# Polymethylhydrosiloxane (PMHS) as an Additive in Sonogashira Reactions

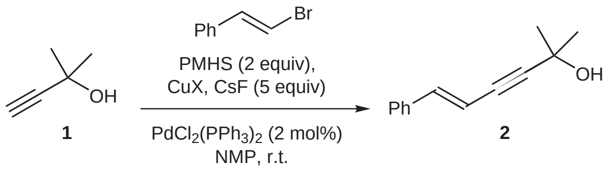
William P. Gallagher, Robert E. Maleczka Jr.*
Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA
Fax +1(517)3531793; E-mail: maleczka@cem.msu.edu

*Received 24 January 2003*

**Abstract:** Polymethylhydrosiloxane (PMHS) in combination with CsF facilitates the Sonogashira reaction of a variety of alkynes and electrophiles. These couplings appear to involve the in situ formation and reaction of an alkynylsiloxane. Such couplings can be run amine free at room temperature, reaction times are short, workup is easy, and product purification is straightforward. Thus, the advantages (and disadvantages) of running Sonogashira couplings with 1-silylalkynes are realized, without the need to preform the alkynyl silane.

**Key words:** Sonogashira reaction, enynes, alkynes, palladium, copper, cross-coupling

During the course of our studies on palladium mediated one-pot hydrostannation/Stille reactions,[1] enyne production was occasionally observed. Probing this side product formation further revealed that adding polymethylhydrosiloxane (PMHS) and CsF to a mixture of alkyne, electrophile, CuX and Pd-catalyst facilitates Sonogashira coupling.[2,3] Because these conditions are relatively neutral[4] and amine free,[5] and because PMHS is easily handled, inexpensive, non-toxic, and mild,[6] we deemed this reaction worthy of additional study. The objectives of this study would be to establish the best conditions for PMHS mediated Sonogashira reactions and determine the role of PMHS.



**Equation 1**

Preliminary experiments carried out on the coupling of 2-methyl-3-butyn-2-ol (**1**) with (*E*)-β-bromostyrene (Equation 1) revealed that treatment of alkyne **1** with CsF (5 equiv) and PMHS (2 equiv) in NMP followed by addition of $PdCl_2(PPh_3)_2$ (2 mol%), CuX and (*E*)-β-bromostyrene, afforded the corresponding enyne (**2**) (Sonogashira product) after stirring for 2 hours at room temperature (Table 1, entry 1). Use of less CsF (2 equiv) resulted in a slower reaction, while no reaction was observed in the absence of PMHS or CsF. In addition, substituting KF for CsF resulted in no observable coupling reaction.

As shown in Table 1, the choice and quantity of copper salt employed were crucial. The reaction failed in the absence of copper (or palladium). With stoichiometric amounts of 2-thiophenecarboxylate (CuTC)[7,8] or CuCl (entries 1 or 3) the reaction proceed efficiently, but little coupling occured when catalytic quantities of these copper(I) reagents were used (entries 2 or 4). Furthermore, the use of either catalytic or stoichiometric amounts of CuI, CuBr, or CuCN afforded only trace amounts of enyne (entries 4–7). Mori et al. observed similar copper effects in the coupling of 1-silylalkynes[3i,l] and concluded that copper(I) chloride or a 'CuO' can affect transmetalation between silicon and copper, whereas the corresponding bromides or iodides can not. Thus, our data suggested the possible involvement of a silicon bearing alkyne.

**Table 1** Effect of Cu(I) Salts on Equation 1[a]

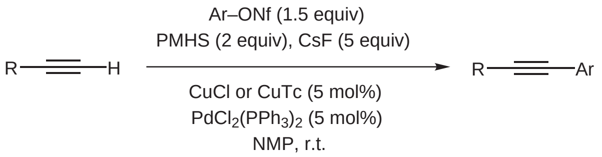
| Entry | CuX (equiv) | Time (h) | Yield |
|---|---|---|---|
| 1 | CuTC (2.0) | 2 | 99% |
| 2 | CuTC (0.02) | 24 | 2% |
| 3 | CuCl (1.5) | 2 | 95% |
| 4 | CuCl (0.02) | 24 | 2% |
| 5 | CuI (0.02–1.5) | 24 | <1% |
| 6 | CuBr (0.02–1.5) | 24 | <1% |
| 7 | CuCN (0.02–1.5) | 24 | <1% |

[a] See Equation 1 for reaction conditions.

