Novel Method for Halomethylation of Cross-Linked Polystyrenes

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The chemical modification route is particularly attractive with polystyrene-based resins as their aromatic rings can be modified readily by electrophilic aromatic substitution or through other simple reactions.[1] Thus halomethylation of polystyrene is one of the most important functionalization that have been applicable for a variety of preparations of reactive polystyrenes.[1,2] This is due to the ease with which displacement or addition reactions can be carried out on chloromethylated polystyrene. The most commonly employed procedure[3] for introduction of a chloromethyl group has been the use of chloromethyl methyl ether or bis(chloromethyl) ether, which are listed as carcinogens.[4] Several alternative procedures to chloromethylated polystyrenes have been suggested,[5,6] but it has been noted that the level of substitution is difficult to control.[6]

We now describe a very simple and efficient process for the chloromethylation of cross-linked polystyrenes. The method involves the reaction of cross-linked polystyrene with trioxane and chlorotrimethylsilane in the presence of stannic chloride in chloroform. An activated formaldehyde generated from trioxane in the presence of stannic chloride as Lewis acid may react with chlorotrimethylsilane to form a trimethylsilyl ether of the chlorohydrin (**1**), having a structure similar to chloromethyl methyl ether, to act as chloromethylating agent for cross-linked polystyrenes as shown in Scheme I. The major advantage of this chloromethylation process is that the reaction is performed in a one-pot manner without contact with the chloromethylating agent generated in the flask. Excess chloromethylating agent can be easily decomposed by a hydrolytic process after the reaction has been completed. The easily decomposable reagent should be much safer than the conventional chloromethylating agents.[7]

Results are summarized in Table I.[8] The yield of the functionalized polystyrene beads was quantitative. For comparison,

Scheme I

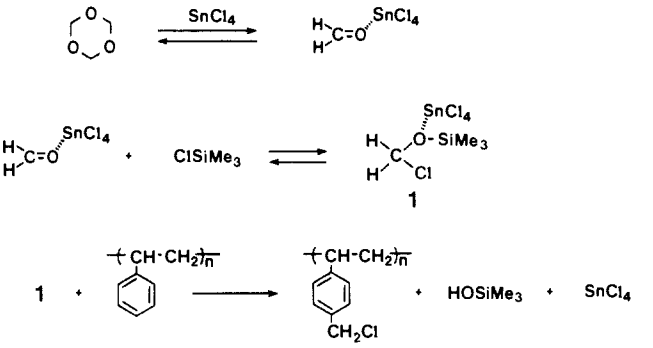

Table I. Chloromethylation of Polystyrene Resins

run	degree of cross-linking, %	$SnCl_4$ equiv	time, h	chloromethylated resin: mequiv of Cl/g	chloromethylated resin: DF
1[a]	1	0.54	1.5	1.80	0.205
2	2	0.00	3.5	0.00	0.00
3	2	0.43	1.5	2.23	0.26
4[b]	2	0.43	1.5	1.09	0.12
5[c]	2	0.43	1.5	3.03	0.37
6[d]	2	0.43	2.5	2.22	0.26
7	2	0.10	2.5	2.07	0.24
8	2	0.43	2.5	3.21	0.40
9	2	1.00	5	4.27	0.56
10	2	1.00	40	5.41	0.76
11	2	0.43	22	4.10	0.53
12	8	0.43	2.5	2.47	0.29
13[e]	10	0.43	17	2.46	0.29
14[f]	0	0.43	2.5	3.77	0.48
15[f,g]	0	0.43	2.5	1.18	0.13
16[h]	2	0.43[i]	2.5	1.41[j]	0.17
17[h]	2	1.00[i]	40	2.03[j]	0.26

[a] Experimental data reported by Frēchet.[9] [b] $BF_3{\cdot}OEt_2$ was used as Lewis acid catalyst. [c] Reaction was performed at 0 °C for 30 min and then at 60 °C for 1 h. [d] Reaction was performed at 0 °C. [e] Macroporous resin was used. [f] Linear polystyrene was used. [g] Low concentration: 100 mL/g of polystyrene. [h] Bromomethylation using bromotrimethylsilane. [i] $SnBr_4$. [j] Milliequivalents of Br per gram.

