# New Solid Phase Triorganogermanium Hydrides for Radical Synthesis

W. Russell Bowman,*[a] Sussie L. Krintel,[a] Mark B. Schilling[b]

[a] Department of Chemistry, Loughborough University, Loughborough, Leics. LE11 3TU, UK
Fax +44(1509)223925; E-mail: w.r.bowman@lboro.ac.uk

[b] Process Development, GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK

*Received 16 December 2003*

**Abstract:** New solid phase triorganogermanium hydrides have been synthesized by the addition of a simple triorganogermanium hydride unit onto Quadragel™ and Merrifield resins. The new solid phase germanium hydrides have been used to mediate a range of synthetic radical reactions.

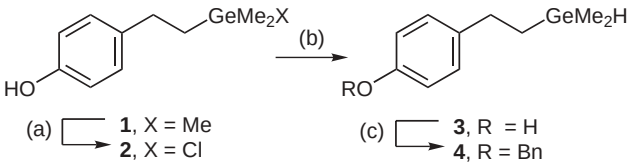
**Key words:** solid-phase synthesis, triorganogermanium hydride, radicals, radical reactions, triorganogermanium radicals

As part of our studies towards developing the use of triorganogermanium hydrides to replace the toxic tributyltin hydride ($Bu_3SnH$) as radical generating reagents, we report our initial studies of robust and easy to prepare solid phase triorganogermanium hydrides. The application of solid phase to radical reactions is a new and growing area of interest.[1] The use of a solid phase reagent to replace $Bu_3SnH$ has a number of important advantages. Firstly, the radical reagent is held on the resin, thereby facilitating easy purification of products, a notorious problem for $Bu_3SnH$-mediated radical reactions. Secondly, although triorganogermanium compounds have low toxicity,[2] the attachment to solid phase will help obviate organogermanium impurities in the products of radical reactions.

Several solid phase triorganotin hydride resins have been developed[1,3] but only one example of a solid phase germanium hydride has been reported.[4] Diethylgermanium dichloride was used for adding the germanium moiety. The resins were used synthetically for reducing alkyl and aryl halides and showed good recyclability.

We considered that the best protocol would involve attaching an easily prepared triorganogermanium moiety to the solid phase resin so that once attached, the resin would be ready for carrying out radical reactions without further modification.

To this end, we adapted the 'traceless' germanium linker developed by Spivey.[5] The germanium hydride moiety **3** was synthesized in high yielding steps (Scheme 1). The trimethylgermane **1** was prepared in three steps using the procedure of Spivey.[5] The conversion of the trimethylgermane **1** to the dimethylgermanium chloride **2** gave impure products. Difficulty in purification of **2** was obviated by not isolating the product and reducing directly to yield the required germanium hydride **3**. The germanium hydride **3** was stable with good shelf life and proved useful as a radical generating species in its own right.

