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LETTERS

Phosphazene bases for the preparation of biaryl thioethers from aryl iodides and arenethiols

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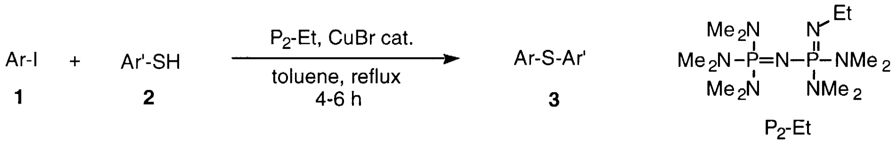
Abstract

In the presence of phosphazene P_2-Et base as well as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) the coupling of aryl iodides with arenethiols only requires catalytic amounts of CuBr. Under these conditions the reaction can be performed in refluxing toluene to give biaryl thioethers in excellent yields. © 2000 Elsevier Science Ltd. All rights reserved.

The reaction of aryl halides with sodium or potassium arenethiolates, promoted by copper additives, results in the formation of diaryl sulfides.[1] This reaction, which is analogous to the Ullmann biaryl ether synthesis,[1,2] frequently requires temperatures up to 200–300°C, long reaction times and strong polar and often toxic solvents such as quinoline, hexamethylphosphoric triamide, and *N*,*N*-dimethylacetamide.[3] In addition to these requirements, the main problem associated with this reaction is the formation of isomeric diaryl compounds via substitution through an elimination–addition mechanism.[4] As a consequence, most investigations on this subject have dealt with the use of stoichiometric amounts of copper additives to facilitate the coupling reaction.[1,2] However, under these conditions the reductive homocoupling of the aryl halide component[5] which, for instance, occurs easily when hindered nucleophiles are involved, constitutes another inherent problem of this reaction. Despite considerable success to date,[6] these efforts have identified the same solution to these problems, namely, the preactivation of the aryl halide component through, for instance, the use of transition metals,[7,8] or by placing an electron withdrawing substituent *ortho* or *para* to the leaving group.[9]



Scheme 1.

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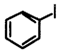
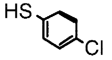
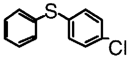
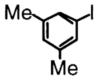
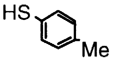
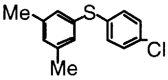
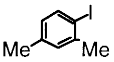
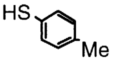
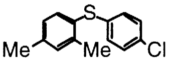
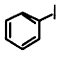
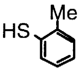
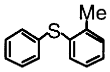
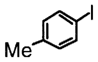
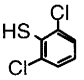
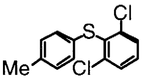
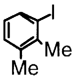
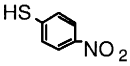
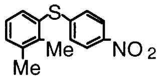
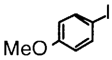
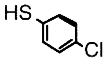
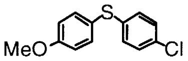
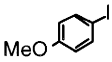
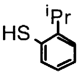
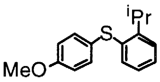
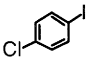
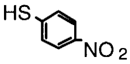
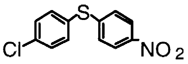
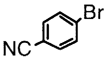
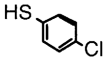
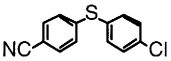
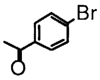
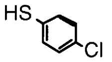
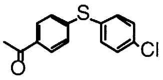
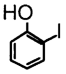
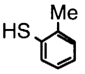
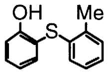
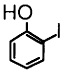
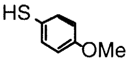
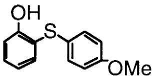
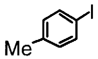
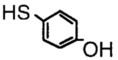
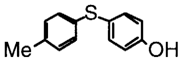
Table 1
The Ullmann type biaryl thioether synthesis promoted by P$_2$-Et base in combination with CuBr[a]

Entry	Halide, **1**	Arenethiol, **2**		Product, **3**	Yield (%)[b]
1			**a**		91[c] (90)[d]
2			**b**		92
3			**c**		100
4			**d**		90
5			**e**		85
6			**f**		88
7			**g**		82
8			**h**		60 (70)[d]
9			**i**		81
10			**j**		86 (88)[d]
11			**k**		89
12			**l**		63, 81[e]
13			**m**		65, 95[e]
14			**n**		79[f]

