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Thiophenol Protecting Groups for the Palladium-Catalyzed Heck Reaction: Efficient Syntheses of Conjugated Arylthiols

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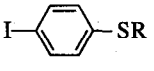
Abstract: A variety of *S*-thiophenol protecting groups have been evaluated for the Heck reaction. Of these, the *S*-acetyl group appears to be the best suited for facile removal under mild conditions to provide the corresponding free thiols in high yields.

The formation of highly ordered self-assembled monolayers (SAMs) of organic structures through the chemical modification of metal and metal oxide surfaces has been shown to be a powerful tool which can be used to control the interfacial properties of these surfaces.[1] In this regard, we are interested in exploring the formation, properties, and potential applications of SAMs derived from the self-assembly of conjugated arylthiols on gold since the ability of these new classes of SAM structures to mediate electron-transfer across the interfacial barrier represented by the monolayer may be superior to that of SAMs derived from n-alkanethiols.[2] Accordingly, we set out to develop synthetic methodology that would aid these studies by providing rapid access to a variety of novel conjugated arylthiols, and herein, we report the first results of this program which entail an evaluation of a number of thiol protecting groups that are compatible with the palladium-catalyzed Heck coupling reaction of terminal alkynes with aryliodides.[3]

The Heck reaction has previously been used to prepare a large number of organic structures, however, to the best of our knowledge, of these, only one thiophenol substrate has ever been employed.[4] Thus, from the outset, it was not clear which type of thiol protecting group would be best suited for this metal-mediated process, nor for providing the free thiols in high yield after deprotection.[5] Consequently, a variety of *S*-protected *p*-iodothiophenol derivatives, represented by compounds **1** - **4**, were prepared by straightforward procedures,[6] and as Table 1 reveals, the palladium-catalyzed couplings of these aryliodides with a variety of

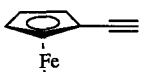
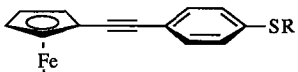
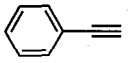
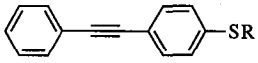
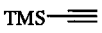
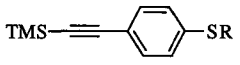
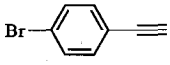
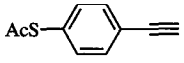
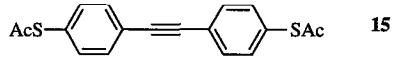
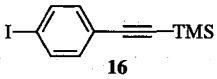
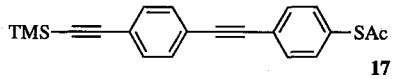
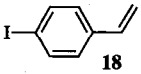
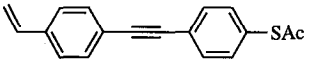
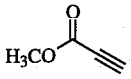
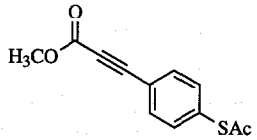


1: R = CH_3
2: R = benzyl (Bn)
3: R = acetyl (Ac)
4: R = CPh_3

terminal alkynes proceeded in high yields to produce a number of conjugated arylthiol derivatives.[7,8] For instance, the coupling of ferrocenylacetylene (**5**)[9] with the aryliodides **2** and **4** provided the corresponding protected arylthiols **6** and **7** in 89% and 91% yields, respectively.[10] In addition, compounds **8**, **10**, and **16** could be co. niently obtained from the coupling of the aryliodide **1** with phenylacetylene, trimethylsilyl-acetylene, and romophenylacetylene (**12**), respectively (entries 3, 5, and 7). For couplings involving *S*-

acetyl protected substrates (entries 4, 6, and 8-11), it was found that use of a 1:1 mixture of anhydrous THF and diisopropylethylamine (Hunig's base) was critical for obtaining high yields due to the lability of the *S*-acetyl

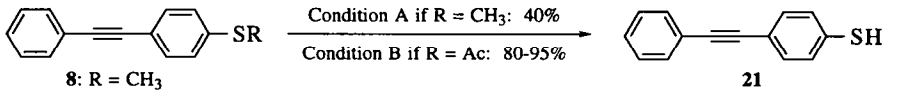
Table 1: Palladium-catalyzed Coupling Reactions of Terminal Alkynes with *S*-Protected *p*-Iodothiophenols **1** - **4**.[a,b]

Entry	Alkyne	Aryliodide[b]	Time (h)	Product	Yield[c] (%)
1	 **5**	**2**	20	 **6**: R = Bn	89
2		**4**	18	**7**: R = CPh_3	91
3		**1**	16	 **8**: R = CH_3	94
4		**3**	24	**9**: R = Ac	99
5		**1**	20	 **10**: R = CH_3	99
6		**3**	32	**11**: R = Ac	94
7	 **12**	**1**	22	 **13**	95
8	 **14**	**3**	20	 **15**	89
9	 **16**		28	 **17**	95
10	 **18**		20	 **19**	80
11		**3**	4d	 **20**	96[d]

