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Synthesis and Allylic Reactivity of α-Bromomethyl β-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)oxy α,β-Unsaturated Carbonyl Compounds

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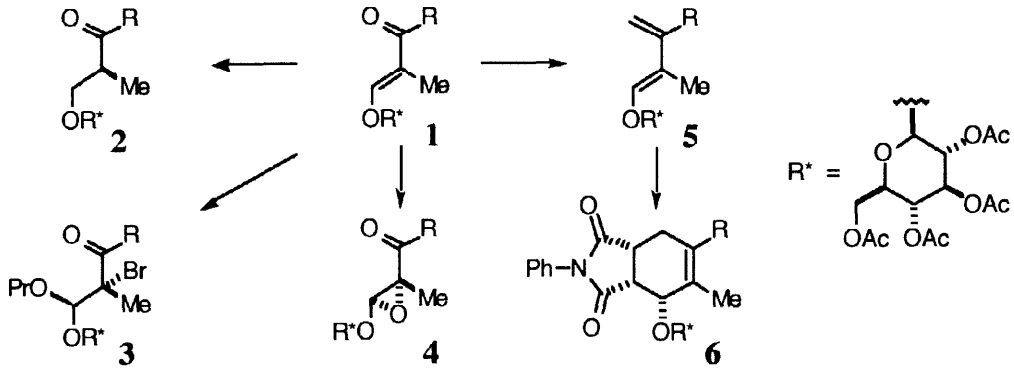
Abstract

Under radical conditions, *N*-bromosuccinimide converts α-methyl β-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy α,β-unsaturated carbonyl compounds into their α-bromomethyl derivatives. The bromides undergo nucleophilic displacement reactions without rearrangement with azide, *O*-ethyl dithiocarbonate and thiocyanate anions; with acetate anion, there is a preference for the formation of rearranged acetates with reasonable stereoselection.

Keywords: Carbohydrates; radicals and radical reactions; rearrangements; regioselection.

As Scheme 1 illustrates, α-methyl β-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)oxy α,β-unsaturated carbonyl compounds of type **1** are versatile units in asymmetric synthesis. Thus, they exhibit reasonable *Re*-face selectivity in hydrogenation [1], bromopropoxylation [2] and epoxidation [3] reactions, affording predominantly products of types **2**–**4**.[1] They can also be converted into dienes of type **5** that display excellent *Re*-face selectivity in Diels–Alder reactions, *e.g.* furnishing cycloadducts of type **6** with *N*-phenylmaleimide [4].



Scheme 1

[1]Removal of the auxiliary in the case of compounds of types **3** and **4** (under transacetalisation/transdithioacetalisation conditions) leads to chirons with tertiary carbon stereogenic centres featuring bromo and hydroxy substituents [2,3].

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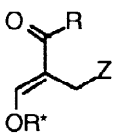
The synthetic versatility of compounds of type **1** would be significantly enhanced if regioselective brominations of their allylic methyl groups could be effected to give bromo derivatives of type **7** (Z = Br);[2] nucleophilic displacements could then lead to a range of products of type **7** (*e.g.* Z = *N*-, *O*- or *S*-substituent). Hopefully, compounds of type **7** would react in a manner similar to their methyl counterparts (*c.f.* Scheme 1), permitting access to related products with additional functionality. Of course, the projected brominations and displacements could be accompanied by double bond isomerisations to give products of type **8** and allylic rearrangements to give products of types **9** and **10**. In this letter, we report on the regio- and stereo-chemical outcomes of the allylic bromination reactions [using *N*-bromosuccinimide (NBS)] and of the nucleophilic substitution reactions of the products.



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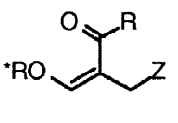

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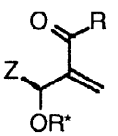

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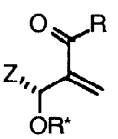

