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Free radical-mediated addition of peracetylated 1-bromo-β-D-glucopyranosyl chloride to acrylonitrile

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ABSTRACT

Dropwise addition of a benzene solution of tri-*n*-butylstannane to a solution of 2,3,4,6-tetra-*O*-acetyl-1-bromo-β-D-glucopyranosyl chloride in boiling benzene containing acrylonitrile in excess led predominantly, under photolytic conditions, to a mixture of nonononitriles, either chlorinated or unsaturated.

INTRODUCTION

It is now well established that addition of free radical intermediates to substituted alkenes constitutes an efficient route for the creation of C–C bonds [1,2]. The success of this method relies mainly on the nucleophilic [1] character of carbon-centered free radicals which, in the presence of appropriately substituted alkenes, undergo rapid addition to C–C double bonds. The role of the electron-withdrawing group *Z* present on the alkene is manifold [1a]. Essentially, the induced polarization of the alkene results in enhanced reactivity towards nucleophilic free radicals, a behavior that can be rationalized using the frontier molecular-orbital theory [1b]. Such a high reactivity is an essential feature of the synthetic rationale, to avoid the alternative competitive reduction of the initial free radical. For example, if this species is generated by way of the tin hydride method, the aforementioned requisite is fulfilled, owing to the presence of the withdrawing substituent which ensures fast addition to the alkene (step b: C–C bond formation) as compared to hydrogen abstraction from tin hydride (step c: reduction) [1a]. Moreover, the alkene

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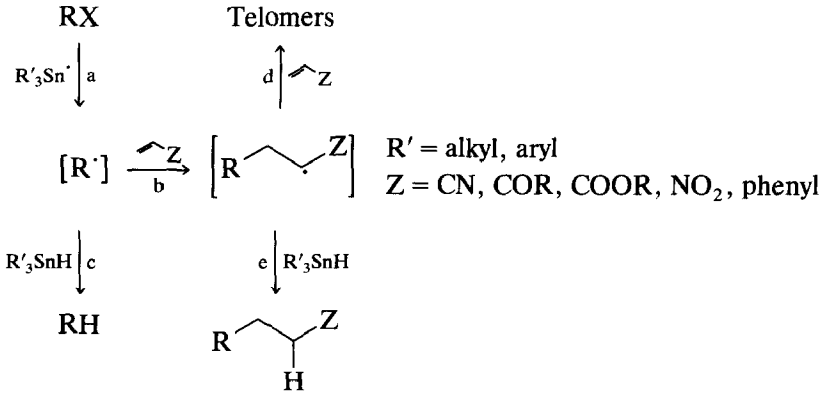
substituent stabilizes the resulting radical intermediate $RCH_2CH^{\cdot}Z$ and is responsible for its electrophilicity, so that telomerization (step d) is minimized [1d].



Such a methodology, which has also been extended to electrophilic carbon-centered free radicals [3], has been developed in several recent synthetic studies, particularly in the carbohydrate field [4,5], owing to its great flexibility. The addition process is not restricted to C–C double bonds, but may also proceed efficiently with other unsaturated functionalities, such as alkynes [6], nitriles [7], oxime ethers [8], and aldehydes [9,10]. Moreover, in the case of appropriately functionalized substrates, serial radical cyclizations may occur, allowing the elaboration of complex carbocycles, as exemplified recently for pyranoside diquinanes [7].

In this context, 2,3,4,6-tetra-*O*-acetyl-1-bromo-β-D-glucopyranosyl chloride [11] **1** appeared a promising substrate. The possible generation of a 2,3,4,6-tetra-*O*-acetyl-1-chloro-D-glucopyranos-1-yl radical has already been demonstrated by both our synthetic [11] and spectroscopic [12] studies. Moreover, it was envisaged that the presence of two halogen atoms at the anomeric center would permit a stepwise radical addition onto radicophilic alkenes, leading to bis-C,C-glycosyl compounds. The syntheses of such compounds have been achieved in only a few cases [13,14].

RESULTS AND DISCUSSION

Provided the structures of both the radical precursor and the alkene meet the requirements for fast C–C bond formation, the experimental protocol can tolerate great flexibility [14]. The reaction can be performed by either boiling (addition of a radical initiator) or irradiating (visible or UV light) a reaction mixture in an organic solvent (diethyl ether, oxolane, benzene, toluene, etc.). Tin hydride may be introduced at once or slowly to maintain its concentration at a low level, thus minimizing the competitive reduction. Alternatively, slow addition of both the tin hydride and either the alkene or the radical precursor had proved to be successful in circumventing unwanted side-reactions promoted by light or prolonged heating [14].