Based on this hypothesis, the employment of nonaflates or triflates as electrophiles should produce the necessary 'CuO' species and allow CuTC or CuCl to be used catalytically. With aryl nonaflates prepared from their corresponding phenols by treatment with NfF and $NEt_3$ in $CH_2Cl_2$,[9] Sonogashira couplings were investigated (Equation 2). After some experimentation, we found that room temperature reactions run with 1.5 equivalents of nonaflate along with the alkyne, PMHS, CsF, catalytic $PdCl_2(PPh_3)_2$, and catalytic CuCl (or CuTC) (5 mol %) in NMP afforded the corresponding cross-coupled products in good to excellent yields (Table 2).[10] In the absence of PMHS, CsF, Pd, or Cu no Sonogashira reaction was observed.

Synlett 2003, No. 4, Print: 12 03 2003.
Art Id.1437-2096,E;2003,0,04,0537,0541,ftx,en;S10303ST.pdf.

ISSN 0936-5214



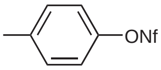
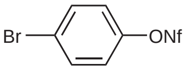
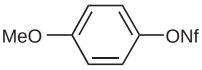
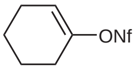
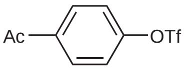
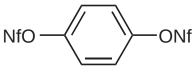
**Equation 2**

This protocol was amenable to the reaction of alkynes that were mono-, di-, or tri-substituted at the propargylic position. Free hydroxyls were tolerated and an aryl nonaflate was selectively reacted in the presence of an aryl bromide (entry 7). Vinyl nonaflates (**21**) and aryl triflates (**23**) coupled with similar levels of efficiency (entries 9, 10) and a bisnonaflate could be reacted at both positions in high yield (entry 11).

Iterative application of the coupling method could be used to synthesize disubstituted alkynes. For example, a masked acetylene such as 2-methyl-3-butyn-2-ol (**1**) can be coupled with an aryl nonaflate (Scheme 1). Treatment of the product with base leads to an elimination of acetone to furnish the corresponding aryl alkyne. Subjecting the newly formed aryl alkyne a second coupling afforded internal aryl alkyne **27** in 68% yield from 2-methyl-3-butyn-2-ol (**1**).

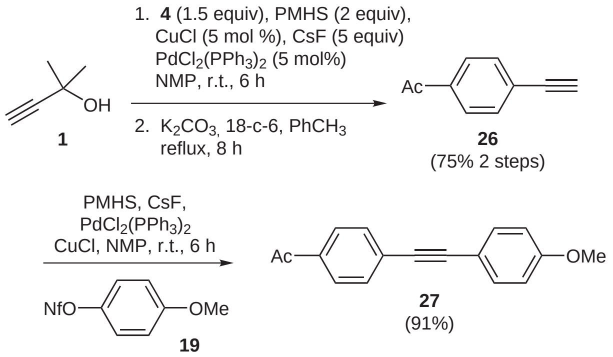
For coupling aryl or vinyl bromides or iodides (Equation 3, Table 3), we found 2 equivalents of CuTC[11] along with the PMHS and CsF in THF/NMP (1:1) worked best.[12] Unfortunately, these conditions are not universally effective as bromobenzene, *p*-bromoanisole, and an aryl chloride could not be made to couple. Reaction occured with CuCl, but in slightly lower yields. The need for at least stoichiometric amounts of copper(I) is again presumably due to the aforementioned involvement of a putative alkynylsiloxane intermediate. The CuBr or CuI formed with each coupling is unable to efficiently undergo transmetalation with such a species[3i,l] and therefore cannot cycle catalytically.