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Although NBS has been extensively used as an allylic brominating agent [5,6], we are unaware of any studies involving α-methyl β-oxy α,β-unsaturated carbonyl compounds. When heated in carbon tetrachloride with the reagent and 2,2'-azobisisobutyronitrile (AIBN),[3] the butenone **1a** [7] was converted into one main product (72% yield), mp 137–138 °C, $[\alpha]_D^{24}$ +30 (*c* 0.4 in $CHCl_3$), which was assigned the structure **12a**.[4,5] That the product had been formed without double bond isomerisation was suggested by its olefinic proton chemical shift (δ 7.47) {which was very similar to that of the reactant **1a** (δ 7.36) [7]} and corroborated by an NOED spectroscopic study (in which mutual enhancements were observed between the olefinic proton and the methyl ketone protons). Similarly, the pentenone **1b** [4] was transformed into the bromide **12b**[4] (79% yield), mp 92–94 °C, $[\alpha]_D^{26}$ +29 (*c* 0.4 in $CHCl_3$), the propenoate **1c** [1] into the bromide **12c**[4] (61% yield), mp 108–110 °C, $[\alpha]_D^{19}$ +59 (*c* 0.41 in $CHCl_3$), and the propenoate **1d** [1] into the bromide **12d**[4] (63% yield), mp 98–99 °C, $[\alpha]_D^{19}$ +45 (*c* 0.27 in $CHCl_3$).

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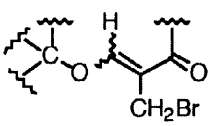
[2]Surprisingly, searches of databases (STN International, Beilstein Crossfire) using the following substructure failed to provide any representative compounds.

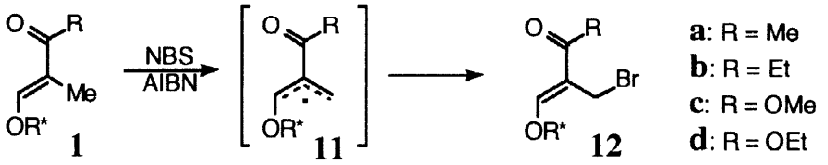


[3]Typical procedure: Recrystallised NBS (0.890 g, 5 mmol) and a catalytic quantity of AIBN were added to a stirred suspension of the compound of type **1** (4 mmol) in dry carbon tetrachloride (60 cm^3) and the mixture was heated under reflux for 1 h. The product, obtained after evaporation, was dissolved in dichloromethane and the solution washed sequentially with aq. sodium metabisulfite and water. Evaporation of the dried ($MgSO_4$) organic phase left the product of type **12**, which was purified by crystallisation (*e.g.* from EtOAc–hexanes for compound **12a**).

[4]All new compounds gave satisfactory elemental analyses and displayed spectral properties that were in accord with their assigned structures.

[5]For **12a**: λ_{max} (EtOH)/nm 245 (ε 13 100); ν_{max} (KBr)/cm^{-1} 1750 (ester C=O), 1675 (vinylogous ester C=O) and 1645 (C=C); δ (300 MHz; $CDCl_3$) 2.045, 2.051 and 2.10 (3, 3 and 6 H, each s, 4 x $MeCO_2$), 2.31 (3 H, s, 1-H_3), 3.87 (1 H, ddd, *J* 2.5, 4.5 and 9.5 Hz, 5'-H), 4.16–4.21 (3 H, m, 6'-H and 3-CH_2Br), 4.31 (1 H, dd, *J* 4.5 and 12.5 Hz, 6'-H), 5.02 (1 H, d, *J* 7.5 Hz, 1'-H), 5.15–5.32 (3 H, m, 2'-, 3'- and 4'-H) and 7.47 (1 H, s, 4-H); *m/z* (FAB) 511 and 509 (MH^+, 28 and 35%) and 331 ($C_{14}H_{19}O_9^+$, 100).

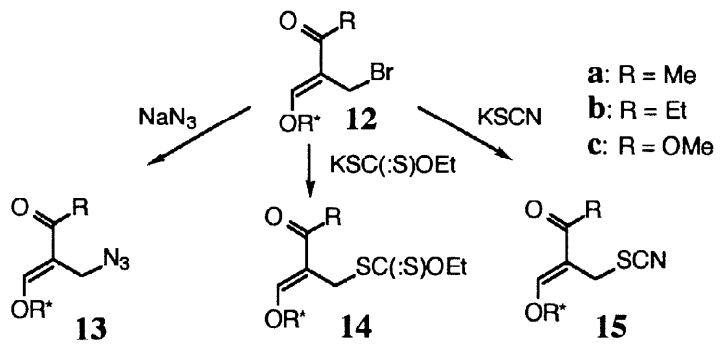
Clearly, the foregoing allylic bromination reactions were highly regioselective, with attack occurring at the unsubstituted primary carbon of the presumed radical intermediates **11a–d** (Scheme 2). It is worth noting that high site selectivity was realised in the case of the reactants **1a** and **1b** (no products arising from bromination alpha to the vinylogous ester carbonyl groups were detected).



