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Solvomercuration and demercuration of alkenes on solid-phase†

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Abstract—The first report of alkoxy and amino mercuration of alkenes on solid-phase is reported. The organomercurial has been transformed into alkanes, iodo ethers and Giese adducts in good yield. Cleavage by mild acid treatment released the product from the solid-support in excellent purity.

The merit of solid-phase synthesis of small organic molecules is well recognized and is extensively employed in drug discovery programs.[1] The solid-phase synthesis of small organic molecules depends greatly on the adaptation of solution reactions to solid-phase, which requires considerable effort and time, mainly due to the different requirements and properties of the two phases. There is an ever increasing need to find strategically important processes which are efficient and lead to greater structural variation in a shorter period of time. The electrophile-mediated functionalisation of alkenes[2] is one such reaction which affords products with vicinal functionalities that can be further transformed by replacement with hydrogen, substitution via radical intermediates, nucleophilic substitution and β-elimination. We wish to disclose herein for the first time, amino mercuration[3] and alkoxy mercuration[3] of alkenes tethered to the solid-support, followed by demercuration that includes reduction, halogenation and the Giese reaction, of the organomercurial.

Eugenol and 3-hydroxybenzoic acid allyl ester were anchored to Wang resin through the phenolic group using the Mitsunobu protocol.[4] Treatment of the alkene **1** with aniline (6 equiv.) and mercuric trifluoroacetate (3 equiv.) in dry THF under a nitrogen atmosphere at rt overnight afforded the amino mercurial **2a** after filtration and washing the resin (Scheme 1). The difference in the FT-IR data of **1** and **2a** point to complete reaction. Mercuric trifluoroacetate was used primarily due to its solubility in organic solvents that swell polystyrene based resins and its enhanced reactivity. The attempted reduction of the mercurial **2a** using the standard conditions, sodium borohydride in the presence of aqueous sodium hydroxide,[5] in THF followed by cleavage from the solid support using 25% TFA in DCM, afforded the reduction product along with sizeable amounts of eugenol arising from elimination. After much experimentation, lithium borohydride[6] in THF was found to be the reagent of choice for reduction to afford **5a** after cleavage in 80% yield. Attempted Giese reaction of the amino mercurial **2a** with sodium borohydride and excess acrylonitrile (50 equiv.) in solvents like DMF,[7] THF and DCM in the presence and in the absence of aqueous sodium hydroxide, followed by cleavage from the solid support afforded only trace amounts of the adduct **6a**. The reduction product was the major component under these reaction conditions. Finally, when the reaction was performed in dimethoxyethane using sodium borohydride in the presence of aqueous sodium hydroxide under nitrogen,[8] followed by cleavage, the desired product **6a** was obtained in 65% yield. The eugenol ether **1** was reacted in a similar fashion with morpholine to afford mercuric compound **2b**, which underwent smooth reduction with lithium borohydride to afford **5b** in 70% yield after cleavage. The carbon–carbon bond formation reaction employing conditions identical to that used for **2a** proceeded without incident to yield **6b** in 60% yield (Scheme 1).

The polymer bound allyl ester **7** was converted to the amino mercurial **8**, which was reduced with sodium borohydride in THF to afford the amine **11** after cleavage. Lithium borohydride was not used for fear of reductive cleavage. The Giese reaction afforded aminonitriles **12** after cleavage, employing the conditions detailed earlier (Scheme 2).

Keywords: alkoxy mercuration; amino mercuration; demercuration; solid-phase; Wang resin.

