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On-Water Chemistry: Copper-Catalyzed Straightforward Synthesis of Benzo[*b*]furan Derivatives in Neat Water[§]

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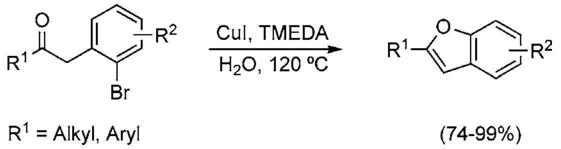
ABSTRACT



A more sustainable protocol leading to 2-alkyl- or 2-aryl-substituted benzo[*b*]furans is reported, involving a copper–TMEDA complex which catalyzes the transformation of readily available ketone derivatives into the corresponding benzofurans in good to excellent yields. The reaction is accomplished using water as the solvent without organic cosolvents, and one example of catalyst reutilization is also presented.

In recent years, amid growing concern about the development of more environmentally friendly protocols in organic chemistry, water has become the solvent of choice to successfully perform many organic transformations.[1] The advantages derived from the use of water, instead of organic solvents, are clear in terms of safety, cost, and reduced toxicity. Furthermore, the insolubility of organic compounds in water causes them to react on its surface, thereby giving rise to the term "on-water" chemistry, which implies that hydrogen-bond-type interactions are responsible for rate accelerations and greater selectivities observed in aqueous reaction media compared with organic ones.[1]

The properties of water, either as a solvent or as an additive, have been extensively applied to different types of organic transformations including coupling reactions catalyzed by transition metals, thus broadening the scope of on-water chemistry and its contribution to green chemistry.[2] Examples of such transformations include the palladium-catalyzed coupling reactions enhanced by the presence of small amounts of water such as in our recently reported route to the antiepileptic drug Trileptal.[3] In connection with this previous work and continuing with our research on the synthesis of valuable heterocycles through direct arylations in the absence of transmetalating agents, we report here the first copper-catalyzed synthesis of benzo[*b*]furan derivatives accomplished in aqueous media,[4] as well as a recovery and reutilization of the copper catalyst.

Benzo[*b*]furans are of great interest because of their applications in pharmacology and their wide distribution in nature.[5] For instance, 2-arylbenzofurans and their derivatives exhibit a broad range of biological activities, such as their antineoplastic,[6] antiviral,[7] antioxidative,[8] and antiinflamma-

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[§] Dedicated to the memory of Prof. Marcial Moreno Mañas.

(1) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275 and references therein. (b) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.

(2) For a review on palladium-catalyzed reactions in aqueous media, see: (a) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. For other metal-catalyzed protocols, see: (b) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755. (c) Sanz, R.; Castroviejo, M. P.; Fernández, Y.; Fañanas, F. J. *J. Org. Chem.* **2005**, *70*, 6548. (d) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022.

(3) Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2005**, *7*, 4787.

(4) While this work was being carried out, an elegant protocol for the synthesis of benzo[*b*]furans based on copper catalysis has been recently reported, but in the absence of water (DMF was the solvent employed). See: Chen, C.-Y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964.

(5) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (b) Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, *2*, 3521.

(6) Navarro, E.; Alonso, S. J.; Trujillo, J.; Jorge, E.; Pérez, C. *J. Nat. Prod.* **2001**, *64*, 134.

(7) Kraus, G. A.; Kim, I. *Org. Lett.* **2003**, *5*, 1191.

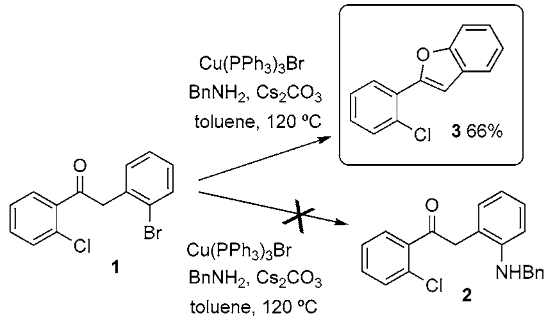
(8) Lu, H.; Liu, G.-T. *Planta Med.* **1992**, *58*, 311.

10.1021/ol060274c CCC: $33.50

tory properties.[9] As a result, a number of routes leading to differently substituted benzo[*b*]furans have been described in the literature, although currently no general synthetic methodology exists.[10]

In the course of our ongoing investigations into the synthesis of several N-heterocyclic compounds, we found that when the copper-catalyzed N-arylation reaction between deoxybenzoin **1** and benzylamine was tested, instead of the expected product **2**, 2-arylbenzo[*b*]furan **3** was isolated in 66% yield (Scheme 1). This unexpected result, due to an intramolecular O-arylation process probably catalyzed by copper, prompted us to search for a general methodology (based on copper catalysis) for constructing the benzo[*b*]furan framework. In addition, given the previously mentioned advantages provided by the use of aqueous media, we decided to investigate whether water would be effective as a solvent for performing such reactions.

