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Microwave assisted synthesis of selected diaryl ethers under Cu(I)-catalysis

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ABSTRACT

A practical synthesis of diaryl ethers has been achieved from cross coupling reaction between aryl halides and phenols under Cu (I)-catalysis and using ACHN as a ligand. The presence of catalysis and microwave-assistance benefitted the synthesis by increasing the yield of diaryl ethers with a reduction of reaction time.

Functionalized diaryl ethers are important scaffolds found in a variety of biologically active natural products.[1] Diaryl ethers constitute an important class of organic intermediates for the synthesis of compounds with significant industrial interest[2] or therapeutically activity.[3] Drugs with anti-inflammatory and analgesic properties such as *Fenoprofen*[4] or antitumor agents such as *Sorafenib*[5] contain a diaryl ether subunit in their structure (Figure 1).

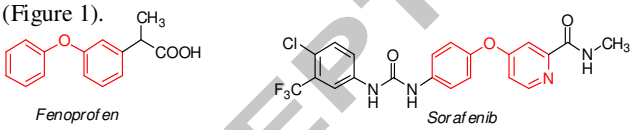

Figure 1. Structures of *fenoprofen* and *sorafenib*

Diaryl ethers have been synthesized by arylation of phenols with aryl halides using different methodologies. The classical Ullmann coupling reaction,[6] involving stoichiometric amounts of copper or copper salts, high reaction temperatures in polar solvents, and long reaction times, has been gradually replaced by new carbon-oxygen bond-forming chemical strategies.[7] The drive toward environmentally friendly processes has resulted in the increasing use of catalytic amounts of transition metals in the presence of ligands[8] or avoiding catalysts altogether.[9] The S_NAr reaction of electron–deficient aryl halides has received considerable attention.[10] In a recent study, we attempted to form complex synthetic scaffolds requiring diaryl ethers as intermediates using conditions reported in the literature.[11]

Our lack of success prompted us to approach the target by assaying a variety of alternative methods. We needed diaryl ethers substituted in *meta*, whereas the majority of reports only give examples of diaryl ethers from *para*-substituted aryl halides.[12] Though there are many methods for the preparation of diaryl ethers, none are of general application.

Here we report the extension of our strategy for the *O*-arylation of several aryl halides using new ligands such as ACHN (1,1′-azo*bis*(cyclohexane carbonitrile)), which besides a radical initiator is capable to form complexes with Cu(I) stabilizing this one. Azo-derivatives were not considered as ligands for the Ullmann diaryl ether synthesis in the study of Opatz et al.[13]

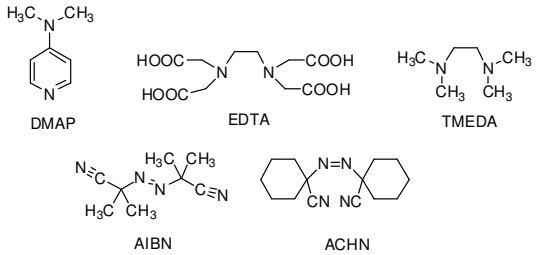

Figure 2. Structures of tested ligands

In preliminary studies oriented to the preparation of 3-phenoxyphenyl methyl sulfone from phenol and 3-bromophenyl methyl sulfone, the use of Pd[14] or Cu[7] catalysts and strong conditions did not afford the required diaryl ether (Table 1, entry 1). However, using the Pd/BINAP catalyst provided the corresponding ether in 19% yield (Table 1, entry 2) when the 3-bromomethyl phenyl sulfone (electron-withdrawing substituent) was substituted by the 3-bromomethyl thiobenzene (electro-donating substituent) as the starting aryl halide.

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