TABLE I

Products distribution (%) observed for the free-radical coupling of **1** with acrylonitrile

Compounds		Solvent		
		Oxolane [a]	Diethyl ether [a]	Benzene [b]
2	*Reduction*	28	30	8
3		10	12	4
4		20	19	5
		58	61	17
6(4*R*)	*Addition*	5	6	16
7		7	9	22
8		8	10	25
		20	25	63

[a] The tin hydride was introduced at once in the refluxing solution or [b] dropwise.

Our investigations showed that the generation of a 2,3,4,6-tetra-*O*-acetyl-1-chloro-D-glucopyranos-1-yl radical from **1**, in the presence of acrylonitrile, led, using a variety of conditions, to a complex mixture of products which was resolved by column chromatography. Whereas boiling a mixture of **1**, acrylonitrile and tri-*n*-butyl tin hydride in diethyl ether or oxolane favored the reduction reaction (**2**, ~ 30; **3**, ~ 10; and **4**, ~ 20%), higher yields of triglyconitriles were achieved when the tin hydride was added dropwise to a reaction mixture in boiling benzene (63% combined yield for **6**, **7**, and **8**) (Table I). Under such conditions, the reduction was either partial (**2** and **3**, this later compound resulting from hydrolysis during work-up and/or purification) or complete (**4**), whereas the skeletal elongation by 3 carbon atoms in **6**, **7**, and **8** showed the monoaddition to predominate, particularly when the tin hydride was added dropwise.

Although the formation of the observed products can be readily understood, the anomeric configuration of the chlorides **2** and **6** (4*R*) and the failure to observe bis-C,C-glycosyl compounds deserve some comments. In accordance with the reactivity of organic halides towards tri-organo tin radicals (RBr > RCl) and with the easier homolysis of axially oriented bonds at the anomeric center of sugar derivatives adopting the $^4C_1$(D) chair conformation, **1** should at first lead to a peracetylated-1-chloro-D-glucopyranos-1-yl radical. Since it is well established that peracetylated D-glucopyranos-1-yl [1,14] radicals as well as their 1-substituted analogs [11,15], react stereoselectively in such a way that the newly created bond adopts the α orientation [16], the β-chlorides **5** and **6** (4*S*) could be the kinetic products produced by reduction or addition processes. The great reactivity of **5** and its susceptibility towards nucleophiles are well known [17] and account for its ready hydrolysis or anomerization in favor of the more stable α anomer **2**. Such an anomerization (**5** → **2**) probably occurred during the 6-h boiling period, maybe through catalysis by the hydrochloric acid released during the elimination reaction leading to **7** and **8**. In addition, hydrolysis of the remaining **5** during work-up or column chromatography is to be expected. Similarly, the presumed kinetic product

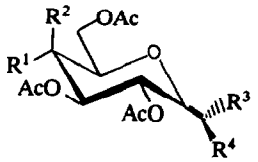
6 (4*S*) could anomerize in favor of **6** (4*R*). However, since the heterolytic cleavage of the C-1–Cl bond in **6** (4*S*) would lead to a stabilized tertiary cation, competitive E_1 eliminations leading to **7** and **8** constitute other probable reaction pathways. Stereoselective addition of the hydrochloric acid liberated to these unsaturated products could also provide a route towards **6** (4*R*). The absence of detectable amounts of bis-C,C-glycosyl compound can be explained on the basis of the aforementioned heterolysis of the C-1–Cl bond which results in decreased amounts of the chlorides **6** which are susceptible to attack by tin radicals. Conversely, the possibility of attaching an alkyl residue to tertiary carbon-centered free radicals, generated from nitro sugars [14], probably results from the poorer leaving group ability of the nitro group.

Identification of compounds **2**, **3** and **4** was straightforward. However, closer examination was found necessary in the structure elucidation of **6** (4*R*), **7**, and **8**. The orientation of the C-1–Cl bond in **6** (4*R*) was deduced from ^{1}H-NMR spectroscopy. The peracetylated α- and β-glyconitriles similarly prepared by Giese et al. [14], exhibited proton resonances for H-6 and H-8, respectively, at 5.23, 5.20 and 3.88, 3.58 ppm, showing that only H-8 in the α anomer experienced a deshielding effect of 0.3 ppm, which was ascribed to the axial anomeric linkage. The fact that halogen atoms induce a larger deshielding (0.4–0.5 ppm) on 1,3-*syn* axially oriented protons [11] led to the conclusion that the H-6 and H-8 resonances in **6** (4*R*) (5.52 and 4.24 ppm) could only be compatible with the axial orientation of the C-1–Cl bond. This conclusion was also supported by the H-5 resonance in **6** (4*R*) (5.08 ppm) which appeared at higher field as compared to H-2 resonances recorded for peracetylated 1-substituted-β-D-glucopyranosyl chlorides ($\sim$ 5.30, 5.19, and 5.44 for the following C-1 axial substituents [11]: H, Br, and Cl).