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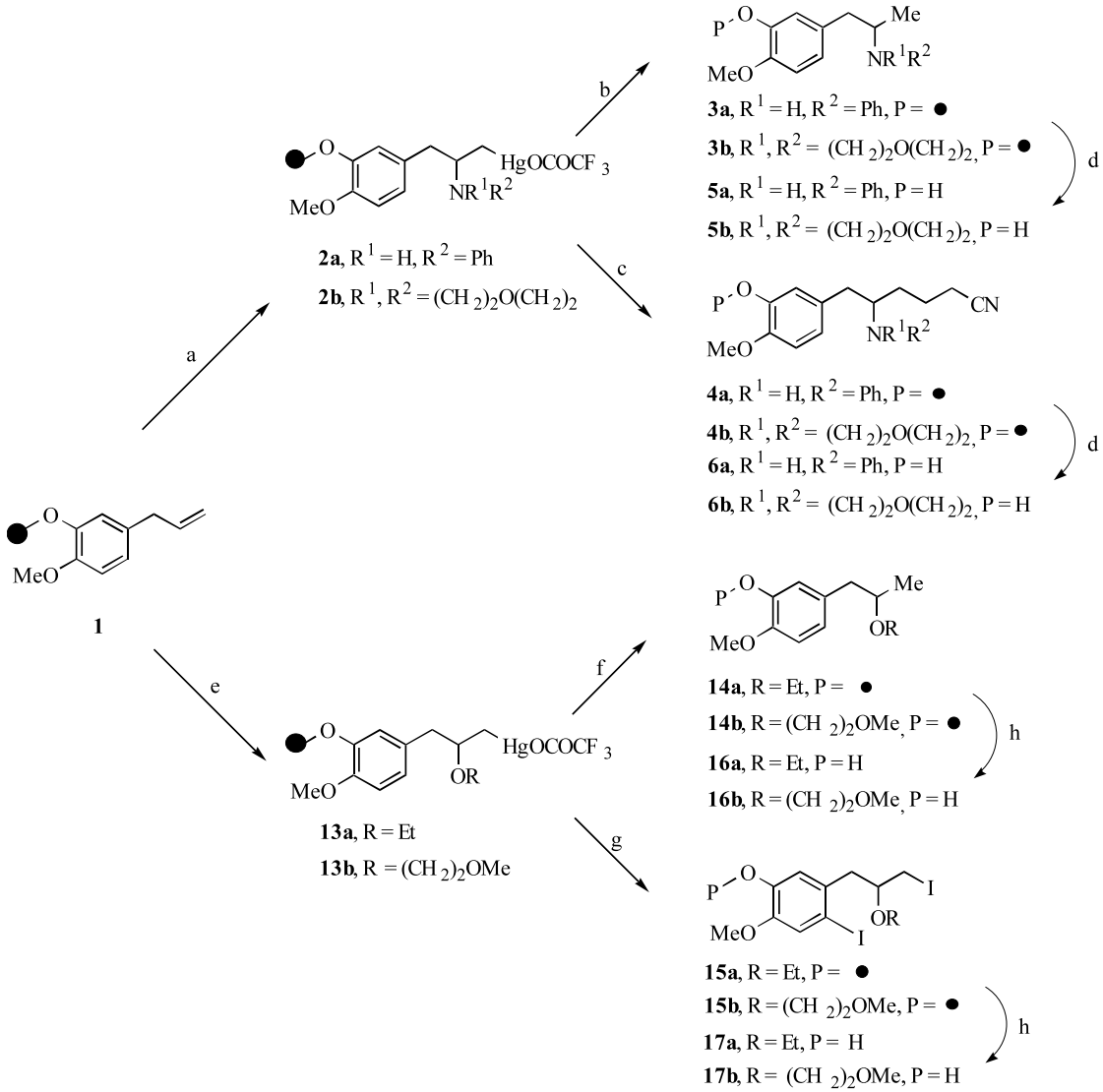
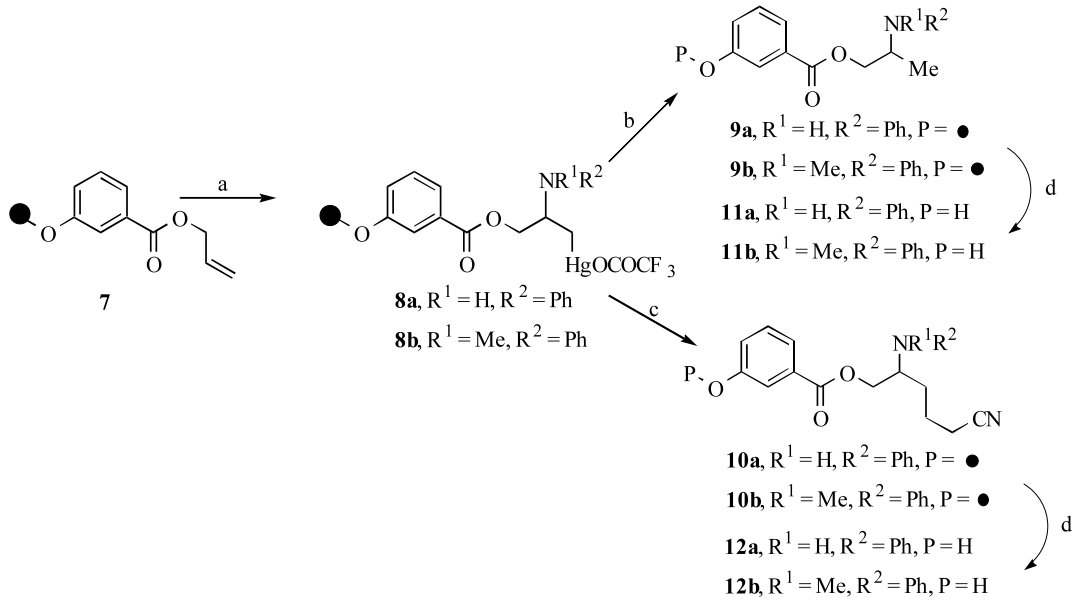


