ORGANIC
LETTERS

1999
Vol. 1, No. 5
689−691

An Allylstannane Reagent on Non-Cross-Linked Polystyrene Support

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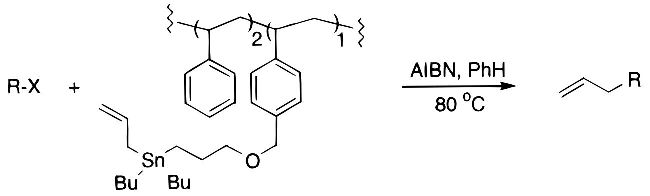
Received April 22, 1999

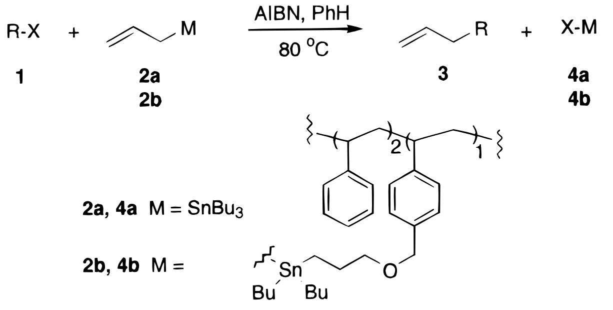
ABSTRACT



A new allylstannane reagent on non-cross-linked polystyrene was developed for the first time. This support differs markedly from standard cross-linked polymers because it is completely soluble in organic solvents; moreover, the reactions can be conveniently monitored directly by standard ^{1}H NMR methods. The allylstannane underwent a free radical reaction with an alkyl halide to form a new allyl appendage. Tin byproducts can be easily recovered from cold methanol as white crystalline solids.

The free radical reaction of allylstannanes with alkyl halides is an excellent and frequently utilized reaction for the formation of carbon−carbon bonds in organic synthesis.[1] In this reaction, the allyl group in **2a** readily replaces an organohalide or another homolytic function X in **1**, under neutral nonpolar conditions to give **3**, as shown in Scheme 1. The reaction is stereoselective and tolerates a variety of other functionalities present in **1**.[1b] One of the great remaining difficulties with allylstannane reactions, which has not been adequately addressed, is the removal of the tin halide **4a** and tin byproducts at the end of the reaction.[2]

Scheme 1



In this communication, an allylstannane moiety was tethered to soluble polystyrene support **2b** and the free radical transfer of an allyl unit to alkyl halides was investigated. This soluble polymer support for liquid-phase organic chemistry (LPOC) differs markedly from the standard 1−2% divinylbenzene cross-linked polymers currently used in solid-phase organic chemistry (SPOC).[3,4] The use of non-cross-linked polystyrene allows for the complete organic solubility (EtOAc, benzene, $CHCl_3$, CH_2Cl_2, and THF) of each product

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(1) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. (c) Webb, R. R.; Danishefsky, S. *Tetrahedron Lett.* **1983**, 1357. (d) Keck, G. E. Kachenski, D. F.; Enholm, E. J. *J. Org. Chem.* **1984**, *49*, 1462.

(2) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200. (b) Light, J.; Breslow, R. *Tetrahedron Lett.* **1990**, *31*, 2965. (c) Clive, D. L.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607. (d) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531. (e) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4.

(3) For a review see: Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.

(4) (a) Green, B.; Garson, L. R. *J. Chem. Soc. C* **1969**, 401. (b) Narita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1477. (c) Narita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1299. (d) Narita, M.; Itsuno, S., Hirata, M.; Kusano, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1477. (e) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, 3943. (f) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724.

