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Communications to the Editor

A Practical and Improved Copper-Catalyzed Synthesis of the Central Intermediate of Diafenthiuron and Related Products

Thomas Schareina,[†] Alexander Zapf,[†] Alain Cotté,[‡] Nikolaus Müller,[‡] and Matthias Beller*[,†]

Leibniz-Institut für Katalyse e.V., an der Universität Rostock, Albert-Einstein-Strasse 29A, 18059 Rostock, Germany, and Saltigo GmbH, Building Q 18-2, 51369 Leverkusen, Germany

Abstract:

A bioinspired Cu(I)/*N*-methylimidazole catalyst system is used for the synthesis of the diaryl ether part of diafenthiuron, a widely used insecticide. The convenient protocol proceeds smoothly with high selectivity and quantitative yield. Applying the optimized procedure various diaryl ether analogs are synthesized in good to excellent yield.

The diaryl ether moiety is present in numerous naturally occurring and biologically active compounds.[1] Important medicinal products having this structural motif include polycyclic glycopeptide antibiotics like vancomycin,[2] teicoplanin,[3] and the antineoplastic agent combretastatin D-2.[4] In addition, a number of diaryl ethers are used in industrial polymers.[5] Selected examples are shown in Scheme 1.

Until recently, the most general method for the synthesis of diaryl ethers has been the classic copper-mediated Ullmann coupling of aryl bromides/iodides and phenols with the drawback of harsh reaction conditions and the need of a stoichiometric amount of metal. Due to these problems significant efforts have been undertaken in the past decade to develop more efficient and environmentally benign coupling processes of phenols.[6] The current status of this improved methodology is described in detail by Frlan and Kikelj,[7] Beletskaya et al.,[8] and by Kunz et al.[9] Notably, several catalyst systems have been developed, which enable aryl ether formation under much milder conditions compared to the classical Ullmann and Goldberg reactions.[7,9,10] Until now mainly copper[11] and palladium[12] complexes evolved as catalysts for this type of reaction. While palladium catalysts are more productive (catalyst turnover numbers > 100) and active compared to copper, they have the common disadvantage of high metal and ligand costs (and sometimes the air-sensitivity of special phosphines). Although a larger amount of metal has to be used, copper catalysis is generally considered to be less expensive. Clearly, this statement is only true for easily available copper precatalysts and ligands. In this respect there is still a need for improved and more general catalysts.

Since 2004 we have developed new catalyst systems for the cyanation of aryl halides based on palladium and copper.[13,14] Inspired by nature we assumed that imidazoles should be good ligands to control the stability and selectivity of copper catalysts.[15] This idea resulted from the fact that the most

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[*] To whom correspondence should be addressed. E-mail: matthias.beller@catalysis.de. Fax: 49 381 12815000. Telephone: 49 381 1281113.

[†] Leibniz-Institut für Katalyse e.V.

[‡] Saltigo GmbH.

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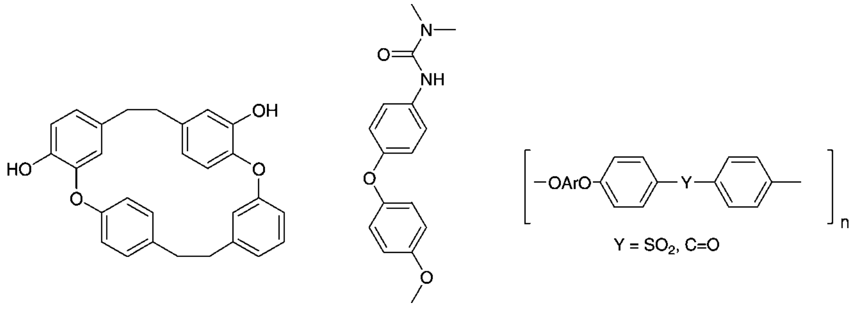
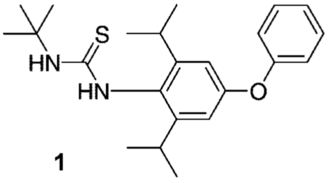
Scheme 1. **From left to right: riccardine from liverwort, the herbicide difenoxuron, poly(aryl ethers) used for high-tech plastics**