Scheme 1. (a) 3.0 equiv. $Hg(OCOCF_3)_2$, 6.0 equiv. R^1R^2NH, THF, rt, 16 h; (b) 3.0 equiv. $LiBH_4$, THF, –23°C to rt, 16 h; (c) 8.0 equiv. $NaBH_4$, aq. 1N NaOH, 50 equiv. acrylonitrile, DME, 0°C–rt, 16 h; (d) 25% TFA, DCM, rt, 12 h, **5a** = 80%, **5b** = 70%, **6a** = 65%, **6b** = 60%; (e) 3.0 equiv. $Hg(OCOCF_3)_2$, 3.0 equiv. ROH, DCM, rt, 16 h; (f) 3.0 equiv. $LiBH_4$, THF, –23°C to rt, 16 h; (g) 3.0 equiv. I_2, THF, rt, 12 h; (h) 25% TFA, DCM, rt, 12 h, **16a** = 85%, **16b** = 80%, **17a** = 90%, **17b** = 90%.

The alkoxy mercuration reaction was performed on eugenol and *trans*-cinnamic acid anchored to Wang resin. Treatment of alkene **1** with ethanol (3 equiv.) and mercuric trifluoroacetate (3 equiv.) in dry DCM at rt under nitrogen afforded the ethoxy mercurial **13a**. Reduction of **13a** with lithium borohydride in THF afforded **16a** in 85% yield after cleavage (Scheme 1). Treatment of **13a** with iodine[9] in THF afforded the iodo ether **15a**, which upon cleavage from the solid support afforded iodo ether **17a** in 90% yield. The ^1H NMR spectrum of **17a** revealed only two protons in the aromatic region that resonated as two singlets, not as two *meta*-coupled doublets, thereby supporting the proposed structure. The mass spectrum of **17a** also supported the presence of two iodine atoms. Unlike β-acetoxy mercurials,[10] β-hydroxy and β-alkoxy mercurials[11] have been employed in carbon–carbon bond forming reactions with moderate success, particularly using sodium trimethoxyborohydride[12] or sodium borohydride in the presence of a phase transfer catalyst, or in DMF[7] as the solvent. Treatment of the ethoxy mercurial **13a** with an excess of acrylonitrile under the standard conditions afforded only traces of the Giese adduct. The eugenol ether **1** was reacted in a similar fashion with 2-methoxyethanol to afford **16b** in 80% yield after reduction and cleavage. Treatment of **13b** with iodine in THF afforded **17b** in 90% yield. The Giese reaction did not proceed to yield any of the desired product with **13b** also (Scheme 1). Although C–C bond formation using alkoxy mercurial **13** failed, the iodo functionality present in **15** would allow C–C bond formation via a radical intermediate.

The polymer bound cinnamate ester **18** was converted to the ethoxy mercurial **19**, which was reduced with tributyltin hydride[13] in THF to afford β-alkoxy cinnamic acid **22** after cleavage. Iodination of **19** proceeded cleanly to afford a single product **23** after



Scheme 2. (a) 3.0 equiv. $Hg(OCOCF_3)_2$, 6.0 equiv. R^1R^2NH, THF, rt, 16 h; (b) 5.0 equiv. $NaBH_4$, DME, 0°C–rt, 16 h; (c) 8.0 equiv. $NaBH_4$, aq. 1N NaOH, 50 equiv. acrylonitrile, DME, 0°C–rt, 16 h; (d) 25% TFA, DCM, rt, 12 h, **11a** = 75%, **11b** = 70%, **12a** = 60%, **12b** = 50%.