a typical result of conventional chloromethylation of cross-linked polystyrene using chloromethyl methyl ether reported by Frēchet[9] is shown in Table I (run 1). In the absence of any Lewis acid catalyst, no reaction occurred in a few hours (run 2). Satisfactory conversions to chloromethylated polystyrene resins were obtained in the presence of stannic chloride. The use of $BF_3{\cdot}OEt_2$ as Lewis acid resulted in lowering the degree of functionalization (DF) (run 4). DF increased with the reaction time. At a higher temperature, somewhat yellow colored polymer was obtained (run 5). A longer reaction time was required for the chloromethylation of nonswellable macroporous resin (run 13). DF varied in proportion to the amount of stannic chloride added. Thus DF can be easily controlled by the amount of stannic chloride added and reaction time. Chloromethylation of linear polystyrene using chloromethyl methyl ether and stannic chloride has been reported to be characterized by gelation phenomenon associated with cross-linking.[10] In our method, unless the reaction was performed in high concentration, the chloromethylated polystyrene obtained was completely soluble in tetrahydrofuran or benzene. No gelation was observed at low concentration (run 15).[11] In the case of cross-linked microporous polymers, the chloromethylation did not affect the swelling properties.

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(7) Care must still be exercised even in this method, because a powerful chloromethylating agent must be generated in situ.

(8) A typical reaction procedure is as follows. Trioxane (0.9 g, 10 mmol) and chlorotrimethylsilane (3.8 mL, 30 mmol) were dissolved in chloroform (10 mL). Cross-linked polystyrene (Bio Beads S-X2, 1 g) was added to the above solution, and then 0.5 mL (4.3 mmol) of $SnCl_4$ was added at 0 °C. The mixture was stirred at 0 °C for 30 min and for another 2 h at room temperature. Polymer beads gradually changed from colorless to red. The color vanished when the reaction was quenched by addition to methanolic water. The polymer was washed on a glass filter with methanol, tetrahydrofuran, and water, successively, to get white powdery beads of chloromethylated polystyrene containing 3.21 mequiv of Cl/g (DF = 0.40). the product had an IR spectra identical with that of an authentic sample. IR (KBr): ν_{C-Cl} 1265 cm^{-1}. Anal. Found: C, 81.65; H, 6.85; Cl, 11.50.

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(11) Gel permeation chromatography data showed that the chloromethylating process was not accompanied by the formation of methylene bridges.

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This procedure enabled the introduction of bromomethyl functionality[12] in polystyrene resins if bromotrimethylsilane was used in place of chlorotrimethylsilane. A reaction time longer than that for chloromethylation was required, however, to obtain a satisfactory DF value.

(12) IR (KBr): ν_{C-Br} 1226 cm^{-1}.

Convergent Synthesis of Vineomycinone B2 Methyl Ester

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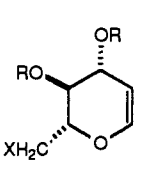
The vineomycines are antitumor antibiotics that were first isolated from a culture of *Streptomyces matensis* subsp. *vineus* which was active against Gram-positive bacteria and sarcoma 180 solid tumors in mice.[2,3] The characteristic features of vineomycinone B2 (**1**) are the *C*-glycosyl bond to the olivose derivative, and the alkyl chain bearing a stereogenic center on the opposite side of the molecule. The combination of the challenging structure and the interesting biological properties has motivated synthetic efforts.[4] To date two groups have disclosed total syntheses of **1**.[5,6] We report a triply convergent total synthesis of **1** which exploits methodology developed earlier in this group.[7]

Vineomycinone B2 methyl ester is easily perceived as arising from the conjunction of three subunits: an olivose linked to anthrarufin through a *C*-glycosyl bond, and a chiral chain terminating in a methyl ester. Recognizing that each of the subunits can be prepared efficiently from commercially available materials simplifies the problem. This strategy has the advantage of a high degree of convergency. The distance between the asymmetric centers of the sugar and the chiral center on the side chain precludes any stereochemical communication between the two appendages.[5] The two homochiral fragments were prepared in high optical purity, and no separation of diastereoisomers was required.

