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Intermolecular Free Radical Reactions on Solid Support. Allylation of Esters

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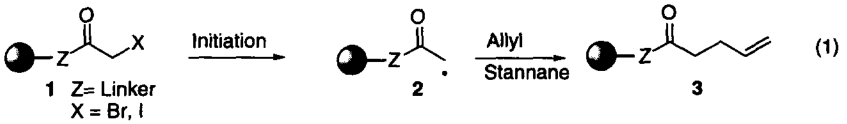
Abstract: The first examples of intermolecular free radical allylation reactions on solid support are reported. The allylation proceeds in good chemical efficiency with a variety of substrates as well as allylating agents. Control experiments indicate that the polymer matrix is inert to the reaction conditions. © 1997 Elsevier Science Ltd.

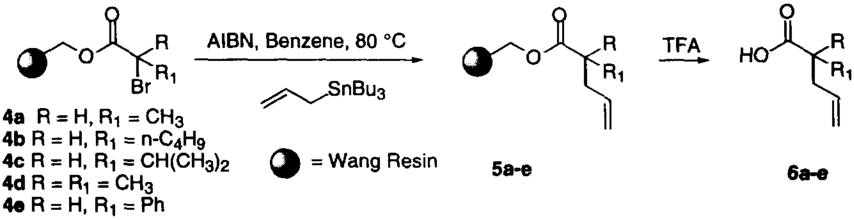
Combinatorial chemistry has emerged as a powerful technology for the rapid development of lead compounds in the pharmaceutical industry and several other disciplines.[1] Because of this new impetus, there has been a wide variety of solution phase organic reactions that have been successfully extended to substrates anchored to a polymer support.[2] Reactions that have been studied extensively on solid support include amide synthesis, aromatic substitutions, cross-coupling reactions, condensations, cycloadditions, Grignard reactions, Michael additions, olefinations, oxidations, and reductions. By comparison, radical reactions on polymer supports remain relatively unexplored.[3] In conjunction with our studies on solution-phase free radical chemistry,[4] we became interested in the viability of these processes on solid support (eqn 1).



(1)

The reaction that we chose to study was the free radical allylation[5] of α-bromoesters on a solid support (4) using allyl tributyltin (eqn. 2). A model substrate, 2-bromopropionate, anchored to several supports such as chloromethyl polystyrene, 4-hydroxy polystyrene, etc., was initially evaluated in the allylation reaction and found to be not very chemically efficient. A modified chloromethyl polystyrene, Wang resin,[6] proved to be the support of choice. Thus a series of substrates were prepared by treating the pre-swelled Wang resin in THF at -78 °C with n-BuLi (2.2 eq.) and quenching the resulting alkoxide with the corresponding α-bromo acid bromide or acid chloride to produce the esters **4**.[7] Loadings were typically 80-85%.[8] Loading analysis was carried out by hydrolytic cleavage of the α-bromo acid from the resin using 80/20 TFA/$CHCl_3$ and isolating the resulting α-bromo acid. With the substrates in hand, the allylations of these substrates was investigated (eqn 2). The results are tabulated in Table 1. Refluxing the bromoesters **4a-e** in benzene with 10 equivalents of allyl tributyltin and 3-4 equivalents of AIBN as an initiator for 14 hours gave the allylated products **5a-e**. After completion, the resin was filtered and washed (methylene chloride, acetic acid followed by methanol) and cleavage of the resin (TFA/chloroform) gave the product acids **6a-e** in 58-76% isolated yields. Reducing the amount of either allyl stannane[9] or AIBN led to lower chemical efficiency. Use of allyl triphenyltin as the allylating agent gave similar chemical yields (for example, **4b** gave 78% of **6b**, not shown in Table 1). In an effort to lower the reaction temperature, radical reaction at room temperature using Et_3B/O_2 as the radical initiator was examined. Unoptimized results from these experiments indicate that the desired reactions do occur, however, they do not go to completion.

As can be discerned from the table, secondary as well as tertiary bromides underwent allylation in moderate to good yields (Table 1, compare entries 1-3 with 4). The yields[10] for allylation using allyl tributyltin are good for simple and branched aliphatic substrates. The yield for the acid **6e** containing a phenyl group is also very satisfactory.[11]



4a $R = H, R_1 = CH_3$
4b $R = H, R_1 = n\text{-}C_4H_9$
4c $R = H, R_1 = CH(CH_3)_2$
4d $R = R_1 = CH_3$
4e $R = H, R_1 = Ph$

5a-e

6a-e

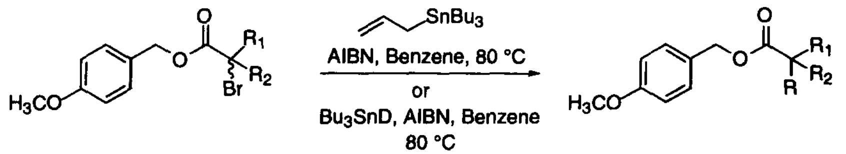
(2)

Table 1. Radical allylation using Allyltributyl stannane[a]

Entry	Substrate	Product	Yield of Acid, %[b]
1	**4a**	**6a**	63
2	**4b**	**6b**	76
3	**4c**	**6c**	63
4	**4d**	**6d**	58
5	**4e**	**6e**	76

[a] The allylation reactions were done with AIBN (3-4 eqs.) as the radical initiator and 10 eq. of the allyltin reagent in benzene as solvent at 80 °C. [b] Isolated Yield.