**Table 2** PMHS-Mediated Couplings of 1-Alkynes with Nonaflates[a]

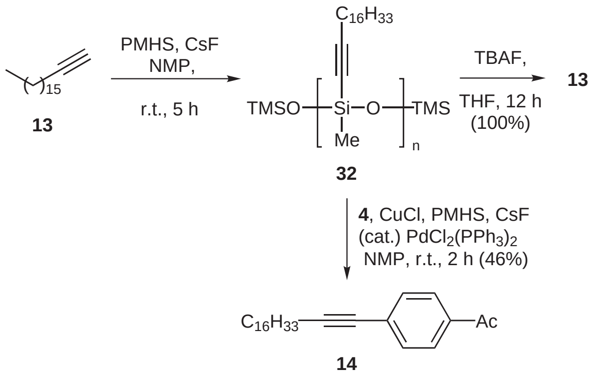
| Entry | Alkyne (R = ) | Ar–NOf | Time (h) | Product (Yield)[b] |
|---|---|---|---|---|
| 1 | Ph (**3**) | <br>(**4**) | 4 | **5** (96%) |
| 2 | HO(Me)$_2$C-<br>(**1**) | **4** | 4 | **6** (96%) |
| 3 | HO(Me)CH-<br>(**7**) | **4** | 5 | **8** (82%) |
| 4 | HO(CH$_2$)$_4$-<br>(**9**) | **4** | 6 | **10** (86%) |
| 5 | CH$_3$(CH$_2$)$_2$-<br>(**11**) | **4** | 8 | **12** (73%) |
| 6 | CH$_3$(CH$_2$)$_{15}$-<br>(**13**) | **4** | 8 | **14** (95%) |
| 7 | HO(Me)(Et)C-<br>(**15**) | <br>(**16**) | 6 | **17** (73%) |
| 8 | HO(Me)(Ph)C-<br>(**18**) | <br>(**19**) | 7 | **20** (52%) |
| 9 | HO(Me)CH-<br>(**7**) | <br>(**21**) | 5 | **22** (82%) |
| 10 | HO(Me)$_2$C-<br>(**1**) | <br>(**23**) | 5 | **6** (86%) |
| 11 | HO(Me)(Et)C-<br>(**15**) | <br>(**24**) | 6 | R′-Ar-R′<br>**25** (76%)<br>R′ = RC≡C- |

[a] See Equation 2 for reaction conditions.

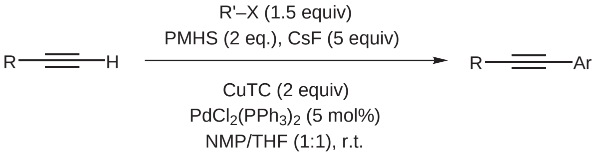
[b] Average isolated yield of two runs.



**Scheme 1**



**Scheme 2**

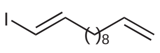
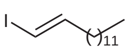


**Equation 3**

While our observations on the copper(I) requirements of these reactions and the lack of coupling in absence of PMHS argue for the intermediacy of a silicon bearing alkyne, we sought further proof of such an intermediate. Reacting octadecyne (**13**), PMHS, and CsF produced a solid material (**32**). $^1$H NMR of the substance showed features of the starting alkyne and PMHS except that the alkynyl proton ($\delta$ = 2.42 ppm) and the Si-H from PMHS ($\delta$ = 4.85 ppm) were absent (Scheme 2). Subjecting this new product to our coupling conditions produced the desired cross-coupled product in 44–49% yield. Treatment with TBAF regenerated the original alkyne.

To complement these reactivity studies, we followed the reaction of the alkyne, PMHS, and CsF by ReactIR™. Octadecyne (**13**) and CsF were mixed and an initial reading was obtained. PMHS was then added slowly via a syringe[13] over which time the alkyne C–H stretch at $\nu$ = 3231 cm$^{-1}$ diminished (Figure 1). In contrast, mixing **13** and CsF alone over the same period of time witnessed little change in the C–H stretch. Further studies are underway to access more evidence for an alkynylsiloxane intermediate.

**Table 3** PMHS-Mediated Couplings of 1-Alkynes with Halides[a]

| Entry | Alkyne (R = ) | R′–X | Time (h) | Product (Yield)[b] |
|---|---|---|---|---|
| 1 | HO(Me)$_2$C- (**1**) | *E*-($\beta$)-bromostyrene | 2 | **2** (99%) |
| 2 | HO(Me)CH- (**7**) |  (**28**) | 5 | **29** (82%) |
| 3 | HO(Me)$_2$C- (**1**) | *p*-iodoacetophenone | 5 | **6** (87%) |
| 4 | HO(Me)$_2$C- (**1**) | *p*-bromoacetophenone | 5 | **6** (80%) |
| 5 | HO(Me)CH- (**7**) |  (**30**) | 7 | **31** (88%) |

[a] See Equation 3 for reaction conditions.
[b] Average isolated yield of two runs.