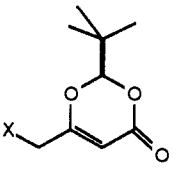
The olivose derivative **5** was prepared from iodide **2**[8] in 95% overall yield (Chart I) by treatment with lithium aluminum hydride,[9,10] followed by protection of the hydroxyl groups.[11] Seebach's excellent method[12] was brought to bear on the synthesis of the side chain. Allylic bromination of **3** with *N*-bromosuccinimide and catalytic benzoyl peroxide in carbon tetrachloride, under irradiation by a floodlamp, gave a 40% yield of monobromide **6** accompanied by ca. 20% of the starting material and 15% of dibrominated product. The chromatographic separation of these materials, though tedious, was easily accomplished. Anthrarufin was converted in four steps to protected iodoanthracene **7** in 44% overall yield.[7]

Chart I



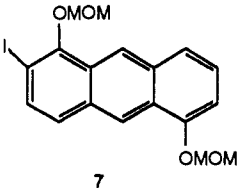
2: X = I; R = Ac

5: X = H; R = TBDMS

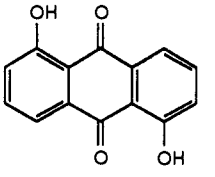


3: X = H

6: X = Br



7



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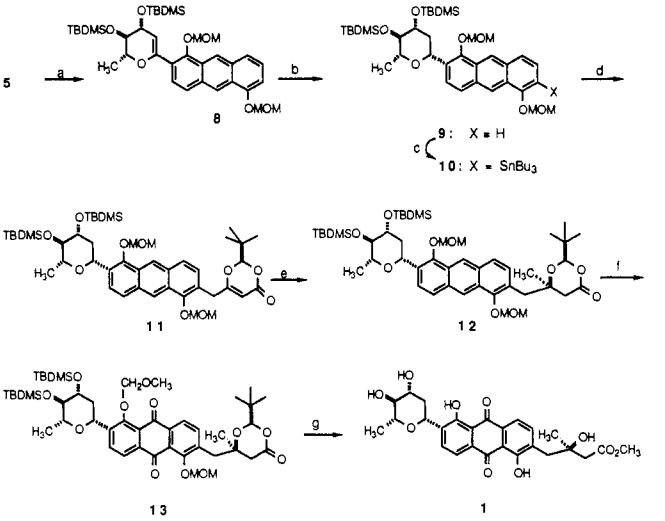
Scheme I[a]



[a] (a) (i) *t*-BuLi, pentane–THF, 0 °C; (ii) $ZnCl_2$, THF, 23 °C; (iii) **7**, $Pd(PPh_3)_2Cl_2$ + DIBAL-H, THF, 23 °C, 75%; (b) $NaBH_3CN$, HCl, EtOH, 88%; (c) *n*-BuLi, TMEDA, THF, 0 °C, then Bu_3SnCl, 90%; (d) **6**, $Pd_2(dba)_3{\cdot}CHCl_3$, PPh_3, THF, 70 °C, 45–50%; (e) $(CH_3)_2CuLi$, ether, 60%; (f) bis(pyridine) silver permanganate, silica gel, CH_2Cl_2; (g) HCl, MeOH, 23 °C, 35% overall from **12**.

The assembly of **1** was accomplished according to Scheme I. The aryl *C*-glycosyl bond was formed first: the lithio anion which was derived from **5**[13] was treated with a solution of 2.0 equiv of anhydrous zinc chloride in tetrahydrofuran (THF) at 0 °C and was stirred at 23 °C for 1 h. The organozinc reagent was transferred to a solution of 0.66 equiv of iodoanthracene **7** and palladium (0) catalyst. The catalyst was generated from 0.10 equiv of $(PPh_3)_2PdCl_2$ and 0.30 equiv of diisobutylaluminum hydride in THF at 23 °C. These reaction conditions were described originally by Negishi.[14,15] *C*-Glycosyl anthracene **8**[16] was obtained as a clear oil in 75% yield after 12 h at 23 °C. The next task was to reduce the styryl double bond stereospecifically. This step provided an unexpected challenge. Catalytic hydrogenation either failed to reduce **8** or led to reaction mixtures in which both the central ring of the anthracene and the styrene double bond

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