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Practical Thiol Surrogates and Protective Groups for Arylthiols for Suzuki−Miyaura Conditions

Takahiro Itoh* and Toshiaki Mase

Process Research, Process R&D, Banyu Pharmaceutical Co. Ltd., 9-1, Kamimutsuna 3-chome, Okazaki, Aichi 444-0858, Japan

takahiro_itoh@merck.com

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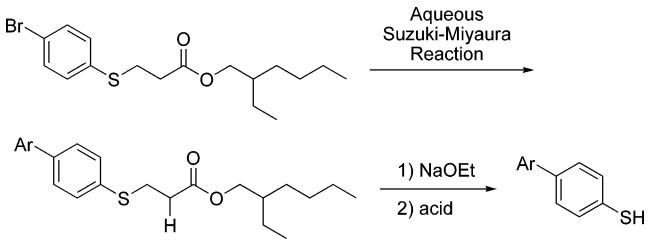
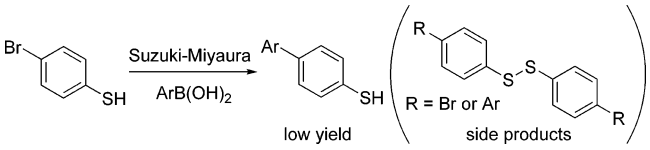


We have developed practical thiol surrogates and arylthiol protective groups for the Suzuki−Miyaura reaction. 2-Ethylhexyl-3-mercaptopropionate and 4-(2′-mercaptoethyl)pyridine were shown to be not only good thiol surrogates but also good protective groups for thiol. We have demonstrated toleration of these protective groups under aqueous Suzuki−Miyaura conditions.

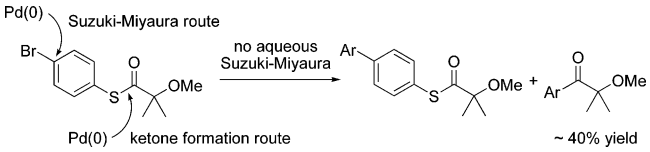
The biaryl scaffold has received much attention in the pharmaceutical industry as a privileged structure. This motif has shown activity across a wide range of therapeutic classes, and compounds that contain it have been shown to exhibit antifungal, antiinflammatory, antirheumatic, antitumor, and antihypertensive properties.[1] For the preparation of biaryl compounds, the Suzuki−Miyaura coupling reaction[2] is the most useful method, as it has been proven to offer distinct practical advantages over other approaches. Cross-coupling reactions have been developed for a tremendous variety of substrates containing various functional groups. However, thiols are one of the few compound types not suitable for the Suzuki−Miyaura reaction, as they tend to poison catalysts. For example, the coupling of 4-bromobenzenethiol with arylboronic acid did not proceed in high yield under typical conditions and resulted in the production of disulfide side products (Scheme 1).[3]

There are few studies in the literature that address this problem. The protective groups for thiols are well established;[4] in particular, *S*-acetyl is considered to be a favorable choice for arylthiols,[5] since arylthiol acetates undergo cleavage under mild basic conditions. Thioethers and thioheterocycles are good protective groups for thiols in the Suzuki−Miyaura reaction under aqueous or anhydrous basic conditions. However, the deprotection of thioethers to thiols is problematic due to the requirement of the harsh conditions. Acetyl groups are suitable for the Heck reaction,[6] but acyl groups are potentially not suitable as protective groups for aqueous basic Suzuki−Miyaura conditions. Terfort et al. reported that a suitable protective group for anhydrous Suzuki−Miyaura conditions is not an acetyl group but a 2-methoxyisobutyryl group, which is easily cleaved by aqueous bases; however, the carbonyl group may cause problems in the Suzuki−Miyaura reaction. They suggest that a ketone is formed by insertion of palladium between the sulfur atom and the carbonyl group, leading to a palladium−acyl complex with one thiolate ligand (Scheme 2).[7]

SCHEME 1. Problems Associated with Thiol Groups in the Suzuki−Miyaura Reaction



SCHEME 2. Issues with Using Carbonyl Groups for Thiol Protection



Recently, we have developed a method of efficient arylsulfur bond formation using aryl bromide/triflate and aryl/alkanethiols with $Pd_2(dba)_3$ and Xantphos.[8] 2-Ethylhexyl-3-mercaptopropionate **1** and 4-(2′-mercaptoethyl)pyridine hydrochloride **2**, which are odorless and inexpensive reagents, are good thiol surrogates for coupling under these conditions, and should be easily cleaved to the corresponding thiols under mild basic conditions via a β-elimination mechanism (Scheme 3).[9]

We expected that these thiol surrogates would be suitable for the Suzuki−Miyaura reaction even under aqueous basic conditions. This proved to be the case, and we report herein

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(2) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513−519. (b) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178−184. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (e) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (f) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470. (g) Suzuki, A. *Proc. Jpn. Acad., Ser. B* **2004**, *80*, 359. (h) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419−2440.