The allylation of model substrates **7a,b** were examined to compare solution-phase with solid-phase reactions as well as to determine whether hydrogen atom transfer was occurring inter- or intramolecularly from the benzylic sites or from the polymer backbone (eqn 3). Allylation of **7a,b** under standard conditions gave **8a,c** in 92% and 71% yield respectively. The chemical yields for the resin supported substrates **4b** and **4d** are only slightly lower than that for the solution-phase reaction (**6b** vs **8a** = 76% vs 92%; **6d** vs **8c** = 58% vs 71%) indicating that the reaction characteristics are similar for both sets. The stability of the polymer matrix to the reaction conditions was also evaluated. For instance, reduction of **7b** and **4d** with tributyltin deuteride gave ~94% and 93% deuterium incorporation respectively indicating that at best <7% of hydrogen atom transfer may occur from the polymer backbone.[12]

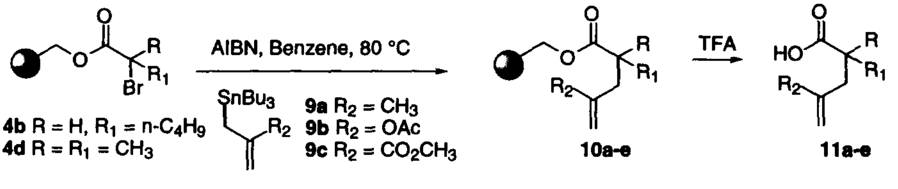


(eqn 3)

7a $R_1 = H$, $R_2 = C_4H_9$
7b $R_1 = R_2 = CH_3$

8a R = Allyl, $R_1 = H$, $R_2 = C_4H_9$, 92 % yield
8b R = D, $R_1 = H$, $R_2 = C_4H_9$, 78% yield, 93 ± 2%D
8c R = Allyl, $R_1 = R_2 = CH_3$, 71% yield
8d R = D, $R_1 = R_2 = CH_3$, 83% yield, 93 ± 2%D

The allylation reaction of **4b** and **4d** with three functionalized allyl stannanes were investigated and the results from these experiments are presented in Table 2 (eqn 4). From the limited data we have obtained so far, it appears that the electronic nature of the substituent at the 2- position of the allyl stannane does not impact significantly on the chemical efficiency (entries 1-5, Table 2). However, an electron withdrawing substituent at the 2-position provides higher chemical yields in the allylation (see entries 2 and 5, Table 2) reaction.



4b R = H, R_1 = n-C_4H_9
4d $R = R_1 = CH_3$

9a $R_2 = CH_3$
9b R_2 = OAc
9c $R_2 = CO_2CH_3$

10a-e

11a-e

(4)

Table 2. Radical Allylation of 4b and 4d Using Functionalized Allyltributyl Stannanes[a]

Entry	Substrate	Allyl Stannane	Product	Yield of acid **11**, %[b]
1	**4b**	**9a**	**11a**	66
2	**4b**	**9c**	**11c**	95
3	**4d**	**9a**	**11d**	70[c]
4	**4d**	**9b**	**11b**	95
5	**4d**	**9c**	**11e**	95

[a]The allylation reactions were done with AIBN (3 eq.) as the radical initiator and 10 eq. of the allyltin reagent in benzene as solvent at 80 °C. [b]Isolated Yield. [c] Under the acidic conditions of resin cleavage, the product acid undergoes lactonization.

In summary we have successfully carried out intermolecular free radical reactions on solid support and established that the polymer matrix is compatible with the reaction conditions. Additionally, the often problematic removal of excess tin reagents or tin byproducts from the reaction mixture is easily accomplished in the solid-phase methodology by simple washing of the resin with solvents. Transformation of the allylated esters on the resin to lactones by hydroboration or dihydroxylation is under investigation. Extension of the solid-phase methodology to conjugate free radical additions and examination of enantioselective variants are also underway.

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7. Substrate **4e** was prepared by coupling Wang Resin with α-bromo phenylacetic acid using DCC/DMAP.
8. Wang resin from Advanced ChemTech, Louisville, USA, (0.8-1 mmol/g) was used in all of the scale experiments.
9. Greater than 90% of the excess allyl stannane could be recovered from the reaction.
10. The reactions have not been optimized for each substituent. The low molecular weight product acids are very volatile and may account for their moderate yields.
11. The product acids were characterized by ^1H NMR and ^{13}C NMR. The analysis of the substrate on the resin was carried out by IR.
12. Amount of deuterium incorporation was determined by ^1H NMR integration of the product acid (obtained by TFA cleavage of the resin) and by mass spectral analysis. A comparison of reduction data (%D incorporation) for **7a** and **4b** also gave similar results.

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