Scheme 2. **Diafenthiuron**



Scheme 3. **Synthesis of the central intermediate 4 of diafenthiuron**

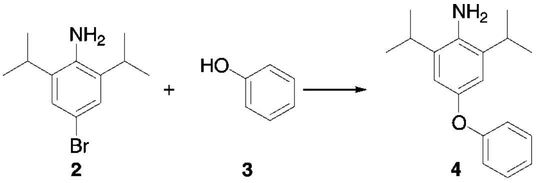
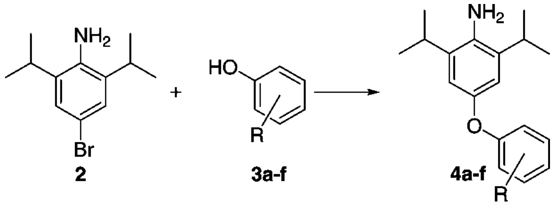
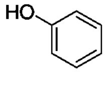
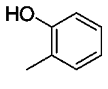
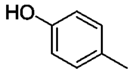
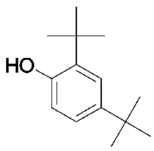
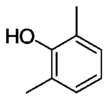
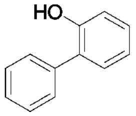


Table 1. **Screening results of the reaction of different phenols with 4-bromo-2,6-diisopropylaniline**[a]



Entry	Phenol	Conversion [%][b]	Yield [%][b]
1		>99	>98
2		>99	95
3		>99	95
4		82	80
5		56	55
6[c]		>99	95

[a] Ace pressure tube, 2.0 mmol 4-bromo-2,6-diisopropylaniline, 2.4 mmol phenol, 5 mol % CuCl, 4 mmol K_2CO_3, 1 mmol 1-methylimidazole, 2 mL toluene, 200 μL of tetradecane as internal standard for GC, 16 h, 140 °C. [b] GC-conversion and yield, average of two parallel experiments. [c] 10 mol % CuCl.

abundant metal-binding amino acid in nature is histidine. Indeed, the combination of copper(I)/1-alkylimidazoles showed unprecedented selectivity and substrate range in catalytic cyanation reactions. Consequently, we believed that this and similar systems might be useful for other coupling reactions of aryl halides, too. In fact we discovered that copper(I)/1-alkylimidazoles allowed for the formation of diaryl ethers from aryl bromides and phenols.[16] On the basis of this work, here we present a novel and practical synthesis of the diaryl ether part of the insecticide diafenthiuron.

Diafenthiuron is used mainly in the Pacific and Latin-American regions as an acaricide/insecticide against sucking pests and mites that infest cotton plants.[17] The active molecule is the carbodiimide, formed from diafenthiuron via elimination of hydrogen sulfide by the action of light and/or air after dissemination.

The synthesis of the aniline precursor is generally performed by reaction of the phenol **3** with 4-bromo-2,6-diisopropylaniline according to Scheme 3 employing classical Ullmann reaction conditions. The final attachment of the thiourea group follows standard chemistry and is performed on multiton scale. Potential improvements of this step are not considered in this article.

In the first patent application covering diafenthiuron by Ciba-Geigy AG in 1981[18] potassium hydroxide was used as base and 1.5 mol % CuCl as catalyst for the aryl ether formation. Unfortunately, no yield of the intermediate **4** is given. In a newer publication by Knox et al.[19] the authors used an overstoichiometric amount of copper(I) chloride. They claimed that the isolated yield (39%) of pure product **4** after chromatography is superior compared to the yield obtained with the original method.