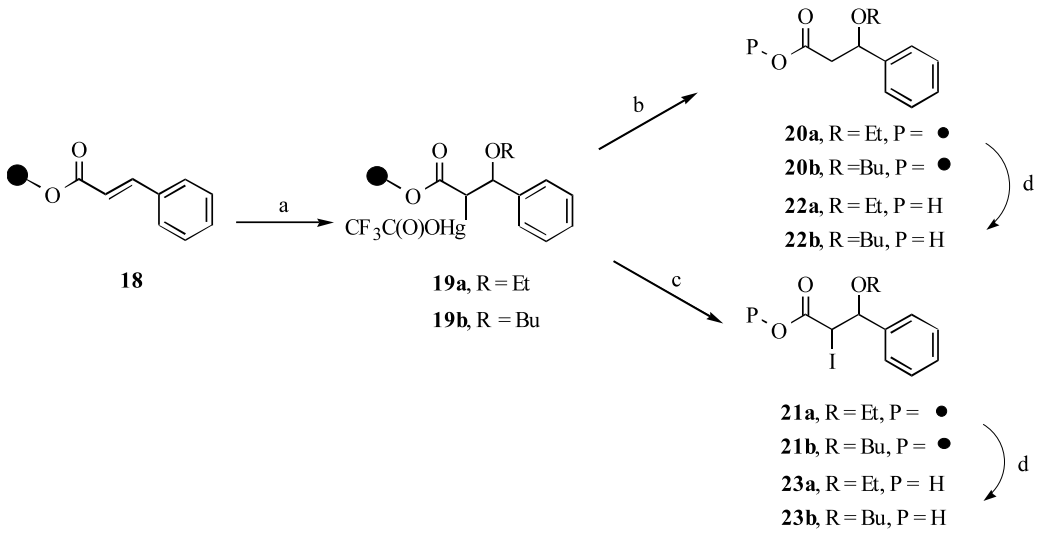
cleavage (Scheme 3). Since the radical generated from **21** is not nucleophilic, the Giese reaction was not attempted.

In summary, we have demonstrated alkoxy and amino mercuration on solid-phase using a limited number of examples. The organomercurials have been used successfully to access structurally diverse compounds through C–C bond forming reactions, halogenation and reduction.

Typical experimental procedure

Mitsunobu reaction: Wang resin (1. 25 g, 1.7 m eq./g), eugenol (1.72 g, 6.3 mmol, 3.0 equiv.) and PPh_3 (2.75 g, 6.3 mmol, 3.0 equiv.) were gently stirred in NMP (11 mL) for 15 min at 0°C under a nitrogen atmosphere. DEAD (1.82 g, 6.3 mmol, 3.0 equiv.) was added at 0°C and the mixture stirred at rt for 16 h. The resin was collected by filtration and washed successively with DMF (3×20 mL), dioxane (3×20 mL), DCM (3×20 mL), 1:1 DCM/MeOH (3×20 mL), MeOH (3×20 mL), DCM (3×20 mL) and finally with ether (3×20 mL). Resin **1** was dried in vacuo and used in the next step.

Amino mercuration: Mercuric trifluoroacetate (1.41 g, 3.3 mmol, 3.0 equiv.) and aniline (613 mg, 6.6 mmol, 6.0 equiv.) were added successively to the resin (820 mg, 1.35 m eq./g) suspended in THF (11 mL) and allowed to stir at rt for 16 h under nitrogen. The resin was filtered and washed as detailed earlier to afford resin **2a**.



Scheme 3. (a) 3.0 equiv. $Hg(OCOCF_3)_2$, 3.0 equiv. ROH, DCM, rt, 16 h; (b) 3.0 equiv. nBu_3SnH, THF, 0°C–rt, 16 h; (c) 3.0 equiv. I_2, THF, rt, 12 h; (d) 25% TFA, DCM, rt, 12 h, **22a** = 85%, **22b** = 70%, **23a** = 90%, **23b** = 90%.