Scheme 1



To optimize the process, we chose deoxybenzoin **1** as the model compound and the efficiency of different copper sources and bases was then tested. Because water was present, we considered that water-soluble inorganic bases, such as K_3PO_4, would be suitable to effect the reaction. However, neither K_3PO_4 nor the commonly used organic base triethylamine provided benzofuran **3** in more than 12% yield (Figure 1), with significant amounts of unreacted substrate **1** being recovered from the reaction mixture.

Interestingly, shifting to different 1,2-diamine derivatives resulted in a clear improvement of the yields, as shown in Figure 1. This fact, along with the colors observed during the course of the reaction (violet and green for the Cu/DMEDA and Cu/TMEDA systems, respectively), suggested a double role for the 1,2-diamines. On one hand, they might be acting as ligands,[11] and on the other, they might be coordinating to the copper facilitating the formation of enol-type intermediates through a coordination to the oxygen, as shown in Scheme 2. Thus, having determined that the combination of CuI and TMEDA was the most efficient of these two reagent systems, providing the benzofuran **3** in 91% yield, we subsequently directed efforts toward optimizing the reaction conditions.

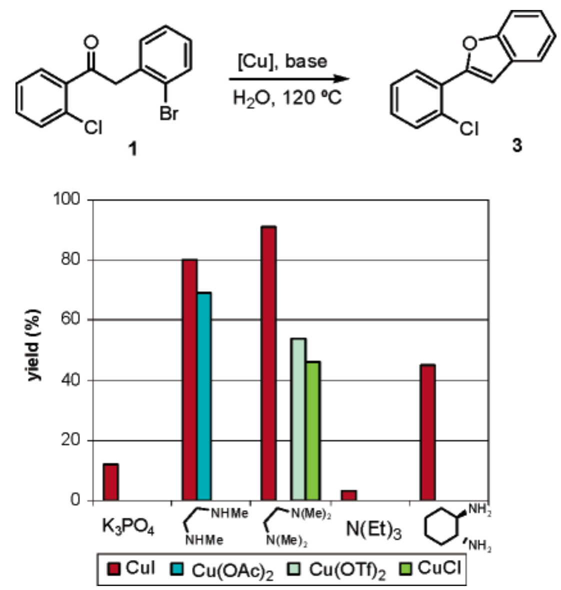
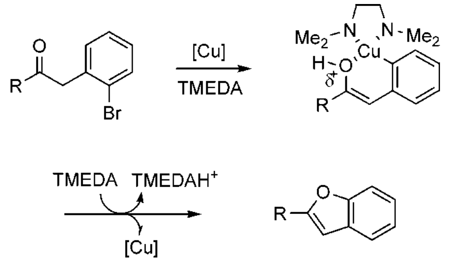


Figure 1. Copper source and base screening for the ring closure of **1** performed in neat water.

Scheme 2. Mechanistic Pathway Proposal



Remarkably, when the catalyst loading was decreased from 8.5 mol % to 5.6 mol %, only slightly lower yields of product were obtained, and the reaction proceeded smoothly even with less than 2 mol % of CuI. However, the presence of catalyst, even in small amounts, was absolutely necessary for the reaction to occur. In addition, it was observed that a decrease in temperature from 120 °C to 60 °C resulted in

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[9] (a) Sun, M.; Zhao, C.; Gfesser, G. A.; Thiffault, C.; Miller, T. R.; Marsh, K.; Wetter, J.; Curtis, M.; Faghih, R.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. *J. Med. Chem.* **2005**, *48*, 6482. (b) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878.

[10] The most common approach to these heterocycles consists of the palladium-catalyzed cyclization of the corresponding 2-(1-alkynyl)phenols. See: (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292 and references therein. For other methodologies, see: (b) Kraus, G. A.; Schroeder, J. D. *Synlett* **2005**, 2504. (c) Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613. (d) For a recent contribution of our group to the synthesis of 2,3-diarylbenzofurans and phenanthrofurans based on a palladium-catalyzed tandem C-/O-arylation, see: Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Eur. J. Org. Chem.* **2005**, *12*, 2481.

[11] Such complexes have been previously reported for being involved in other copper-catalyzed coupling reactions and are probably responsible for the color of the solution. See: Kaplars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

lower yields of target benzofuran **3** (91% vs 33%) together with unreacted substrate **1** (Figure 2).