[a]See Ref. 7. [b]All reactions were carried out in anhydrous Et_2NH except for entries 4, 6, and 8-11, where the reactions were carried out in anhydrous THF / Hunig's base (1:1). [c]Isolated yields. [d]The coupling was only 15% complete after 4 d, and the yield is based on reacted aryliodide **3**. The product formation was monitored by ^1H NMR and found to be quantitative.

group with less hindered amines. Finally, it is important to note that some of the products of Table 1 are useful as starting materials for the synthesis of other conjugated arylthiol derivatives. Thus, coupling of the phenylacetylene derivative **14**, obtained from compound **11** through selective removal of the trimethylsilyl group using n-Bu_4NF in CH_2Cl_2 at -85° C, with aryliodides **3**, **16**, and **18**, led to the respective products **15**, **17**, and **19** in high yields (entries 8-10). In this regard, it is clear that the synthesis of longer conjugated arylthiol derivatives should be possible through the iterative use of the aryliodide **16** and terminal alkynes such as the one that can be derived from **17**.[11]

Although the *S*-methyl, -benzyl, and -trityl moieties serve as excellent protecting groups for thiophenols in the Heck reaction, we have found that their removal is not easy due to the reactive nature of the triple bond of the protected arylthiol products. This is especially true for ferrocenyl derivatives, such as **6** and **7**, which are very sensitive towards a variety of the standard deprotecting conditions.[11] However, based on the observed lability of *S*-acetyl derivatives towards bases, we found that this protecting group could be easily removed through a simple two-step deacetylation process in high yield. Hence, while the *S*-methyl group of **8** was removed in a 40% overall yield via a Pummerer rearrangement of the corresponding sulfoxide to provide the arylthiol **21**,[12] treatment of **9** with 2-5 eq of either Et_2NH or n-$BuNH_2$ in $CHCl_3$ at 50° C, followed by reduction of the resulting disulfide intermediate with Zn and HOAc in CH_2Cl_2 provided **21** in 80 - 95% yield. This latter process has since proven very effective for deprotecting a variety of sensitive *S*-acetyl protected conjugated arythiol derivatives, and especially those possessing the ferrocene unit.[11]



8: R = CH_3
9: R = Ac

21

Condition A: 1) *m*-CPBA, CH_2Cl_2, 0°C; 2) $(CF_3CO)_2O$, CH_2Cl_2, reflux; 3) CH_3OH, Et_3N, rt.
Condition B: 1) 2-5 eq of Et_2NH or n-$BuNH_2$, $CHCl_3$, 50°C; 2) Zn, HOAc, CH_2Cl_2, rt.

In conclusion, we have evaluated a number of *S*-thiophenol protecting groups that can be used in conjunction with the Heck reaction to generate a variety of conjugated arylthiol derivatives. Of these, the *S*-acetyl group appears to be the best suited for facile removal under mild conditions to provide the free thiol in high yield. We are now in the process of using this methodology for the design and fabrication of a number of novel SAM structures and will report on the progress of these studies in due course.

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4. (a) Malek, N. J.; Moormann, A. E. *J. Org. Chem.* **1982**, *47*, 5395. (b) Patel, B. A.; Ziegler, C. B.; Cortese, N. A.; Plevyak, J. E.; Zebovitz, T. C.; Terpto, M.; Heck, R. F. *ibid.* **1977**, *42*, 3903.
5. Recently, Tour and co-workers have proposed using the *S*-acetyl group for the synthesis of arylthiols; (see: Tour, J. M. *Trends in Polymer Science* **1994**, *2*, 332, referece 26.)
6. Compound **1** was prepared in 99% yield via halogen exchange (i. t-BuLi / -78° C; ii. I_2) of 4-bromophenyl methyl sulfide. Compound **2** was prepared in two-steps (76% overall yield) from 4-bromobenzenethiol via benzylation and halogen exchange. Compounds **3**[10] and **4**[11] were prepared through acetylation (82%) and tritylation (91%), respectively, of 4-iodobenzenethiol.