10.1021/ol990613k CCC: $18.00

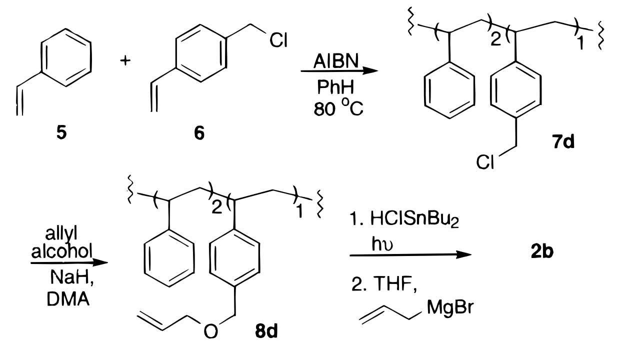
in the synthesis and in subsequent free radical reactions of the allylstannane reagent.[4e] Because a single phase is utilized with non-cross-linked polystyrene, the reactions have rates up to 100 times faster than with standard cross-linked solid-phase methods.[4d,5] Moreover, the reactions can be conveniently monitored by standard ^{1}H NMR spectroscopy without cleavage from polymer support.[3] Intermediate products used to prepare the allylstannane reagent and the tin halides obtained after the radical reaction are obtained as white crystalline solids filtered from cold methanol.

An optimization study of the loading capacity of the polymer revealed that a 2:1 ratio of styrene to *p*-(chloromethyl)styrene functioned best in these experiments and allowed for a concentrated number of reactive sites on the polymer, exceeding standard SPOC supports. Allyltin reagent **2b** reacted with several electronically deficient carbon-centered free radical centers and was regioselective in dihalides where two reactive sites were present in the same substrate. Another important aspect of these studies is that this work represents the first time an allylstannane has been covalently linked to a polymer support, to the best of our knowledge.[6]

We began these studies by investigating several concentrations and loading capacities for the polymer backbone. It was our intention to prepare a polymer with the most concentrated sites for attachment of the allyl tin. Janda's previous work with non-cross-linked polystyrene indicated that a 0.3 mmol/g (3%) loading capacity polymer functioned well in a total synthesis of prostaglandin $F_{2\alpha}$.[4e,f] Although this loading capacity was sufficient and possibly ideal for that work, our efforts focused on maximizing the amount of loading sites in the soluble polymer. This increases the density of reactive sites available and allows less polymer to be used in the reactions.

The precursors for the preparation of **7d** are inexpensive and allow the polymer to be "tailor-made" by the user via varying the number of reactive sites desired, as shown in Scheme 2. Thus, a study was conducted to explore the different loading capacities of the non-cross-linked soluble polymer. A simple free radical reaction was utilized to prepare **7a**–**e**, by varying the amounts of **5** and **6** and investigating the increase in the reactive sites on the polymer backbone (i.e. loading capacity) from 3 to 50%.[4d]

Scheme 2



The resulting polymers were then reacted with allyl alcohol anion (Scheme 2) to obtain **8a**–**e** and the loading capacity of the soluble polystyrene and the loading efficiency of the displacement. Through NMR integration analysis, the efficiency of the displacement was calculated as shown in Table 1. Up to a maximum of 33% loading capacity on the polymer backbone, all substrates functioned well; however, at concentrations greater than 33%, the polymer becomes gelatinous and intractable and loses its ability to readily crystallize from cold methanol. It appears that a practical balance of 33% active sites is struck between trying to achieve the largest number of reactive sites with the best crystallization properties of the polymer itself.

Table 1. Increased Loading Capacity of the Non-Cross-Linked Polystyrene

Loading Capacity:	3%	15%	27%	33%	50%
5 (equiv.)	32	6.5	3.2	2	1
6 (equiv.)	1	1	1	1	1
Non-Cross-Linked Polymer	**7a**	**7b**	**7c**	**7d**	**7e**
Allyl Alcohol					
% displacement	>99	93	92	>99	98
Allyl Ether	**8a**	**8b**	**8c**	**8d**	**8e**

The polystyrene-supported allyltin reagent was prepared by hydrostannylation of the allyl ether in **8d** using the method of Imori in 90% yield, shown in Scheme 2.[7] The disappearance of the olefin was readily monitored by ^{1}H NMR. The polymer-bound tin chloride was then treated with allylmagnesium bromide, which afforded the desired allyltin reagent **2b** in 85% yield.

Table 2 shows the free radical reaction of **2b** with several alkyl halides. Electron-poor substrates containing an α-bromo carbonyl functioned best. Electron-rich alkyl halides (i.e. bromodecane) did not undergo reaction, and only starting materials were recovered. It is interesting to note that hindered tertiary bromide **13** does not react at all with allyltributyltin (**2a**) but does react with **2b** to give **14** in 50% yield.[8] Allyl product **14** formed in this case due to the increased nucleophilicity of allylstannane **2b**.