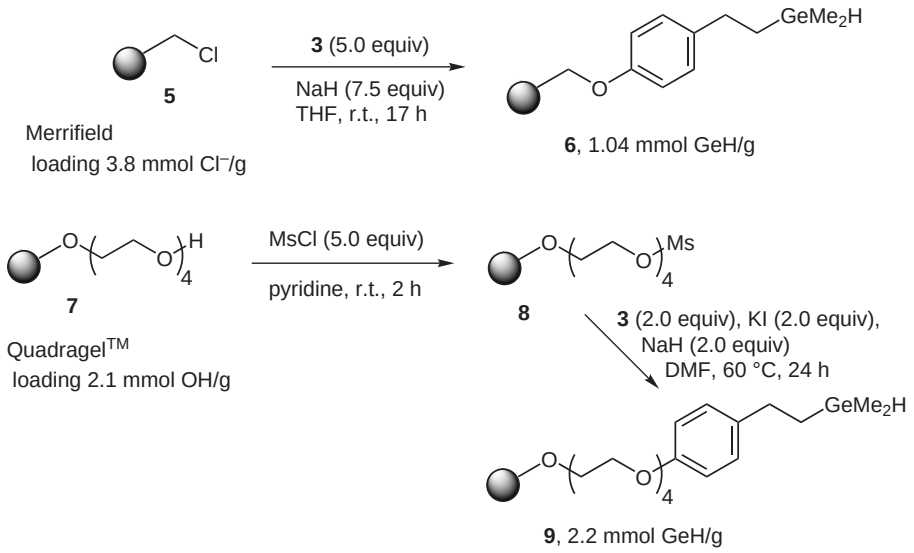



**Scheme 1** Synthesis of the organogermanium moiety for solid phase usage. *Reagents and conditions*: (a) $SnCl_4$, $MeNO_2$, 50 °C, 18 h, not isolated. (b) $NaBH_4$ (2.0 equiv), MeOH, r.t., 7 h, 67% over two steps. (c) NaH, BnBr, THF, reflux, 3 h, 87%.

Initially, several standard radical reactions were tested with the germanium hydrides **3** and **4** to determine whether these moieties would act as radical mediators, so that once attached to the resins, we could be certain of steric and reactivity factors (Table 1). The hydride **4** was prepared as a more accurate model for the solid phase reagent. Both germanium hydrides **3** and **4** gave good yields of radical deoxygenation of the thiocarbonyl-imidazolide ester of glucofuranose **10** in a Barton–McCombie reaction[6] and moderate yields in the cyclisation of the α-chloroamide **14**.[7] The yields of the 3-deoxy glucofuranose **11** (94% and 91% respectively) were comparable to the yield (87%) we obtained using $Bu_3GeH$.[8] Similarly, the yields of the γ-lactam **16** (47% for both reactions) were also comparable to our earlier studies with $Bu_3GeH$.[8] These results confirmed our prediction that our germanium hydride moiety would show comparable activity to $Bu_3GeH$ on the solid phase resins.

The germanium hydride moiety **3** was loaded onto Merrifield resin **5** and Quadragel™ **7** (Scheme 2) to deliver good loadings of GeH. The resins were 'swollen' in toluene and the germanium hydride moiety **3** added by standard methodology. The Quadragel™ was first converted into the mesylate **8** prior to loading. The resins were analyzed by FTIR and $^1H$ and $^{13}C$ NMR spectroscopy. The Ge–H stretching frequency was observed at $\nu_{max}$ 2030 $cm^{-1}$ for **6** and 2028 $cm^{-1}$ for **9**. The value for $Bu_3GeH$ is 2006 $cm^{-1}$.[8] The germanium hydrogen which appears as a septet in the $^1H$ spectrum at $\delta$ = 3.68 ppm for $Bu_3GeH$ could not be observed. The loadings were calculated by weight difference after drying and should be regarded as approximate due to the inaccuracy in the use of small amounts of resins (ca. 5 g). The resins did not appear to lose efficacy with storage.

***SYNLETT*** 2004, No. 7, pp 1215–1218
Advanced online publication: 10.05.2004
DOI: 10.1055/s-2004-825585; Art ID: D29503ST




**Scheme 2** Synthesis of solid phase germanium hydrides

We carried out representative radical reactions to show the efficacy of solid phase germanium hydrides, i.e. generation of alkyl, vinyl and aryl radicals in cyclisation reactions and deoxygenation, using radical addition to the sulfur of the thiocarbonyl group of thiocarbonyl imidazolides, in the Barton–McCombie reaction. The results are shown in Table 1.

We initially carried out the reactions by rotation of the reaction mixture at 85 °C [with the α-bromoamide **15** and 2-iodo-1-(prop-2-enyloxy)benzene (**18**)] to avoid damage to the resin beads. This temperature was not high enough to facilitate the radical reactions and almost no reaction took place. The latter compound was reacted at a higher temperature (95 °C rising to 110 °C) which gave a 26% yield of the cyclised product. Finally, at reflux a high yield (78%) was obtained which compares with the reaction using $Bu_3GeH$ (91%).[8] Gentle heating under reflux did not damage the beads.

The Barton–McCombie deoxygenation of the thiocarbonyl imidazolide ester cholesterol **12** gave a good yield (68%) with the Quadragel™-germanium hydride **9.** In contrast, the deoxygenation of the glucopyranose with the Merrifield-germanium hydride **6** the yield (36%) was lower, especially as compared to the 'unattached' germanium hydrides **3** and **4**.