7. General Procedure: The alkyne (0.08-1.2 mmol scale), aryliodide, $Pd(PPh_3)_2Cl_2$ (1.8 mol%), CuI (5.5 mol%) and the appropriate solvent, either anhydrous diethylamine or an anhydrous THF / Hunig's base (freshly filtered through dry basic alumina) 1:1 solvent mixture, were sealed under nitrogen in a Kontes Schlenk tube equipped with a teflon screw cap. The mixture was then stirred at 50° C for 16 - 96 h with the reaction being monitored by TLC analysis. When complete, the solvents were removed *in vacuo* and the desired product was isolated by flash column chromatography on silica gel.
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10. Selected spectral and analytical data (^1H NMR were taken at 300 or 500 MHz in $CDCl_3$).
3: mp 54.0-55.0 °C; ^1H NMR δ 2.43 (s, 3H), 7.13 (d, 2H, J = 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz); m/e (%relative intensity) 278 (100) M^+, 236 (100), 191 (3), 127 (9), 109 (100), 82 (28), 69 (48).
6: mp 93.0 - 94.0° C; ^1H NMR δ 4.13 (s, 2H), 4.24 (brs, 5H), 4.25 (t, 2H, J = 1.7 Hz), 4.48 (t, 2H, J = 1.7 Hz), 7.23 (d, 2H, J = 8.3 Hz), 7.30 (brd, 5H, J = 3.5 Hz), 7.36 (d, 2H, J = 8.3 Hz); HRMS m/e calcd: $C_{25}H_{20}FeS$ 408.0635, found: 408.0621.
7: mp 183.0 - 185.0° C; ^1H NMR δ 4.18 (s, 5H), 4.19 (t, 2H, J = 1.8 Hz), 4.41 (t, 2H, J = 1.8 Hz), 6.84 (d, 2H, J = 8.3 Hz), 7.05 (d, 2H, J = 8.3 Hz), 7.15 (t, 3H, J = 6.9 Hz), 7.18 (t, 6H, J = 7.8 Hz), 7.34 (d, 6H, J = 6.7 Hz); m/e (%relative intensity) 560 (2) M^+, 418 (23), 318 (100), 286 (8).
8: mp 83.0 - 84.0° C; ^1H NMR δ 2.48 (s, 3H), 7.16 (d, 2H, J = 8.2 Hz), 7.28 (m, 3H), 7.39 (d, 2H, J = 8.2 Hz), 7.46 (brd, 2H, J = 4.6 Hz); HRMS m/e calcd: $C_{15}H_{12}S$ 224.0660, found: 224.0648.
9: mp 84.0 - 86.0° C; ^1H NMR δ 2.42 (s, 3H), 7.30 (m, 3H), 7.35 (d, 2H, J = 8.2 Hz), 7.48 (dd, 2H, J = 1.3, 9.1 Hz), 7.50 (d, 2H, J = 8.2 Hz); HRMS m/e calcd: $C_{16}H_{12}OS$ 252.0609, found: 252.0592.
11: mp 42.0 - 44.0 C; ^1H NMR δ 0.25 (s, 9H), 2.40 (s, 3H), 7.29 (d, 2H, J = 8.1 Hz), 7.43 (d, 2H, J = 8.1 Hz); HRMS m/e calcd: $C_{13}H_{16}OSSi$ 248.0691, found: 248.0673.
14: pale yellow oil; ^1H NMR δ 2.41 (s, 3H), 3.12 (s, 1H), 7.32 (d, 2H, J = 8.0 Hz), 7.46 (d, 2H, J = 8.0 Hz); m/e (%relative intensity) 176 (46) M^+, 134 (100), 108 (4), 89 (33), 63 (16).
15: mp 111.0 - 113.0° C; ^1H NMR δ 2.44 (s, 6H), 7.41 (d, 4H, J = 8.1 Hz), 7.56 (d, 4H, J = 8.1 Hz); HRMS m/e calcd: $C_{18}H_{14}O_2S_2$ 326.0435, found: 326.0422.
17: mp 104.0 - 106.0 °C; ^1H NMR δ 0.26 (s, 9H), 2.42 (s, 3H), 7.35 (d, 2H, J = 7.7 Hz), 7.40 (brs, 4H), 7.48 (d, 2H, J = 7.7 Hz); HRMS m/e calcd: $C_{21}H_{20}OSSi$ 348.1004, found: 348.0992.
19: mp 90.0 - 92.0 °C; ^1H NMR δ 2.42 (s, 3H), 5.27 (d, 1H, J = 11.0 Hz), 5.75 (d, 1H, J = 17.6 Hz), 6.65 (dd, 1H, J = 11.0, 17.6 Hz), 7.34 (brd, 4H, J = 7.9 Hz), 7.44 (d, 2H, J = 7.9 Hz), 7.50 (d, 2H, J = 7.9 Hz); HRMS m/e calcd: $C_{18}H_{14}OS$ 278.0765, found: 278.0768.
20: mp 76.0 - 78.0° C; ^1H NMR δ 2.43 (s, 3H), 3.82 (s, 3H), 7.38 (d, 2H, J = 7.7 Hz), 7.55 (d, 2H, J = 7.7 Hz); HRMS m/e calcd: $C_{12}H_{10}O_3S$ 234.0351, found: 234.0341.
21: mp 73.0 - 75.0° C; ^1H NMR δ 3.49 (s, 1H), 7.19 (d, 2H, J = 8.1 Hz), 7.28 (m, 3H), 7.34 (d, 2H, J = 8.1 Hz), 7.46 (brd, 2H, J = 5.1 Hz); HRMS m/e calcd: $C_{14}H_{10}S$ 210.0503, found: 210.0495.
11. Syntheses of longer chain ferrocene phenylethynyl oligomers related to **6** for R = Ac and H will be reported elsewhere. Sita, L. R.; Hsung, R. P.; Chidsey, C. E. D. *Organometallics*, submitted for publication.
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