^{1}H-NMR comparisons proved also to be useful in establishing the configuration of the C–C double bond in **7**. The ^{1}H-NMR data (Table II) of a hept-1-enitol and

TABLE II

^{1}H-NMR resonances for the vinylic protons in **7** and related (*E*)- or (*Z*)-acetylated enitols [18] **9–13**



7, 9–13

Compound	R^1	R^2	R^3	R^4	Vinylic hydrogen (δ)	
					$R^3 = H$	$R^4 = H$
7	OAc	H	CH_2CN	H		4.97
9	H	OAc	CH_3	H		4.95
10	H	OAc	H	CH_3	5.44	
11	H	OAc	CN	H		4.85
12	H	OAc	H	CN	5.20	
13	H	OAc	H	H	4.82	4.51

isomeric oct-2-enitols revealed that a ~ 0.3 ppm deshielding effect is experienced by the vinylic proton closely related to the endocyclic oxygen atom as in **13**, whereas an alkyl group attached to the double bond is known [18] to cause a ~ 0.5 ppm shift of the geminal proton signal to lower field (compare **9** and **10**, or **11** and **12** to **13**). Therefore, the chemical shift recorded for H-3 in **7** (4.97 ppm) suggested the *Z* configuration for the double bond. The same stereochemistry was indicated by the long-range couplings (in Hz) observed for **7** ($^5J_{2,5}$ 1.2, $^4J_{3,5}$ 1.5) which corresponded to those previously measured [18] for the (*Z*)-oct-2-enitol **9** ($^5J_{1,4}$ 2, $^4J_{2,4}$ 1.8), whereas the spectrum of the corresponding (*E*)-oct-2-enitol **10**, a substrate for D-glucosidases [19], did not exhibit such couplings [18].

In conclusion, provided precautions are taken to minimize competitive reduction reactions, tri-*n*-butyl stannane mediated addition of peracetylated-1-chloro-D-glucopyranos-1-yl radical to acrylonitrile leads predominantly to a mixture of nononononitriles, either chlorinated or unsaturated.

EXPERIMENTAL

General methods.—Melting points were determined with a Büchi capillary apparatus and are not corrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker AM 300 instrument for solutions in $CDCl_3$ with Me_4Si as the internal reference. All long-range couplings in the ^{1}H-NMR spectrum of **6** clearly appeared when the spectrum was edited by a resolution enhancement function (LB: −3.6, GB: 0.3). Reactions were monitored by TLC on Silica Gel 60 F_{254} (Merck) plates, exposed to H_2SO_4 spray followed by charring. Column chromatography was performed using Silica Gel 60 (Merck).

Free radical coupling of **1** *with acrylonitrile.*—A refluxing solution of **1** [11] (400 mg, 0.9 mmol), acrylonitrile (950 mg, 17.8 mmol) and Bu_3SnH (570 mg, 2 mmol) in 5 mL of dry diethyl ether or oxolane was irradiated for 6 h, under a N_2 atmosphere, with a 60 W sun lamp. When using benzene as the solvent, a benzene solution of Bu_3SnH was added dropwise to a benzene solution of **1** and acrylonitrile, maintained at reflux by the sun lamp. After disappearance of the starting material, the reaction products were taken up in diethyl ether and, after work-up, the mixture was resolved by column chromatography using mixtures of EtOAc and *n*-hexane (25 : 75 then 35 : 65 v/v), yielding successively **2**, **4**, **6** (4*R*), **7** and **8**.

*(4*R*)-5,6,7,9-Tetra-*O*-acetyl-4,8-anhydro-4-chloro-2,3-dideoxy-*D*-gluco-nononitrile* (**6**).—Mp 98–99° (diethyl ether–petroleum ether); $[\alpha]_D^{23}$ + 95° (*c* 0.3, $CHCl_3$); ^{1}H-NMR: δ 5.51 (t, 1 H, $J_{6,7}$ 9.6, H-6), 5.15 (dd, 1 H, $J_{7,8}$ 10, H-7), 5.08 (d, 1 H, $J_{5,6}$ 9.8, H-5), 4.32 (dd, 1 H, $J_{8,9}$ 4.1, $J_{9,9'}$ 12.5, H-9), 4.25 (dq, 1 H, $J_{8,9'}$ 1.9, H-8), 4.13 (dd, 1 H, H-9′), 2.66 (t, 2 H, $J_{2,3}$ 7.8, CH_2CH_2CN), 2.30 (m, 2 H, CH_2CH_2CN), 2.14, 2.11, 2.05, 2.01 (4s, 12 H, OAc); ^{13}C-NMR: δ 118.4 (C-1) 11.7, 36.7 (C-2 and C-3), 103.1 (C-4), 67.2, 71.0, 72.5, 72.5 (C-5 to C-8), 60.9 (C-9), 20.5, 20.8, 20.8 (CH_3), 169.3, 169.6, 169.8, 170.5 (C=O).