(3) Disulfide compounds were identified by LCMS. (a) Khodaei, M. M.; Salehi, P.; Goodarzi, M.; Yazdanipour, A. *Synth. Commun.* **2004**, *34*, 3661−3666. (b) Hori, M.; Kataoka, T.; Shimizu, H.; Ban, M.; Matsushita, H. *J. Chem. Soc., Perkin Trans. 1* **1987**, *1*, 187−194.

(4) (a) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999. (b) Coulon, E.; Pinson, J. *J. Org. Chem.* **2002**, *67*, 8513−8518.

(5) (a) Hsung, R. P.; Chidsey, C. E. D.; Sita, L. R. *Organometallics* **1995**, *14*, 4808−4815. (b) Yao, Y. X.; Tour, J. M. *J. Org. Chem.* **1999**, *64*, 1968−1971. (c) Gryko, D. T.; Clausen, C.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 8635−8647.

(6) Hsung, R. P.; Babcook, J. R.; Chidsey, C. E. D.; Sita, L. R. *Tetrahedron Lett.* **1995**, *36*, 4525−4528.

(7) Zeysing, B.; Gosch, C.; Terfort, A. *Org. Lett.* **2000**, *2*, 1843−1845.

(8) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587−4590.

(9) (a) Katritzky, A. R.; Takahashi, I.; Marson, C. M. *J. Org. Chem.* **1986**, *51*, 4914−4920. (b) Katritzky, A. R.; Khan, G. R.; Schwarz, O. A. *Tetrahedron Lett.* **1984**, *25*, 1223−1226.

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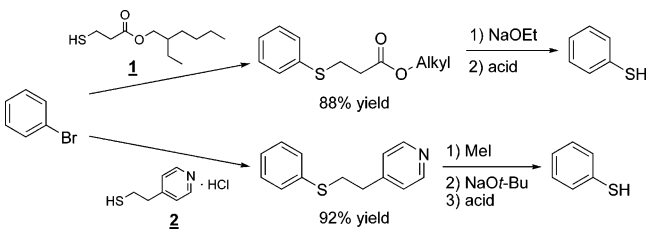
SCHEME 3. Preparation of Thiophenol Using Thiol Surrogates



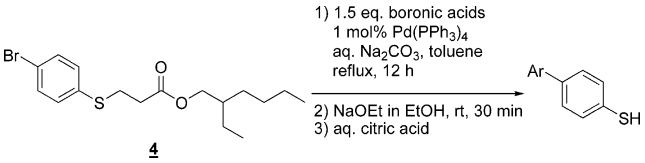
the development of suitable thiol protective groups and thiol surrogates for the Suzuki−Miyaura reaction.

p-Bromobenzene thioether **4** was easily prepared by two routes. 1-Bromo-4-iodobenzene was reacted with 2-ethylhexyl-3-mercaptopropionate **1** under previously reported conditions,[8] affording **4** in 90% yield. An alternative preparation of **4** was achieved via 1,4-conjugate addition of 4-bromobenzenethiol and isooctyl acrylate **3**.[10] The resulting thioether **4** was stable in aqueous Na_2CO_3, which is a typical base in Suzuki−Miyaura conditions (Scheme 4, eq 1). The stability of **4** was also investigated under various other basic conditions. For bases (pK_a) such as Na_2CO_3 (6.35−10.32), K_2CO_3, Cs_2CO_3, Li_2CO_3 (6.2, 9.7), KOH, LiOH (11.6), K_3PO_4 (12.4), $NaHCO_3$, NaF (3.18), CsF, Et_3N (10.8), pyridine (5.2), *N*-methylmorpholine (8.4), $Na_2B_4O_7$ (9.2), and DBU (12) in toluene/water (1:1) or dried toluene at reflux temperature for 12 h, cleavage of the thiol protective group did not proceed, and the recovery yield of **4** was over 95% by HPLC analysis. In addition, it was found that 4-[2-(4-bromophenylthio)ethyl]pyridine **5**, which was prepared in high yield by Pd-catalyzed cross-coupling of 1-bromo-4-iodobenzene with **2** under previously reported conditions,[8] was stable not only under aqueous Suzuki−Miyaura conditions but also to stronger bases such as NaO-*t*-Bu (Scheme 4, eq 2). Although the 2-(4-pyridinyl)ethyl protective group has been used for the Sonogashira reaction,[11] there have been no previous reports of this group being used for the introduction of a thiol moiety to aryl halides via a Pd-catalyzed coupling reaction.