Reduction: The above resin (180 mg, 0.75 m eq./g) was suspended in THF (2.50 mL) and $LiBH_4$ (0.36 mL, 2 M/THF) was added at −23°C under nitrogen. The reaction mixture was allowed to attain rt and allowed to stir for 16 h. The resin was filtered and subjected to the wash cycle as described earlier to afford **3a**.

Cleavage: The resin **3a** (145 mg) was treated with 25% TFA in DCM (2 mL) at rt for 16 h. The resin was filtered and washed thoroughly with DCM. The combined filtrates were evaporated and the residue dissolved in ethyl acetate and washed successively with satd aq. sodium bicarbonate, water, brine, dried over sodium sulfate and evaporated to afford **5a** (50 mg, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14 (m, 2H), 6.80 (d, $J=8.0$ Hz, 1H), 6.67 (m, 2H), 6.60 (m, 3H), 5.40 (bs, 1H), 3.83 (s, 3H), 3.75 (m, 1H), 2.80 (dd, $J=10.6$, 8.5 Hz, 1H), 2.70 (dd, $J=10.6$, 5.3 Hz, 1H), 1.06 (d, $J=6.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 146.4, 144.3, 130.1, 129.3, 122.3, 117.8, 114.3, 114.0, 112.1, 55.9, 50.0, 41.7, 20.1. m/z (EI) 257, 183.

C–C bond formation: Resin **3a** (180 mg, 0.75 m eq./g) was suspended in DME and cooled to 0°C. Acrylonitrile (0.8 mL, 12 mmol, 50 equiv.) was added. Sodium borohydride (71 mg, 1.92 mmol, 8.0 equiv.) dissolved in 1N NaOH (1.92 mL) was added dropwise at 0°C under nitrogen. The reaction mixture was allowed to attain rt and stirred for 16 h. The resin was filtered and washed as before to afford resin **4a**.

The resin **4a** was cleaved as was resin **3a** to afford the amino nitrile **6a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20–7.10 (m, 2H), 6.85–6.52 (m, 6H), 5.37 (bs, 1H), 3.82 (s, 3H), 3.66 (m, 1H), 2.85–2.75 (m, 2H), 2.35 (t, $J=6.8$ Hz, 2H), 1.85–1.50 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.5, 144.4, 129.4, 122.2, 119.3, 117.5, 114.4, 113.3, 112.2, 55.9, 53.1, 39.9, 33.2, 22.4, 17.0. m/z (EI) 310, 270, 235.

Alkoxy mercuration: Resin **18** was prepared in the same way as resin **1**.

Reduction: The above resin (142 mg, 0.94 m eq./g) was suspended in toluene (1.6 mL) and tributyltin hydride (0.1 mL, 0.39 mmol, 3.0 equiv.) was added at 0°C under nitrogen. The reaction mixture was allowed to attain rt gradually overnight. The resin was filtered and washed as detailed earlier to afford resin **20a**.

Cleavage from the solid-support using 25% TFA–DCM afforded **22a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.20 (m, 5H), 4.74 (dd, $J=9.4$, 4.7 Hz, 1H), 3.40 (q, $J=7.0$ Hz, 2H), 2.80 (dd, $J=12.9$, 9.4 Hz, 1H), 2.60 (dd, $J=12.9$, 4.7 Hz, 1H), 1.20 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 140.9, 128.6, 128.0, 126.4, 77.8, 64.5, 43.4, 15.0. m/z (EI) 194, 165, 149.

Iodination: The resin **18** (295 mg, 0.94 m eq./g) was suspended in dry THF (3 mL) and stirred at rt for 5 min. Iodine (205 mg, 0.8 mmol, 3.0 equiv.) in THF (1 mL) was added to the resin dropwise at rt under nitrogen and allowed to stir at the same temperature for a further 12 h. The resin was filtered and washed to afford **21a**. Cleavage afforded iodo ether **23a**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.50 (d, $J=9.4$ Hz, 1H), 4.40 (d, $J=9.4$ Hz, 1H), 3.38 (q, $J=7.0$ Hz, 2H), 1.18 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 137.2, 128.9, 128.7, 128.4, 81.1, 65.0, 26.8, 14.9. m/z (EI) 193, 164.

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