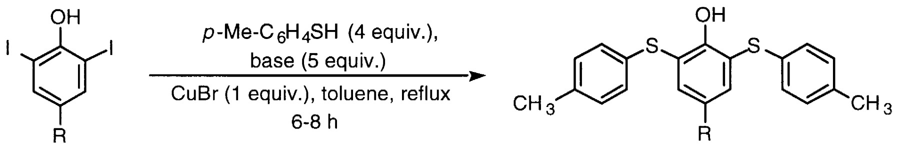
(a) The following procedure was employed: a mixture of the aryl halide (1 mmol), the corresponding thiophenol (2 mmol), P$_2$-Et (2 mmol) and CuBr (0.2 mmol) in dry, deoxygenated, toluene (3 mL) was refluxed under a nitrogen atmosphere until consumption of the halide as determined by GC (typically 1-4 h). The reaction mixture was allowed to cool to r.t., diluted with EtOAc, and washed sequentially with saturated aq. NH$_4$Cl, 0.1 M NaOH and water. The organic layer was dried over Na$_2$SO$_4$ and the solvent evaporated under vacuum. (b) Yields of isolated pure products obtained by flash chromatography on silica gel using mixtures of hexane-ethyl acetate as eluants. (c) Dioxane as solvent. (d) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead. (e) 2 equiv. of CuBr were used and 3 equiv. of P$_2$-Et. (f) 4 equiv. of P$_2$-Et were used.

Recently, we have reported a procedure for the Ullmann biaryl ether synthesis[10] that combines the concept of the 'naked anion' phenomenon[11] with the use of Schwesinger's phosphazene bases.[12] Now we have found that these bases,[13] Scheme 1, in combination with a catalytic amount of Cu(I) salts, are extremely effective in promoting reactions of aryl halides with a variety of thiophenols. As shown in Table 1, the method is suitable for electron neutral (entries 1–6), electron rich (entries 7, 8) and electron poor (entry 9) aryl iodides with a variety of thiophenols. Aryl chlorides, on the other hand, did not react under these conditions with thiophenols to form biaryl thioethers. Accordingly, *p*-chloroiodobenzene (entry 9) reacted chemoselectively to afford **3i**. By the same token, it was possible to perform chemoselective couplings between chlorothiophenols and aryl iodides (entries 1, 5, and 7) without any self-condensation. Aryl bromides, with the exception of those bearing electron withdrawing groups (entries 10, 11), did not react with thiophenols to give the expected products. This method is particularly suitable for aryl iodides and *ortho*-substituted thiophenols. For example, 2,6-dichlorothiophenol (entry 5) provided the corresponding biaryl thioether in good yield, and even the *o*-isopropylthiophenol (entry 8) coupled with *p*-methoxyiodobenzene to give the desired biaryl thioether in 60% yield.

We have systematically employed the P_2-Et base, but P_1-Bu^t base was also effective. Most notably, in the presence of any of these bases and a catalytic amount of CuBr, the reaction can be carried out in toluene as solvent thus avoiding the use of high-boiling or water soluble solvents.[14] Other common bases, such as triethylamine, *N,N*-dimethylaminopyridine, diisopropylethylamine, and Cs_2CO_3[15] failed to produce the coupling product. However, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[16] afforded similar results to those attained with P_2-Et base, albeit with somewhat longer reaction times. On the other hand, copper salts such as CuCl, CuI and $Cu(OTf)_2$–benzene, were also effective, but in their absence no coupling products were formed.

Next, we have evaluated the reaction selectivity when both a phenol and a thiophenol group are present simultaneously under the conditions employed. In this respect, we knew, from the results in our previous report,[10] that the P_4-Bu^t-assisted coupling of aryl iodides with phenols requires stoichiometric amounts of CuBr. Therefore, we predicted a higher reactivity for thiophenols as compared to phenols. Indeed, in experiments carried out with a catalytic amount of CuBr, the expected biarylthioethers were formed in a completely chemoselective manner in isolated yields of 63% and 65% (entries 12 and 13). The same selectivity level and improved yields (81% and 95%) were observed for the latter reactions when stoichiometric CuBr was employed. In a similar way, the coupling of hydroxybenzenethiol with *p*-methyliodobenzene (entry 14) led to the corresponding biaryl thioether exclusively.

From the examples in Table 1, it also seems that the reaction conditions used are compatible with various functional groups. Nevertheless, neither the amino nor the amido functionalities were inert under these reaction conditions. For example, whereas the reaction of **4a** with *p*-methylbenzenethiol, Scheme 2, hardly proceeded to give **5a**, **4b** and **4c** led to **5b** and **5c** in 50% and 52% yields, respectively.[17] Although moderate yields are attained, it should be noted that, once again, other common bases, i.e. triethylamine, tributylamine and diisopropylethylamine, were completely ineffective in promoting this coupling reaction.



4

5

a R: (RS)-$CH_2CH(NHBoc)CO_2Me$ (5-10%)
b R: $CH_2CH_2CO_2Me$ (50%)
c R: $CH_2CH_2CO_2{}^tBu$ (52%)

Scheme 2.

In summary, the present work shows a new application of the Schwesinger phosphazene bases for an efficient Cu(I) catalyzed conversion of aryl iodides to biarylthioethers.

Acknowledgements

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