Metal-Free Arylation of Phenols and Carboxylic Acids

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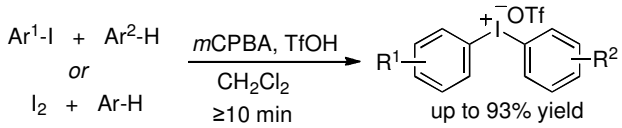
INTRODUCTION

Diaryl ethers and aryl esters are common structural features in pharmaceuticals, agrochemicals, polymers and numerous natural products. Despite more than a century of immense focus on finding efficient synthetic routes to these compound classes, the synthesis of substituted diaryl ethers and aryl esters remain difficult.[1]

The use of diaryliodonium salts has recently gained considerable attention in organic synthesis. Their properties allow for both metal-catalyzed and metal-free reactions, avoiding the drawbacks of organometallic chemistry, such as cost, toxicity, and threshold values in pharmaceutical products.[2]

We have developed several efficient one-pot routes to diaryliodonium salts, and these compounds are now inexpensive and easily available (Scheme 1).[3]

Scheme 1. One-Pot Synthesis of Diaryliodonium Salts

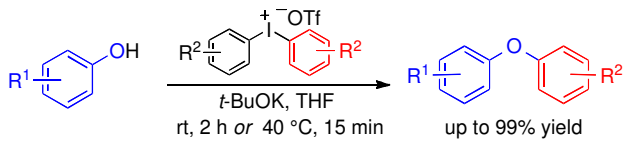


We are presently investigating these selective and nontoxic reagents as electrophilic arylating agents,[4] and herein we present our results on the arylation of phenols and carboxylic acids.[4b-c]

RESULTS AND DISCUSSION

The arylation of phenols with diaryliodonium salts proceeds at room temperature to give diaryl ethers in high yields (Scheme 2). The reaction time can be shortened to 15 minutes by heating to 40 °C. The metal-free conditions are compatible with a range of functional groups, including heteroaromatics, halides and racemization-prone amino acid derivatives.

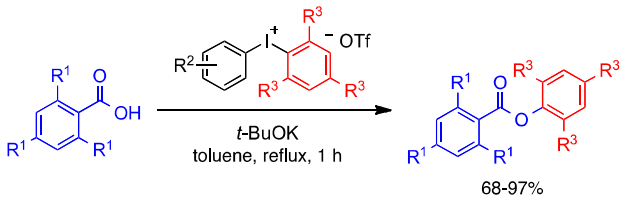
Scheme 2. Synthesis of Diaryl Ethers



The reactions were run without precautions to avoid air or moisture. *t*-BuOK was chosen as base for practical reasons, but NaOH can also be employed.

We subsequently developed a route to aryl esters by metal-free arylation of carboxylates (Scheme 3). Good to excellent yields were obtained without the use of metal catalysts, halogenated solvents or excess reagents. Aryl esters can be synthesized in the presence of primary alcohols, *N*-Boc substituents and ketones, and both aromatic and aliphatic substrates are tolerated. The scope includes synthesis of remarkably hindered esters, which are impossible to obtain via other esterification methods.

Scheme 3. Synthesis of Aryl Esters



CONCLUSION

Fast and high-yielding routes to diaryl ethers and aryl esters have been developed using mild and metal-free conditions. The scope includes many functional groups and bulky *ortho*-substituted products, which are difficult to obtain by metal-catalyzed protocols.

The methodology is expected to be of high utility in the synthesis of complex molecules and in the pharmaceutical industry.

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