The Suzuki−Miyaura coupling of **4** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ (1 mol %) and aqueous Na_2CO_3 in toluene at reflux temperature proceeded in high yield without formation of the corresponding disulfide byproduct. After coupling, NaOEt in EtOH was added to the reaction mixture for deprotection of propionate group via a β-elimination mechanism. Finally, the reaction mixture was acidified with aqueous citric acid to afford biphenyl-4-thiol in 85% yield (Table 1, entry 1). In the same manner, electron-deficient and electron-rich substituted arylboronic acids were coupled with **4** under aqueous conditions with high yields; the corresponding thiols were obtained in 82% and 81% yields, respectively (entries 2 and 3).

Next, we investigated the stability of these protective groups under strong basic conditions and the harsher conditions required for palladium-catalyzed coupling reactions. The stability of the thiol protective group in **4** was investigated in Sonogashira coupling,[12] the Heck reaction,[13] the Suzuki−Miyaura reaction, and Buchwald−Hartwig amination[14] (Scheme 5). The Sonogashira reaction with **4** and phenylacetylene in the presence of 0.1 mol % of $Pd_2(dba)_3$, 0.5 mol % of PPh_3, and 0.1 mol % of CuI, in combination with DMF/*i*-Pr_2NH, was successfully carried out at 70 °C, forming the desired thioether **6** in 91% yield (eq 1). For the Heck reaction, the coupling of **4** and styrene with 0.1 mol % of $Pd(PPh_3)_4$ in NMP proceeded well at 110 °C to afford the corresponding thioether **7** in 80% yield (eq 2).

TABLE 1. Suzuki−Miyaura Reactions of Protected Bromobenzenethiol 4



entry	arylboronic acid	yield of thiol[a] (%)
1	$PhB(OH)_2$	85
2	4-F-$C_6H_4B(OH)_2$	82
3	4-MeO-$C_6H_4B(OH)_2$	81

[a] Yields refer to the average isolated yield over two runs.

Thioether **5** was also tolerated in the Suzuki−Miyaura reaction. The coupling of **5** with phenylboronic acid in the presence of $Pd(PPh_3)_4$ (1 mol %) and aqueous Na_2CO_3 in toluene at reflux temperature proceeded in high yield without cleavage of the protective group to give the biaryl product **8** in 87% yield (eq 4). The thiol protective group in **4** was not suitable for treatment with a strong base such as NaO-*t*-Bu under typical Buchwald−Hartwig amination conditions, but cleavage of the protective group in **5** did not occur in the presence of the same base. The amination of **5** with morpholine proceeded well using 0.1 mol % of $Pd(OAc)_2$ and 0.1 mol % of 1,1′-bis(di-*tert*-butylphosphino)ferrocene (D-t-BPF)[15] in the presence of NaO-*t*-Bu in toluene at reflux temperature to afford the desired product **9** in 84% yield (eq 5). Using 1,1′-bis(diphenylphosphino)ferrocene (DPPF) instead of D-t-BPF was not effective. Cleavage of the protective groups did not occur in these reactions. The resulting thioethers **6**, **7**, **8**, and **9** underwent β-elimination to generate the corresponding thiols in quantitative yields.

There are few suitable protective groups for thiol against a strong base such as *n*-BuLi.[4a] The protective group of **4** was stable to treatment with *n*-BuLi at −78 °C. Cleavage of the propionate group with *n*-BuLi was slow even at −15 °C (about a 30% yield in 2 h). Halogen−metal exchange with **4** proceeded smoothly at −78 °C, and the resulting lithiated product was quenched with D_2O to obtain the deuterated product in 90% yield. For formylation, the resulting lithiated product was quenched by DMF instead of H_2O to afford **10** in 72% isolated yield (Scheme 6).

To summarize, we have developed practical thiol surrogates and arylthiol protective groups for the Suzuki−Miyaura reaction,

(10) Various other alkyl propionates and acrylates beside **1** and **3** were commercially available at inexpensive prices.

