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# Protecting Groups for Thiols Suitable for Suzuki Conditions

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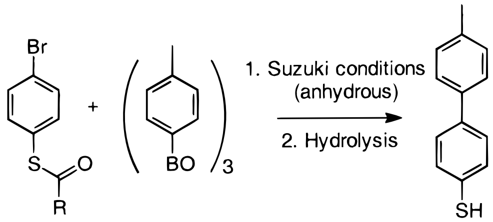
## ABSTRACT



**The thiol group is one of the few groups NOT tolerated by the Suzuki reaction. Therefore, a new protective group, the 2-methoxyisobutyryl group, was developed by tuning the electronic/steric properties of the acyl residue. Other thioesters, such as thioacetate, result in a more or less dominant side reaction, which to date has not been described: sulfur-assisted acylation of boronic acids. The reaction pathway for this new reaction is discussed.**

Since Suzuki's discovery of the palladium-mediated cross-coupling reactions of boranes and boronic acids,[1] this efficient synthesis which tolerates a tremendous variety of functional groups has been used by a large number of chemists.[2] Among the most problematic functional groups, the thiol group with its strong affinity for late transition metals poses special problems: Because of poisoning of the catalyst, more than stoichiometric amounts of palladium would be necessary to obtain a coupling reaction. There are very few publications addressing this problem in the literature. In general, thioethers (sulfides) and thio-heterocycles, such as thiophene, are the only sulfur-containing substrates used for Suzuki couplings which are fully compatible with Suzuki conditions (aqueous or nonaqueous base in a heterogeneous reaction mixture). Although thioethers seem to be suitable protecting groups for thiols, the cleavage of thioethers is problematic. The commonly used reaction conditions for the cleavage are too harsh for a number of functional groups, thus spoiling the advantages of the Suzuki reaction. The more easily cleaved alkyl groups, such as allyl, benzyl, or triphenylmethyl (trityl), are also removed by the palladium reagent, at least under the conditions applied for the Suzuki reaction.

After numerous attempts with other recommended thiol protecting groups,[3] we decided to focus our efforts on acyl groups since these are easily attached to the thiol moiety, resulting in thioesters, which in turn are easily cleaved by aqueous base. The starting point for our investigation was the reported observation that alkynes could be successfully coupled to 4-(thioacetyl)iodobenzene in the presence of $Pd^0$-containing catalyst systems.[4,5] Although we could fully reproduce this reported result, we were not able to achieve satisfactory Suzuki-type cross-coupling reactions either with 4-(thioacetyl)bromobenzene **1a** or with its iodo derivative. Since we assumed that the thioacetyl group was cleaved under the strongly basic conditions ($K_3PO_4$ in 1,2-dimethoxyethane), we decided to check different acyl groups for improved stability. For that, both steric and electronic properties were varied, trying to pinpoint some general tendencies, followed by an optimization of the best protecting groups. As an assay for our investigation we used the

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[1] Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11(7)*, 513.

[2] Suzuki, A. in *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, New York 1997; Chapter 2.

[3] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1991; Chapter 6.

[4] Hsung, R. P.; Chidsey, C. E. D.; Sita, L. R. *Organometallics* **1995**, *14*, 4808.

[5] Hsung, R. P.; Babcook, J. R.; Chidsey, C. E. D.; Sita, L. R. *Tetrahedron Lett.* **1997**, *38(19)*, 4525.

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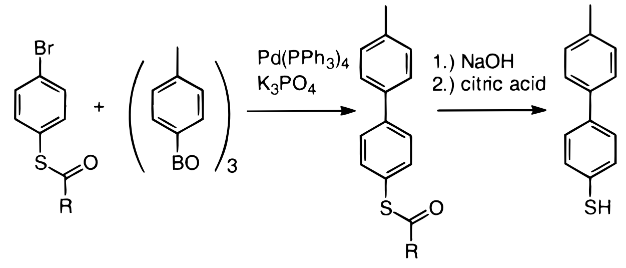
coupling of 4-(thioacyl)bromobenzenes **1a**−**i** with 4-tolylboronic acid anhydride **2** in the presence of tetrakis(triphenylphosphine)palladium, followed by saponification (Scheme 1). For a typical test run, **1** (1.0 mmol), **2** (130 mg, 0.37 mmol), dried $K_3PO_4$ (320 mg, 1.5 mmol), $Pd(PPh_3)_4$ (58 mg, 50 $\mu$mol), and *p*-terphenyl (0.1 mmol, as internal standard) were heated to reflux for 16 h in DME (3.5 mL). Deoxygenated NaOH (1.6 g, 40 mmol) in $H_2O$ (3.5 mL) was added to the reaction mixture, and the resulting solution was stirred at 60 °C for $3^1/_2$ h before citric acid (4.8 g, 25 mmol) was added and the stirring was continued for 30 min. After phase separation, a sample of the organic layer was taken to determine the yield of thiol **4** by gas chromatography. The results are summarized in Table 1.