In the cyclisation of the α-bromoamide **15**, the best yield was obtained with the Quadragel™-germanium hydride **9**. In general, the Quadragel™-germanium hydride gave better results than the Merrifield-germanium hydride. The results again compare with those of $Bu_3GeH$ and $Bu_3SnH$.[8] The best results for this reaction have been obtained with syringe pump addition of $Bu_3GeH$ and $Bu_3SnH$.[7]

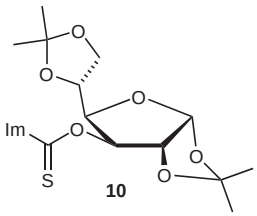
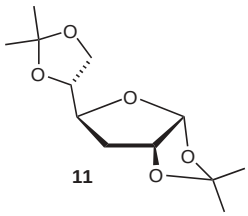
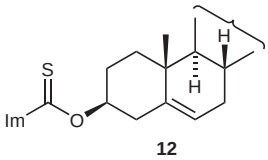
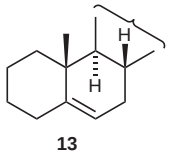
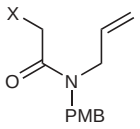
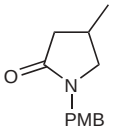
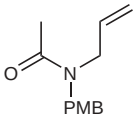
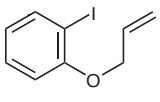
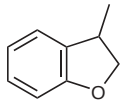
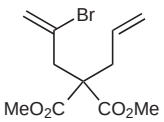
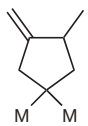
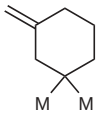
When $Bu_3GeH$ and $Bu_3SnH$ were added only at the beginning of the reaction, more cyclisation relative to reduction to **17** was obtained for $Bu_3GeH$ than $Bu_3SnH$. This is expected because the Ge–H bond is stronger than the Sn–H bond and rates of abstractions are slower allowing more time for cyclisation. Significantly, the solid phase germanium hydrides yield no uncyclised reduced product **17** indicating that the polymer supported germanium hydrides exhibit a dilution effect. This factor could be important in future use of solid phase germanium hydrides for radical cyclisations.

Lastly, in order to test the applicability of our reagents for generating vinyl radicals, we studied the vinyl bromide **20**.[8,9] The 6-membered ring product **22** results largely from rearrangement of the 5-*exo* radical intermediate. This results from the slow rate of H-abstraction from the germanium hydride by the 5-*exo* intermediate allowing time for the rearrangement.

For the cyclisation of the vinyl radical generated from **20**, we checked the competition between the 5-*exo* and 6-*endo* products by using polarity reversal catalysis (PRC) with phenylthiol.[8,10] The PhSH rapidly intercepts the 5-*exo* radical to give only the 5-*exo* product **21** (30% with no 6-*endo* product) before **21** is able to undergo a neophyl rearrangement to **22**.[8,9] The resulting phenylthiyl radical (PhS·) is electrophilic and undergoes rapid reaction with the nucleophilic germanium hydride to complete the chain reaction. The moderate yields are possibly caused by addition of the intermediate germanium radicals to the *gem*-disubstituted alkenes of the products to give triorganogermanium adducts via stable tertiary radical intermediates. With $Bu_3GeH$ this causes considerable problems of purification. This is obviously a drawback for radical reactions, which yield disubstituted alkenes as products. However, with the Quadragel™-germanium hydride and PRC, the adducts remain attached to the resin and only one pure product **21** is formed, albeit in 30% yield. These problems need to be further addressed in future.