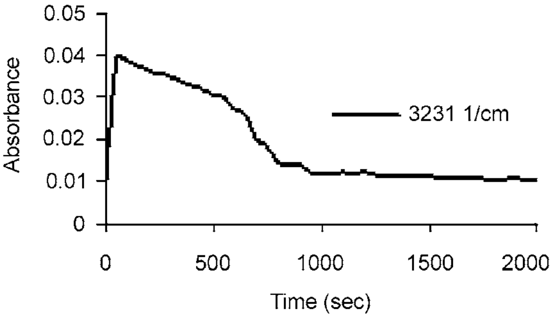


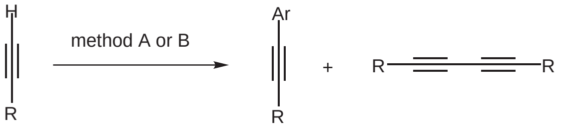
**Figure 1** ReactIR™ analysis of the alkyne C–H stretch at $\nu$ = 3231 cm$^{-1}$

In summary, PMHS in combination with CsF facilitates room temperature Sonogashira couplings of alkynes with various electrophiles. These reactions can be run amine free, which among other things eases reaction workup. The involvement of an in situ generated alkynyl siloxane intermediate appears likely. Thus, some of the advantages of using silylakynes in Sonogashira couplings can be realized without having to preform such a species in a separate step (usually by deprotonation with an alkyl lithium followed by trapping with TMSCl). For example, the use of 1-silylalkynes can limit unwanted homocoupling of the parent alkyne (Equation 4).[14] As shown in Table 4, attempted couplings of 2-methyl-3-butyn-2-ol (**1**) or 2-phenyl-3-butyn-2-ol (**18**) under traditional Sonogashira conditions gives a significant amount of homocoupled products (entries 1 and 3). This problem is particularly acute if the reactions were not run under an Ar atmosphere.[15] In contrast, employment of our protocol in air (Table 4, entries 2 and 4) only afforded the cross-coupled products, albeit in modest 52% yield for the coupling of **18** to **19**.

**Table 4** Traditional vs. PMHS Mediated Sonogashira Couplings

| Entry | Alkyne | Ar–ONf | Method[a] | Cross-Coupled Product | Homocoupled Product |
|---|---|---|---|---|---|
| 1 | **1** | **4** | A[a] | **6** (48%) | **33** (39%) |
| 2 | **1** | **4** | B[a] | **6** (85%) | **33** (0%) |
| 3 | **18** | **19** | A[a] | **20** (0%) | **34** (92%) |
| 4 | **18** | **19** | B[a] | **20** (52%) | **34** (0%) |

[a] See Equation 4 for reaction conditions



**Equation 4** Method A: $Et_3N$ (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuI (0.05 equiv), ArONf (1.5 equiv), THF, r.t. Method B: PMHS (2.0 equiv), $PdCl_2(PPh_3)_2$ (0.05 equiv), CuCl (0.05 equiv), ArONf (1.5 equiv), NMP, r.t.

It must also be acknowledged that some of the disadvantages of employing 1-silylalkynes in Sonogashira couplings remain under these conditions. Namely, stoichiometric amounts of copper are necessary in the coupling of halides.[16] Furthermore, fluoride is required. With respect to this last point, while most of our reactions were run with a five-fold excess of CsF, the fluoride load could be reduced to 1.5 equivalents with no loss of efficiency by using fused CsF/CsOH (2:1).[17]

Currently we aim to increase our mechanistic understanding of this reaction and broaden its scope. Of particular interest is the application of this new method to target synthesis and the coupling of other species. New developments in these areas will be reported in due course.

## Acknowledgment

We thank the Yamanouchi USA Foundation and NSF (CHE-9984644), for their generous support. W.P.G. thanks Pfizer and Dow Chemical for sponsorship of ACS Division of Organic and MSU graduate fellowships, respectively.

## References

(1) Maleczka, R. E. Jr.; Gallagher, W. P. *Org. Lett.* **2001**, *3*, 4173; and references cited.

(2) For reviews see: (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New York, **1998**, Chap. 5. (c) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, **1998**, Chap. 10. (d) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127. (e) Sonogashira, K. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M., Ed.; Pergamon: New York, **1991**, Chap. 2.4.