**Scheme 1.** Test System Used To Optimize the Protective Group for Thiols under Suzuki Reaction Conditions



**1** **2** **3** **4**

**Table 1.** Yields of **4**, As Determined by Gas Chromatography

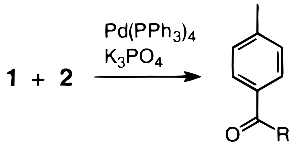
| protective group | yield of Suzuki coupling [%] |
|---|---|
| acetyl (**1a**) | 0.7 ± 0.1 |
| pivaloyl (**1b**) | 35 ± 2 |
| trichloroacetyl (**1c**) | 0 |
| benzoyl (**1d**) | 0 |
| ferrocenoyl (**1e**) | 0 |
| 2,4,6-triisopropylbenzoyl (**1f**) | 0 |
| dimethylphenylacetyl (**1g**) | 0 |
| 2-methoxyisobutyryl (**1h**) | 74 ± 19, 55[a] |
| *tert*-butoxycarbonyl (**1i**) | 1.0 ± 0.1 |

[a] Isolated yield after conventional workup.

The first alternative acyl groups we checked were the pivaloyl (**1b**), the trichloroacetyl (**1c**), and the benzoyl (**1d**) groups. The difference between the yield obtained with the pivaloyl group (35%) and the one obtained with the trichloroacetyl group (0%) suggested that electron-donating substituents are favorable. With this knowledge we tried to improve the benzoyl system, which itself yields no desired thiol. But neither the electron-rich ferrocenoyl group (**1e**) nor the electron-rich *and* sterically crowded 2,4,6-triisopropylbenzoyl (**1f**) group led to thiol **4**. Returning to the aliphatic systems, we varied the pivaloyl group by substitution of one of the methyl groups by a phenyl group (**1g**) or a methoxy group (**1h**) or by insertion of an oxygen atom between the carbonyl group and the *tert*-butyl residue (resulting in the BOC group **1i**). Of these three, the 2-methoxyisobutyryl group (**1h**) resulted in a good GLC yield at the Suzuki reaction (74%). When the reaction was performed on a preparative scale, pure coupling product **4** could be isolated in 55% yield, which should be satisfactory for most synthetic purposes.

Closer examination of the reaction mixtures revealed that in every case, with the exception of **1c**, all of the thioesters **1** were more or less completely consumed and a number of new products were formed. This observation was in contrast to our initial hypothesis that partial cleavage of the esters **1** leads to the formation of 4-bromothiophenol, which in turn poisons the catalyst. Using GLC/MS coupling we were able to identify the main products as 4-tolyl ketones **5** (Scheme 2).

**Scheme 2.** Unexpected Side Reaction Observed with Some Thioesters. This Reaction Is Suppressed When R = $CH_3O(CH_3)_2C$

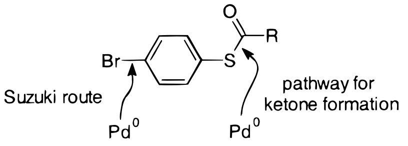


**5**

To the best of our knowledge, this type of reaction has not previously been reported. Only for the R = $CH_3$ case was the yield of ketone determined: Under the conditions optimized for biaryl coupling, about a 40% yield of ketone was obtained. We believe that after readjustment of the reaction conditions a useful synthetic route to ketones may be developed.

Since this reaction does not take place in the absence of palladium catalysts, we suggest that the products are formed by insertion of the palladium between the sulfur atom and the carbonyl group, leading to a palladium−acyl complex with one thiolate ligand. The acyl group then would undergo reductive elimination together with the 4-tolyl ligand which is derived from 4-tolylboronic acid **2** according to the established mechanism for Suzuki coupling,[6] yielding the respective ketone **5**. The different attack sites are illustrated in Scheme 3. We have not yet determined whether the

**Scheme 3.** If Attack of the Pd Catalyst at the Carbonyl Group Is Faster Than Oxidative Addition into the C−Br Bond, the Ketone Formation Dominates



palladium complex first reacts with the 4-tolylboronic acid **2** or with the thioesters **1**; we also could not determine the fate of the thiolate ligand: neither the thiol nor the corresponding disulfide could be detected after the reaction. Investigations to clarify these questions are underway.

**Supporting Information Available:** Detailed description of syntheses and spectroscopic data for **1a**–**i** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221.