Dihalides in entries 5 and 6 were regioselective in the free radical allylation reaction, producing **18** and **20** in 66 and 68% yields, respectively. No other allylstannane reagents show this type of regioselectivity, displaying a strong preference for an electron-deficient radical.

Because free radical reactions often have polarity preferences, allyltin reagent **2b** is electron-rich and prefers to react

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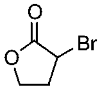
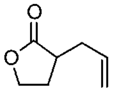
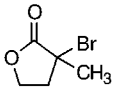
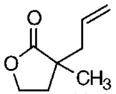
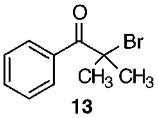
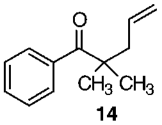
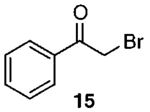
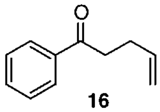
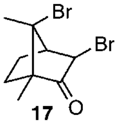
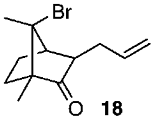
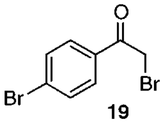
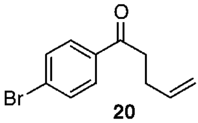
(5) Maher, J. B.; Furey, M. E.; Greenberg, L. J. *Tetrahedron Lett.* **1971**, 27.

(6) For examples of tin hydride reagents mounted on insoluble cross-linked polystyrene, see: (a) Weinshenker, N. M.; Crosby, G. A.; Wong, J. Y. *J. Org. Chem.* **1975**, *40*, 1966. (b) Dumartin, G.; Pourcel, M.; Delmond, B.; Donard, O.; Pereyre, M. *Tetrahedron Lett.* **1998**, 4663. (c) Gerlach, M.; Jordens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, *56*, 5971.

(7) Imori, T.; Lu, V.; Cai, H. Tilley, T. D. *J. Am. Chem. Soc.* **1995**, *117*, 9931.

(8) (a) Bromides **9** and **15** react with **2b** to give **10** (85%) and **16** (78%), respectively. (b) Li, X.; Chen, J. J.; Tanner, D. D. *J. Org. Chem.* **1996**, *61*, 4314.

Table 2. Radical Allylations of **2b**

Entry	Substrate	Time (h)	Product	Yield
1	 **9**	4	 **10**	73%
2	 **11**	12	 **12**	73%
3	 **13**	48	 **14**	50%
4	 **15**	12	 **16**	68%
5	 **17**	12	 **18**	66%
6	 **19**	2	 **20**	68%

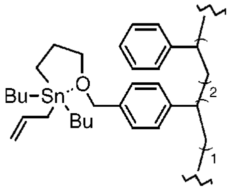


Figure 1. Chelated allylstannane **2b**.

with electron-poor radicals. To explain these results, we propose the chelation effect shown in Figure 1.

Allylstannane reagent **2b** on non-cross-linked polystrene and allyltributyltin **2a** were compared for tin pollution in a typical free radical reaction.[6b] Bromide **15** was reacted with each tin reagent, and the allyl product **16** in both cases was carefully isolated by column chromatography. Compound **16** was dissolved in nitric acid and tested for parts per million of tin using ICP-MS, and each product mixture was tested twice. The first run gave 6.9 (±0.3) and 53 (±1.0) ppm, while the second run gave 15.6 (±0.2) and 79 (±0.7) ppm for the reactions of **2b** and **2a**, respectively. This study clearly demonstrates the effectiveness of removing the tin byproducts by crystallization from cold methanol.

In summary, free radical allylation reactions using non-cross-linked polystyrene are cleaner and less polluting than those using allyltributyltin. The polymer support used in these studies has benefits over standard cross-linked polystyrene, particularly in ease of analysis by ^{1}H NMR. Compounds are readily recovered by crystallization. Efforts are currently underway to apply this support to other free radical reactions.

Acknowledgment. We gratefully acknowledge support by the National Science Foundation (Grant CHE-9708139) for this work. We also thank B. W. Smith, E. E. Austin, and the NSF Engineering Research Center for Particle Science and Technology at the University of Florida for the ICP-MS results.

Supporting Information Available: General procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990613K