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As a starting point of our investigation we examined the reaction of 4-bromo-2,6-diisopropylaniline[20] and phenol (Scheme 3). Optimal results are achieved in the presence of 5 mol% CuCl and 50 mol% *N*-methylimidazole at 140 °C in *o*-xylene or toluene as solvent. After addition of water and phase separation the organic solvent is distilled off, and the crude product can be crystallized. Advantageously, no column chromatography is necessary in this process! On 30-g scale the product is obtained in nearly quantitative yield and high purity (>95% by GC). Compared to our previous work, for practical reasons the solvent was changed to *o*-xylene to avoid working under pressure. It is worth mentioning that the somewhat longer reaction time observed can be overcome by running the reaction at higher temperature. Nevertheless, without doubt the new process is significantly improved compared to those in the known literature.[19]

In order to demonstrate the generality, next a series of derivatives of the diafenthiuron precursor was prepared on 2 mmol scale using the optimized protocol. Starting from 4-bromo-2,6-diisopropylaniline (**2**) a series of alkylated and arylated potentially insecticidal diaryl ethers **4b**−**f** is prepared in 55–95% yield. Most problematic for this coupling reaction is use of the 2,6-disubstituted phenol.

In summary, we have shown that the central intermediate of diafenthiuron is prepared in high yield (>95%) in the presence of a copper/imidazole catalyst. The known patent and literature procedure is significantly improved. The generality of the optimized reaction protocol is demonstrated by the synthesis of five potentially insecticidal diaryl ethers **4b**−**f** in good to excellent yield.

Experimental Section

All manipulations were performed under argon atmosphere using standard Schlenk techniques. Toluene and *o*-xylene were distilled from sodium benzophenone ketyl under argon. 1-Methylimidazole was distilled from CaH_2 under reduced pressure and stored under argon. The starting material 4-bromo-2,6-diisopropylaniline[20] was used after control of purity by gas chromatography. All other chemicals were purchased from fine chemicals suppliers such as Aldrich, Fluka, Acros, AlfaAesar, etc. and used without further purification.

General Procedure. Two mmole experiments: In an Ace pressure tube 4.0 mmol K_2CO_3, 2.4 mmol phenol, 0.1 mmol CuCl, and 2.0 mmol 4-bromo-2,6-diisopropylaniline were weighed in air. Under argon atmosphere, 1.0 mmol 1-methylimidazole, 2 mL of toluene, and 200 μL of tetradecane as internal standard for GC were added; the tube was sealed and heated for 16 h at 140 °C. After cooling, 5 mL of water and 3 mL of *tert*-butyl methyl ether were added, the two-phase mixture was stirred and vigorously shaken, and a sample from the organic phase was analyzed by gas chromatography. All screening experiments were performed twice. For isolation of the products the organic phase was washed successively by 10% K_2CO_3 solution and water and was dried over Na_2SO_4, the solvents were removed in a rotary evaporator, and the residue was subjected to column chromatography on silica gel, with mixtures of hexanes and ethyl acetate as eluent.

Synthesis of the Central Intermediate of Diafenthiuron 2,6-Diisopropyl-4-phenoxyaniline 4a. To 32.4 g (0.234 mol) of K_2CO_3, 0.58 g (5.8 mmol) CuCl, 13.2 g (0.14 mol) phenol, and 30.0 g (0.117 mol) 4-bromo-2,6-diisopropylaniline **2** in a 250-mL three-necked bulb with argon inlet, reflux condenser, and stopper were added 4.7 mL (58 mmol) of 1-methylimidazole and 100 mL of *o*-xylene under argon atmosphere. The mixture was magnetically stirred and heated to 140 °C, until TLC (eluent toluene) showed no residual starting material **2** (ca. 30 h). After cooling, water and methyl *tert*-butyl methyl ether were added, and the organic phase was washed with 10% K_2CO_3 solution, water, and brine and was dried over Na_2SO_4. After evaporation of the solvents, an aliquot of the dark oily material was filtered through a short silica gel plug with toluene as solvent to give, after removal of the solvent and drying in vacuum, a dark solid. The calculated yield is 99%, the purity is determined to be 95% by GC.

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