(11) (a) Yu, C. J.; Chong, Y.; Kayyem, J. F.; Gozin, M. *J. Org. Chem.* **1999**, *64*, 2070−2079. (b) Collman, J. P.; Zhong, M.; Costanzo, S.; Sunderland, C. J.; Aukauloo, A.; Berg, K,; Zeng, L. *Synthesis* **2001**, *3*, 367−369.

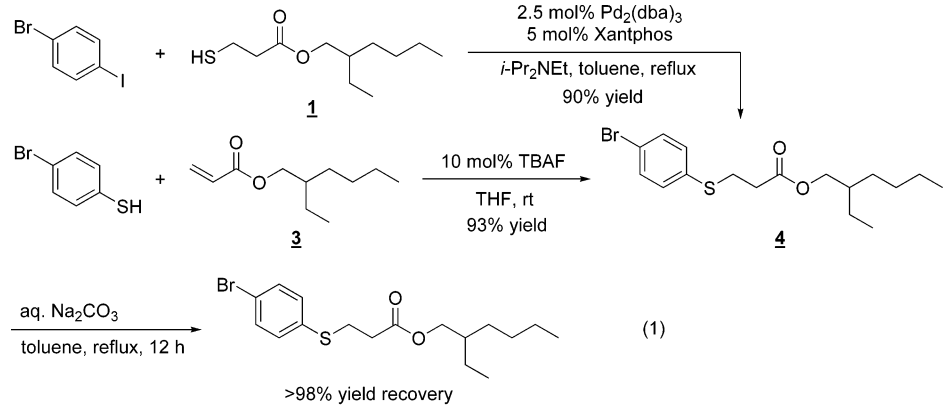
(12) Sonogashira, K.; Tohda, Y,; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467−4470.

(13) Patel, P. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpko, M.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3903−3907

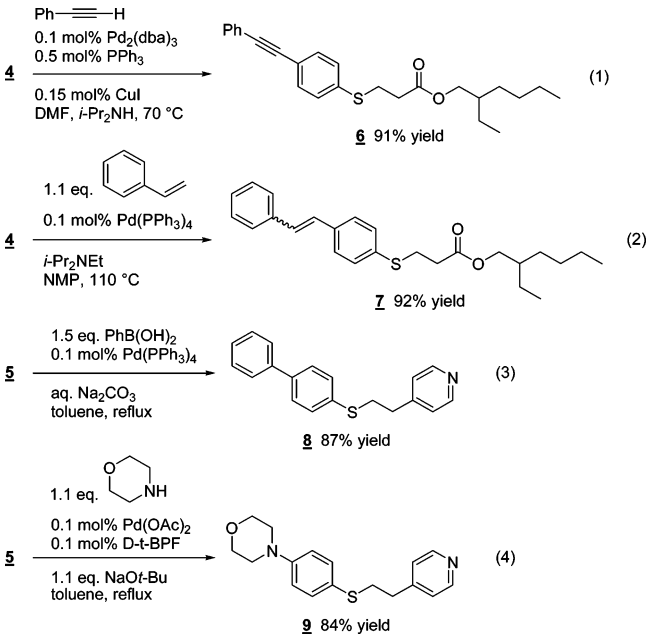
(14) (a) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970. (b) Guram, A. S.; Buchwald. S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901−7902.

(15) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370.

SCHEME 4. Synthesis and Stability of Substrates



SCHEME 5. Pd-Catalyzed Reactions of Protected Thiols 4 and 5

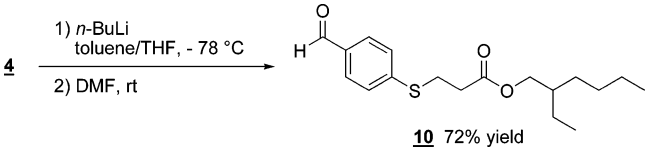


which are suitable even under basic aqueous conditions. These protective groups were also successfully used in other Pd-catalyzed reactions such as the Sonogashira, Heck, and Buchwald−Hartwig reactions and were tolerated in a formylation reaction using *n*-BuLi.