CN
Bu3SnH
1
2 R1 = H, R2 = Cl
3 R1, R2 = H, OH
5 R1 = Cl, R2 = H
4
6 (4R)
7
8

Anal. Calcd for $C_{17}H_{22}ClNO_9$: C, 48.64; H, 5.28; Cl, 8.44; N, 3.34; O, 34.30. Found: C, 48.68, H, 5.49, Cl, 8.26; N, 3.22; O, 34.33.

(Z)-*5,6,7,9-Tetra*-O-*acetyl-4,8-anhydro-2,3-dideoxy*-D-gluco-*non-3-enononitrile* (**7**).—Mp 113–114° (diethyl ether–petroleum ether); $[\alpha]_D^{21}$ + 49° (*c* 0.6, $CHCl_3$); ^{1}H-NMR: δ 5.44 (dq, 1 H, $J_{5,6}$ 7.6, $J_{5,2a}$ 1.2, $J_{5,2b}$ 1.2, $J_{5,3}$ 1.5, H-5), 5.20 (q, 1 H, $J_{7,6}$ 7.9, $J_{7,8}$ 9.6, H-7), 5.14 (t, 1 H, $J_{5,6}$ 7.6, $J_{6,7}$ 7.9, H-6), 4.97 (dt, 1 H, $J_{3,2a}$ 6.9, $J_{3,2b}$ 6.9, $J_{3,5}$ 1.5, H-3), 4.32 (dd, 1 H, $J_{9,9'}$ 12.6, $J_{8,9}$ 4.4, H-9), 4.27 (dd, 1 H, $J_{9',8}$ 2.6, H-9′), 3.99 (dq, H-8), 3.25 (ddd, 1 H, $J_{2,2'}$ 18.0, H-2), 3.09 (ddd, 1 H, H-2), 2.14, 2.12, 2.06, 2.05 (4s, 3 H each, OAc); ^{13}C-NMR: δ 117.6 (CN), 13.0 (C-2), 100.2 (C-3), 149.6 (C-4), 67.9, 68.9, 72.9. 75.7 (C-5 to C-8), 61.6 (C-9), 20.6, 20.6, 20.7 (CH_3), 169.0, 169.3, 169.8, 170.5 (C=O).

Anal. Calcd for $C_{17}H_{21}NO_9$: C, 53.26; H, 5.52; N, 3.65; O, 37.56. Found: C, 53.55; H, 5.65; N, 3.59; O, 37.60.

(E)-*5,6,7,9-Tetra*-O-*acetyl-4,8-anhydro-2,3-dideoxy*-D-arabino-*non-4-enononitrile* (**8**).—$[\alpha]_D^{23}$ + 52° (*c* 0.7, $CHCl_3$); ^{1}H-NMR δ 5.22 (d, 1 H, $J_{6,7}$ 4.0, H-6), 5.19 (dd, 1 H, $J_{7,8}$ 5.1, H-7), 4.47 (dd, 1 H, $J_{9,8}$ 6.8, $J_{9,9'}$ 11.7, H-9), 4.40 (dq, 1 H, $J_{8,9'}$ 2.8, H-8), 4.21 (dd, 1 H, H-9′), 2.5 (m, 4 H, $(CH_2)_2CN$), 2.14, 2.11, 2.10, 2.06 (4s, 3 H each, OAc); ^{13}C-NMR: δ 118.5 (CN), 14.1, 24.3 (C-2 and C-3), 146.1 (C-4), 123.7 (C-5), 66.4, 67.7, 74.5 (C-6 to C-8), 60.8 (C-9), 20.4, 20.7 (CH_3), 169.3, 169.5, 170.1, 170.5 (C=O).

Anal. Calcd for $C_{17}H_{21}NO_9$: C, 53.26, H, 5.52; N, 3.65; O, 37.56. Found: C, 53.23; H, 5.74; N, 3.33; O, 37.19.

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