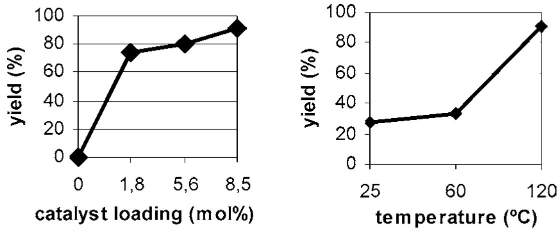
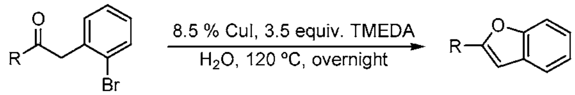
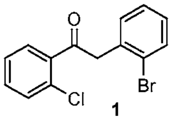
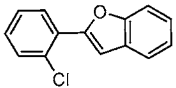
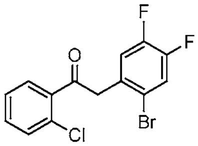
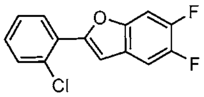
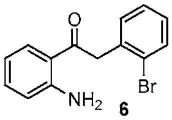
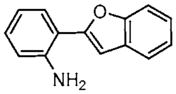
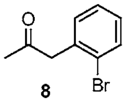
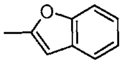
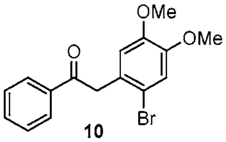
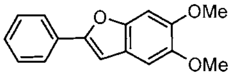
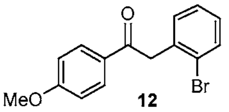
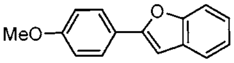
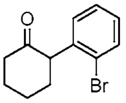
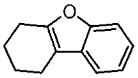


Figure 2. Catalyst loading and temperature screening.

Table 1. Preparation of Differently Substituted Benzo[*b*]furans



Entry	Substrate	Benzofuran[a]
1	 **1**	 **3** (91%)
2	 **4**	 **5** (82%)
3	 **6**	 **7** (99%)
4	 **8**	 **9** (74%)
5	 **10**	 **11** (21%)
6	 **12**	 **13** 1st run 83% 2nd run 78%
7	 **14**	 **16** (76%)

[a] Isolated yields.

It can be concluded that the optimal reaction conditions for the target O-arylation reaction involved stirring the substrate **1** in water at 120 °C in the presence of 8.5 mol % of CuI and 3.5 equiv of TMEDA (Figures 1 and 2).

To determine the scope of the chosen reaction conditions, we decided to apply this methodology to the synthesis of different benzo[*b*]furans, as shown in Table 1. Substituent variations in the bromoaryl moiety allowed us to study the electronic requirements of the reaction. In this regard, the heterocyclization was disfavored by the presence of electron-donating methoxy substituents para to the bromo with, for example, benzofuran **11** only being obtained in 21% yield (Table 1, entry 5). In contrast, nonsubstituted aryl bromides (Table 1, entries 1, 3, and 6) or those bearing fluorine atoms (Table 1, entry 2) had a beneficial effect on the reaction outcome, affording the corresponding benzofurans in good to excellent yields.

Surprisingly, the proposed methodology worked extremely well when the substrate contained a free primary amine substituent, despite such moieties being known to readily couple with aryl bromides in the presence of copper catalysts.[12] In our case, however, the competitive N-arylation process was not observed and benzofuran **7** was selectively obtained in 99% yield (Table 1, entry 3).

Furthermore, the presented method is not limited to the use of deoxybenzoin derivatives as substrates, though the presence of the second aryl ring seems to facilitate the process, given that the alkyl ketones **8** and **14** afforded benzofuran **9** and **15**, respectively, in slightly lower yields (Table 1, entries 4 and 7) than those observed for the above assayed arylated systems. Although the optimized experimental conditions proved suitable for the ring closure of a series of 2-bromo derivatives, when the corresponding 2-chloro analogues were employed as starting materials, only traces of the desired benzofurans were detected by GC-MS.

Because the isolation of the so-obtained benzofurans was easily accomplished by extraction with dichloromethane, an attempt to reuse the copper catalyst, dissolved in the aqueous layer, was an appealing goal to study. Thus, after performing the reaction on substrate **12** and workup, the remaining green aqueous solution, presumably containing the copper–TMEDA complex, was again used to perform a second run of the same reaction. Remarkably, benzofuran **13** was obtained in only slightly lower yield for the second run (78% vs 83%), as shown in Table 1 (entry 6). The addition of an extra amount of TMEDA was required for the second run, otherwise only traces of the benzofuran **13** were detected. This fact strengthens the previous hypothesis that TMEDA plays a double role in the reaction; though a portion behaves as a ligand linked to the copper atom (forming the water-soluble complex), the remainder of the TMEDA is consumed as a base and therefore must be replaced.

Finally, although still preliminary, it should be pointed out that the reported process has been scaled up to 1 g in the case of ketone **6**, providing the corresponding benzofuran **7** in 93% yield.

To sum up, we have developed an environmentally friendlier route to benzo[*b*]furan derivatives based on a

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(12) (a) Kwong, F. Y.; Kaplars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (b) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791.

copper-catalyzed ring-closure reaction performed in water. The benefits derived from the use of such a benign solvent are clear in terms of lack of toxicity, safety, cost, and availability, properties that make water a desirable medium for every organic transformation. Furthermore, the on-water methodology described here delivers a range of benzo[*b*]furans in good to excellent yields starting from readily available substrates. In addition, the easy isolation of the target compounds, by simple extraction with dichloromethane, allows the reutilization of the water solution containing the copper catalyst, thereby providing environmental and economic advantages over previously reported protocols.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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