(3) For recent advances see: (a) Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691. (b) Mori, A.; Ahmed, M. S. M.; Sekiguchi, A.; Masui, K.; Koike, T. *Chem. Lett.* **2002**, 756. (c) Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118. (d) Tzschucke, C. C.; Markert, C.; Glatz, H.; Bannwarth, W. *Angew. Chem. Int. Ed.* **2002**, *41*, 4500. (e) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (f) Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* **2001**, *42*, 1815. (g) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2000**, *3*, 4107. (h) Erdelyi, M.; Gogoll, A. *J. Org. Chem.* **2001**, *66*, 4165. (i) Nishihara, Y.; Ando, J.-i.; Kato, T.; Mori, A.; Hiyama, T. *Macromolecules* **2000**, *33*, 2779. (j) Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114. (k) Hundertmark, T.; Littke, A. L.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729. (l) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780. (m) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679. (n) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233.

(4) Mori et al. (ref.[3i,l]) have found that using 1-silylalkynes in place of their parent 1-alkynes allows one to perform a Sonogashira reaction under neutral conditions with catalytic amounts of Pd(0) and Cu(I). Marshall et al. (ref.[3g]) also reported a similar procedure, utilizing stoichiometric amounts of CuCl and 2 equiv of $Bu_3N$.

(5) For other examples of amine free Sonogashira-type reactions see (a) Alonso, D. A.; Nájera, C.; Pacheco, C. *Tetrahedron Lett.* **2002**, *43*, 9365. (b) Mori, A.; Shimada, T.; Kondo, T.; Sekiguchi, A. *Synlett* **2001**, 649.

(6) (a) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381. (b) Lipowitz, J.; Bowman, S. A. *Aldrichimica Acta* **1973**, *6*, 1. (c) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*, Vol. 4; Wiley: New York, **1974**, 393.

(7) CuTC = Copper(I) thiophene carboxylate. CuTC can be easily made or purchased from Frontier Scientific. This compound is sufficiently stable and does not require any special handling when dry. CuCl must be kept and used under $N_2$ to work efficiently. For other examples of CuTC in coupling reactions see: (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (b) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (c) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

(8) Couplings of **1** and **2** with 1.0 or 1.5 equiv of CuTC were lower yielding (44–68%).

(9) (a) Rottländer, M.; Knochel, P. *J. Org. Chem.* **1998**, *63*, 203. (b) For a review of the preparation of alkenyl triflates see: Lyapkalo, I. M.; Webel, M.; Reißig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015.

(10) **Representative Procedure for PMHS–Sonogashira Coupling of Aryl- and Vinyl Nonaflates/Triflates. Preparation of 1-(4-Phenylethynyl-phenyl)-ethanone (5) (Table 2, Entry 1).** To 30 mL of NMP was added phenylacetylene(**3**) (0.11 mL, 1.0 mmol), PMHS (0.12 mL, 2 mmol), CsF (0.7595 g, 5.0 mmol), CuCl (0.0050 g, 0.05 mmol), 1,1,2,2,3,3,4,4,4-nonafluoro-butane-1-sulfonic acid 4-acetyl-phenyl ester (**4**) (0.6273 g, 1.5 mmol) and $PdCl_2(PPh_3)_2$ (0.0350 g, 0.05 mmol). This mixture was stirred at r.t. until complete by TLC analysis (90/10 hexanes/EtOAc). Once complete (4 h), the reaction was diluted with $Et_2O$ and then washed with sat. aq $NH_4Cl$. The phases were then separated and the combined organics were washed with $H_2O$ (2×), brine (2×), dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography (silica gel; hexane/EtOAc 90:10) to afford 1-(4-phenylethynyl-phenyl)-ethanone(**5**) (212 mg, 96%) as a light yellow solid (mp 95 °C). For spectroscopic data and a prior preparation see the following: Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017.

(11) CuCl could also be used, but the reaction yields tended to be slightly lower.

(12) For the coupling of aryl or vinyl halides. The general procedure noted above (ref.[10]) was followed except that 2 equiv of CuTC were used and the solvent was THF/NMP (1:1, 15 mL at 1.0 mmol scale).

(13) Adding the alkyne, CsF, and PMHS at once caused rapid foaming that made monitoring by ReactIR™ difficult.

(14) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.

(15) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280.

(16) 1-TMS acetylenes have been coupled with triflates or iodides under copper free conditions using a combination of catalytic Pd(0) and Ag(I) salts in the presence of $K_2CO_3$ or TBAF. See: (a) Halbes, U.; Pale, P. *Tetrahedron Lett.* **2002**, *43*, 2039. (b) Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* **2001**, *42*, 8641. (c) Bertus, P.; Halbes, U.; Pale, P. *Eur. J. Org. Chem.* **2001**, 4391.

(17) Edelson, B. S.; Stoltz, B. M.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 6729.