Experimental Section

3-(4-Bromophenylsulfanyl)propionic Acid 2-Ethylhexyl Ester (4). Method A: To a round-bottom-flask were added *p*-bromoiodobenzene (850 mg, 3 mmol), *i*-Pr_2NEt (1.04 mL, 6 mmol), and dry toluene (17 mL). The mixture was evacuated and back-filled with nitrogen (three cycles). $Pd_2(dba)_3$ (69 mg, 0.075 mmol), Xantphos (87 mg, 0.15 mmol), and 2-ethylhexyl-3-mercaptopropionate (0.69 mL, 3 mmol) were added, and then the mixture was degassed twice more. The mixture was heated to reflux for 4 h, and HPLC confirmed the completion of the reaction. The reaction mixture was then allowed to reach ambient temperature. The reaction mixture was then filtered and concentrated. The crude product was purified by flash column chromatography on silica gel to afford 3-(4-bromophenylsulfanyl)propionic acid 2-ethylhexyl ester (**4**) (813 mg, 90% yield) as slightly yellowish oil.

SCHEME 6. Formylation of Protected Thiol 4



Method B: To a round-bottom-flask were added *p*-bromobenzylthiol (5.7 g, 30 mmol), 2-Ethylhexyl-3-mercaptopropionate (5.5 g, 30 mmol), THF (57 mL), and tetrabutylammonium fluoride (30 mL, 30 mmol, 1 M in THF), and then the mixture was aged at ambient temperature for 15 h. The mixture was poured into EtOAc (50 mL) and water (30 mL). After separation, the aqueous layer was extracted with EtOAc (50 mL), and then the organic layers were combined and concentrated to dryness. The crude product was purified by flash column chromatography on silica gel to afford 3-(4-bromophenylsulfanyl)propionic acid 2-ethylhexyl ester (**4**) (10.5 g, 93% yield) as a slightly yellowish oil: column chromatography solvent (*n*-heptane/ethyl acetate = 100:1); R_f = 0.33 (*n*-heptane/ethyl acetate = 100:1); ^{1}H NMR (DMSO, 500 MHz) δ 7.29 (d, 2H, J = 8.5 Hz), 7.29 (d, 2H, J = 8.5 Hz), 3.94 (d, 2H, J = 5.7 Hz), 3.18 (t, 2H, J = 6.8 Hz), 2.62 (t, 2H, J = 6.8 Hz), 1.50−1.51 (m, 1H), 1.24−1.31 (m, 8H), 0.82−0.87 (m, 6H); ^{13}C NMR (DMSO, 125 MHz) δ 171.0, 135.1, 131.9, 130.4, 118.9, 66.2, 38.1, 33.6, 29.8, 28.3, 27.8, 23.2, 22.4, 13.9, 10.8;

IR (neat, cm^{-1}) 2958, 2929, 2859, 1735, 1473, 1387, 1349, 1243, 1175, 1092, 1069, 1008, 810, 480; HRMS *m*/*z* calcd for $C_{17}H_{25}BrO_2S$ 372.0759, found 372.0741.

4-[2-(4-Bromophenylsulfanyl)ethyl]pyridine (5). To a round-bottom-flask were added *p*-bromoiodobenzene (850 mg, 3 mmol), *i*-Pr_2NEt (1.04 mL, 6 mmol), and dry toluene (17 mL). The mixture was evacuated and backfilled with nitrogen (three cycles). $Pd_2(dba)_3$ (69 mg, 0.075 mmol), Xantphos (87 mg, 0.15 mmol), and 4-(2′-mercaptoethyl)pyridine hydrochloride salt (527 mg, 3 mmol) were added, and then the mixture was degassed twice more. The mixture was heated to reflux for 15 h, and HPLC confirmed the completion of the reaction. The reaction mixture was then allowed to reach ambient temperature. The reaction mixture was then filtered and concentrated. The crude product was purified by flash column chromatography on silica gel to afford 4-[2-(4-bromophenylsulfanyl)ethyl]pyridine (**5**) (794 mg, 90% yield) as a white solid: column chromatography solvent (*n*-heptane/ethyl acetate = 10:1); R_f = 0.21 (*n*-heptane/ethyl acetate = 2:1); mp 38−40 °C; ^1H NMR (DMSO, 500 MHz) δ 8.47−8.48 (m, 2H), 7.50−7.51 (m, 2H), 7.28−7.32 (m, 4H), 3.30 (t, 2H, J = 7.5 Hz), 2.89 (t, 2H, J = 7.5 Hz); ^{13}C NMR (DMSO, 125 MHz) δ 1149.5, 148.5, 135.5, 131.8, 130.0, 124.1, 118.6, 33.5, 32.0; IR (KBr, cm^{-1}) 1937, 1600, 1474, 1318, 1240, 1088, 1007, 849, 815, 725, 703, 572, 494; HRMS *m*/*z* calcd for $C_{13}H_{12}BrNS$ 292.9874, found 292.9886.

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Supporting Information Available: Detailed experimental procedures and characterization data for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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