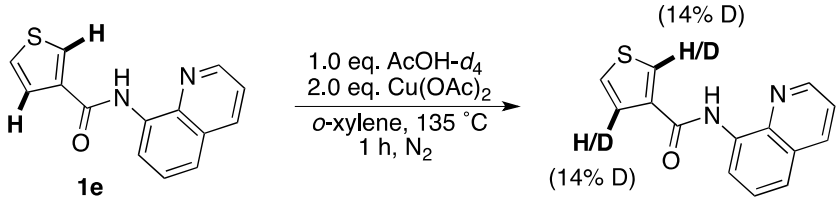


[a] Conditions: **1a** (0.25 mmol), $Cu(OAc)_2$ (0.50 mmol), *o*-xylene (1.5 mL), 165 ˚C, 3 h, N_2. [b] Yields are based on a half amount of **1** employed and estimated by ^{1}H NMR. Isolated yields are in parentheses.

Although the detailed mechanism is not yet clear at the present, the reaction is believed to proceed through 1) N,N-double chelation-assisted C–H cupration of the first thiophene to provide a Cu(II)-containing metalacycle, 2) oxidation of Cu(II) into Cu(III) through disproportionation by additional $Cu(OAc)_2$, 3) C–H metalation of the second thiophene at the Cu(III) center, and 4) productive reductive elimination of two thiophene ligands from the Cu(III) intermediate, as exemplified by the reaction of **1a** shown in Scheme 2. To get some information about the proposed above mechanism, we carried out the reaction of **1e** in the presence of AcOH-d_4 at lower temperature (135 ˚C) (Scheme 3). While neither **2e** nor **2e'** were detected, the recovered **1e** showed significant amount of H/D exchange at both C2 and C4 positions. The result indicates that the C–H cleavage of, at least, the first thiophene, reversibly occurs even at non-productive lower temperature. Thus, the rate-limiting step may be involved in elementary steps after the first C–H cleavage. In view of the rapid reductive elimination from some Cu(III) complexes in the literature,[11] the disproportionation or second C–H cleavage is believed to be rate-limiting. Further efforts on clarification of the detailed mechanism are ongoing.

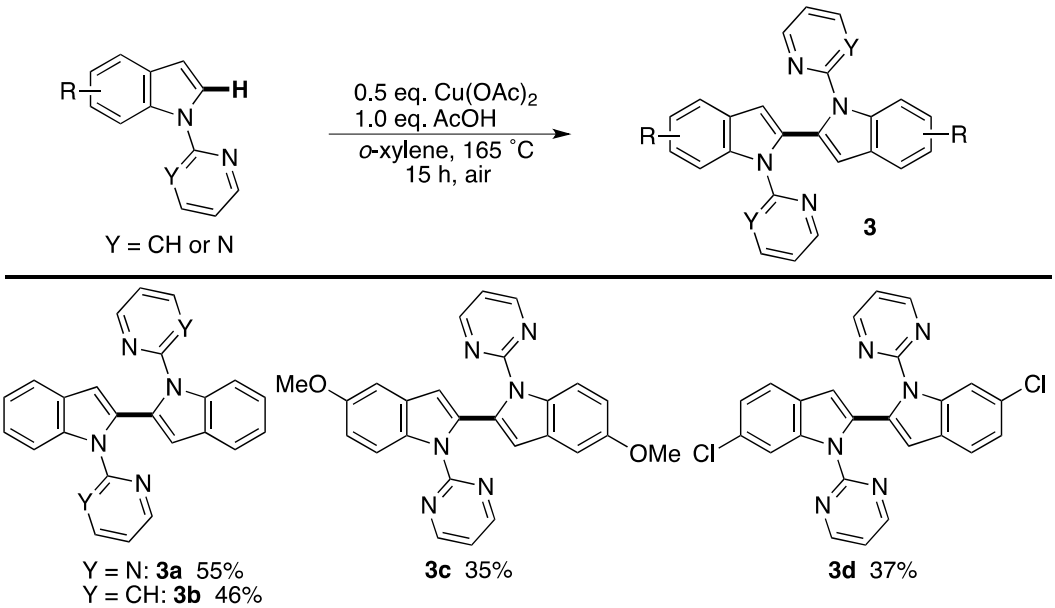


Scheme 2. Plausible mechanism



Scheme 3. Reaction of **1e** in the presence of AcOH-d_4 at lower temperature

Finally, we turned our attention to indoles. To our delight, *N*-(2-pyrimidyl)indole and *N*-(2-pyridyl)indole[6n] underwent the homocoupling under similar copper-based conditions to provide the corresponding 2,2'-bisindoles regioselectively (Scheme 4, **3a** and **3b**). The reaction was compatible with methoxy and chloro groups, and functionalized 2,2'-bisindoles were readily obtained (**3c** and **3d**).



Scheme 4. Copper-mediated direct homocoupling of indoles

In summary, we have developed a precious-metal-free copper-mediated direct homocoupling of thiophenes and indoles via directed C–H cleavage.[12] The copper-based reaction system can provide a facile access to bisthiophenes and bisindoles of fundamental importance in material science and pharmaceutical chemistry. Moreover, the reaction is also regarded as a limited successful example of the copper-mediated direct biaryl formation with nonacidic (hetero)arenes.

EXPERIMENTAL

Copper-mediated homocoupling of thiophenecarboxamides: the reaction of **1a** is representative (Table 1, entry 1). $Cu(OAc)_2$ (91 mg, 0.50 mmol) and *N*-(quinolin-8-yl)thiophene-2-carboxamide (**1a**, 64 mg, 0.25 mmol) were placed in a 20 mL two-necked reaction flask equipped with a reflux condenser. The flask was filled with nitrogen by using the standard Schrenk technique. *o*-Xylene (1.5 mL) was added dropwise via a syringe, and the solution was stirred at 165 °C for 3 h. The resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (1:1, v/v) gave N^2,$N^{2'}$-di(quinolin-8-yl)-[3,3'-bithiophene]-2,2'-dicarboxamide (**2a**, 43 mg, 0.085 mmol) in 67% yield.

ACKNOWLEDGEMENTS

This work was partly supported by Grants-in-Aid from MEXT and JSPS, Japan. M.M. acknowledges Kansai Research Foundation for technology promotion.

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12. Although we tested *N*-(naphthalen-1-yl)thiophene-2-carboxamide and *N*-phenylindole, no corresponding homocoupling products were detected by ^{1}H NMR and MS analysis.