Our initial results indicate that solid phase germanium hydrides show promise for carrying out radical reactions and can facilitate a clean and simple methodology. Further

**Table 1** Radical Reactions Using Triorgano-Germanium Hydride

| Precursor, Germanium-hydride | Products, Yields | Conditions[a] |
|---|---|---|
|  **10** |  **11** | |
| **3** (3.0 equiv) | **10** (0%), **11** (94%) | ACCN,[b] reflux, 2 h |
| **4** (3.3 equiv) | **10** (0%), **11** (91%) | ACCN, reflux, 8 h |
| **6** (1.3 equiv) | **10** (0%), **11** (36%) | ACCN, reflux, 7 h |
|  **12** |  **13** | |
| **9** (4.4 equiv) | **12** (0%), **13** (68%) | ACCN, reflux, 17 h |
|  **14**, X = Cl<br>**15**, X =Br |  **16**  **17** | |
| **14**; **3** (1.2 equiv) | **14** (18%), **16** (47%), **17** (trace) | ACCN, reflux, 8 h |
| **14**; **4** (1.1 equiv) | **14** (trace), **16** (47%), **17** (3%) | ACCN, reflux, 8 h |
| **15**; **6** (0.5 equiv) | **15** (66%), **16** (30%),[c] **17** (0%) | ACCN, reflux, 9 h |
| **15**; **6** (0.5 equiv) | **15** (55%), **16** (35%),[c] **17** (0%) | ACCN, reflux, 24 h |
| **15**; **9** (2.5 equiv) | **15** (ca. 100%), **16** (trace), **17** (0%) | AIBN, 85 °C, 17 h |
| **15**; **9** (2.6 equiv) | **15** (0%), **16** (57%), **17** (0%) | AIBN, reflux, 19 h |
|  **18** |  **19** | |
| **9** (3.0 equiv) | **18** (ca. 100%), **19** (trace) | AIBN, 85 °C, 4 h |
| **9** (3.5 equiv) | **18** (28%), **19** (26%) | AIBN, 95–110 °C, 20 h |
| **9** (3.6 equiv) | **18** (0%), **19** (78%) | AIBN, reflux, 16 h |
|  **20** |  **21**  **22** | |
| **9** (4.0 equiv) | **20** (25%), **21** (19%), **22** (14%) | AIBN, reflux, 19 h |
| **9** (4.0 equiv) | **20** (0%), **21** (30%), **22** (0%) | AIBN, reflux, 4 h, PhSH (0.1 equiv) |

[a] Toluene was used for swelling the resin and for the reaction.
[b] ACCN = 1,1′-Azobis(cyclohexanecarbonitrile).
[c] The % yield was calculated based on **6**.

studies are underway to optimize the conditions for use of the solid phase Ge species as radical mediators and in particular to investigate recycling and shelf life in order to lower the cost.

**Quadragel™-Germanium Hydride 19**: Quadragel™ mesylate **8** (5.0 g, ca. 11 mmol) was swollen in toluene (70 mL). 4-(2-Dimethylgermylethyl)phenol (**3**, 5.02 g, 22.3 mmol), sodium hydride (0.90 g, 22.4 mmol) and KI (3.72 g, 22.4 mmol) were added and the suspension rotated at 60 °C for 24 h. The reaction was cooled to r.t., quenched with aq THF and the resin removed by filtration and washed with aq THF, THF and MeOH. The resin was dried in vacuo overnight to yield a dark brown polymer **9** (6.97 g, equivalent to a loading of 2.2 mmol GeH/g). IR (KBr): 3379, 2929, 2028, 1658, 1606, 1196, 1056 $cm^{-1}$. $^1H$ NMR (250 MHz): δ = 0.17–0.36 (br, Me, $CH_2Ge$), 1.31–1.54 (br s, PS-$CH_n$), 2.48 (br s, C$H_2$Ar), 3.42–4.20 (br s, $OCH_2CH_2O$), 6.56-7.04 (br s, Ph-H, Ar-H). $^{13}C$ NMR (100 MHz): δ = 4.7 (Me), 16.7 ($CH_2Ge$), 31.5 ($CH_2Ar$), 40.0-44.8 (Ph-$CH_n$), 67.8 ($CH_2O$), 70.2–71.0 ($OCH_2$), 115.0 (Ph-2,6-C, Ar-2,6-H), 126.0–127.9 (PS-Ph*C*H), 129.1 (Ar 3,5-C), 137.3 (Ar-C) and 157.2 (Ar-C).

**Cyclisation of 2-Iodo-1-(propen-2-yloxy)benzene (18):** Quadragel™-germanium hydride **9** (0.34 g, 0.75 mmol) was swollen in anhyd toluene (12 mL); 2-iodo-1-(prop-2-enyloxy)benzene (54.0 mg, 0.21 mmol) and AIBN (0.12 g, 0.73 mmol) were added and the mixture was heated under reflux for 16 h. After cooling to r.t., the resin was removed by filtration and washed with $CH_2Cl_2$ several times. Evaporation of the filtrate gave the crude cyclic product as a yellow oil. The yield of 3-methyl-2,3-dihydrobenzofuran (**19**) was 22 mg (78%). $^1H$ NMR (250 MHz): δ = 1.33 (d, *J* = 7.4 Hz, 3 H, Me), 3.47–3.62 (m, 1 H, 3-H), 4.07 (dd, *J* = 7.4, 8.8 Hz, 1 H, 2-$H_a$), 4.68 (dd, *J* = 8.8, 8.8 Hz, 1 H, 2-$H_b$), 6.77–6.89 (m, 2 H, Ar-H), 7.08–7.17 (m, 2 H, Ar-H). $^{13}C$ NMR (62.5 MHz): δ = 20.1 (Me), 37.2 (3-C), 31.5 ($CH_2Ar$), 79.1 (2-C), 110.1 (Ar-*C*H), 121.1 (Ar-*C*H), 124.4 (Ar-*C*H), 128.6 (Ar-*C*H), 132.9 (3a-C), 160.3 (7a-C). MS (EI): *m*/*z* (%) = 134 (84), 119 (95), 91 (100). The data were identical to those of the authentic material.[11]

## Acknowledgment

We thank GlaxoSmithKline and Loughborough University for a postgraduate studentship (SLK), GlaxoSmithKline for generous support, Drs Alan Spivey and Ratnosothy Srikaran for helpful advice and the EPSRC Mass Spectrometry Unit, Swansea University, Wales for mass spectra.

## References

(1) Ganesan, A. In *Radicals in Organic Synthesis*, Vol. 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**, Chap. 1.5, 81.
(2) (a) Craig, P. J.; Van Elteren, J. T. In *The Chemistry of Organic Germanium, Tin and Lead Compounds*; Patai, S., Ed.; Wiley: Chichester, **1995**, Chap. 16, 843. (b) Lukevics, E.; Ignatovich, M. In *The Chemistry of Organic Germanium, Tin and Lead Compounds*; Patai, S., Ed.; Wiley: Chichester, **1995**, Chap. 17, 857.
(3) (a) Enholm, E. J.; Schutte, J. P. *Org. Lett.* **1999**, *1*, 1275. (b) DuMartin, G.; Pourcel, M.; Delmond, B.; Donard, O.; Pereyre, M. *Tetrahedron Lett.* **1998**, *39*, 4663.
(4) Mochida, K.; Sugimoto, H.; Yokoyama, Y. *Polyhedron* **1997**, *16*, 1767.
(5) (a) Spivey, A. C.; Turner, D. J.; Turner, M. L.; Yeates, S. *Synlett* **2004**, 111. (b) Spivey, A. C.; Srikaran, R.; Diaper, C. M.; Turner, D. J. *Org. Biomol. Chem.* **2003**, *1*, 1638. (c) Spivey, A. C.; Turner, D. J.; Turner, M. L.; Yeates, S. *Org. Lett.* **2002**, *4*, 1899. (d) Spivey, A. C.; Diaper, C. M.; Adams, H. *J. Org. Chem.* **2000**, *65*, 5253. (e) Spivey, A. C.; Diaper, C. M.; Rudge, A. J. *Chem. Commun.* **1999**, 835.
(6) (a) Motherwell, W. B.; Crich, D. *Free Radical Reactions in Organic Synthesis*; Academic Press: London, **1991**. (b) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(7) Gilbert, B. C.; Kalz, W.; Lindsay, C. I.; McGrail, P. T.; Parsons, A. F.; Whittaker, D. T. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1187.
(8) Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.* **2004**, 585.
(9) Gómez, A. M.; Company, M. D.; Uriel, C.; Valverde, S.; López, C. J. *Tetrahedron Lett.* **2002**, *43*, 4997; and references therein.
(10) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.
(11) Bhandal, H.; Patel, V. H.; Pattenden, G.; Russell, J. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2691.