Scheme 2

With bromides of type **12** in hand, attention was directed at defining the regio- and stereoselectivities of their reactions with representative heteroatomic nucleophiles.

As shown in Scheme 3, the bromide **12a** reacted with sodium azide (in MeCN at ambient temperature for 6 h) to give the azide **13a**[4] (81% yield), mp 153–154 °C, $[\alpha]_D^{20}$ +14 (*c* 0.25 in CH_2Cl_2), with potassium *O*-ethyl dithiocarbonate (in MeCN at ambient temperature for 0.25 h) to give the dithiocarbonate **14a**[4] (64% yield), mp 104–106 °C, $[\alpha]_D^{20}$ –6 (*c* 0.25 in CH_2Cl_2), and with potassium thiocyanate (in MeCN at ambient temperature for 6 h) to give the thiocyanate **15a**[4,6] (76% yield), mp 152–153 °C, $[\alpha]_D^{20}$ +33 (*c* 0.42 in $CHCl_3$). Similarly, the bromides **12b** and **12c** were converted into the azides **13b** and **13c** (74 and 50% yields), the dithiocarbonates **14b** and **14c** (65 and 78% yields) and the thiocyanates **15b** and **15c** (72 and 60% yields). There was no evidence for the formation of rearranged substitution products (of types **9** and **10**) in any of the reactions.



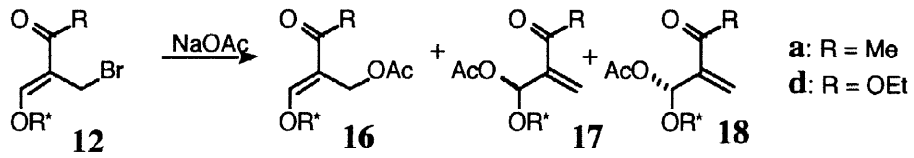
Scheme 3

The reaction of the bromide **12a** with sodium acetate (100 mol%; boiling MeCN) (Scheme 4) was time dependent. After 3 h (when around 60% of the starting material remained), mainly a 6:79:15 mixture of compounds **16a**, **17a** and **18a** was present.[7] After 6 h (when about 35% of the starting material remained), the ratio was unchanged. After 24 h (when no starting material was present), the ratio was 60:26:14. Finally, after 48 h, the product comprised a 75:12:13 mixture of compounds **16a**, **17a** and **18a**. From a 3 h reaction (in which the use of 300 mol%

[6]The isothiocyanate structure was excluded on the basis of IR and NMR spectroscopic evidence. Thus, the IR spectrum featured a sharp but relatively weak absorption at 2153 cm^{-1} typical of an alkyl thiocyanate (alkyl isothiocyanates show broad, intense absorptions in the 2106–2084 cm^{-1} region) [8]. Furthermore, the ^{13}C NMR spectrum displayed a signal at δ 112.2 typical of an alkyl thiocyanate carbon (alkyl isothiocyanate carbons resonate in the δ 128.6–132.3 region) [9].

[7]The assignment of the stereostructures **17a** and **17d** to the major rearranged acetates is tentative.

of NaOAc depleted the starting material and led to a 17:67:16 mixture of compounds **16a**, **17a** and **18a**), the product was separated into two fractions by HPLC. The more-mobile fraction (59% yield) consisted of a 4:1 mixture of compounds **17a** and **18a**; two crystallisations of the material led to a product, mp 123–124 °C, $[\alpha]_D^{19}$ –50 (*c* 0.17 in $CHCl_3$), that comprised a 6:1 mixture of the rearranged acetates **17a** and **18a**.[7,8] The less-mobile fraction (15% yield), mp 103–104 °C, $[\alpha]_D^{20}$ –8 (*c* 0.5 in CH_2Cl_2), was the unrearranged acetate **16a**.[4] When compound **16a** was heated with sodium acetate (100 mol%; boiling MeCN) for 18 h, a 74:12:14 mixture of compounds **16a**, **17a** and **18a** was produced.



Scheme 4

Clearly, in its early stages, the reaction of the bromide **12a** with sodium acetate is under kinetic control and affords mainly the rearranged acetates **17a** and **18a** (with a selectivity of about 5:1). With time, the products interconvert to give an equilibrium mixture in which compound **16a** predominates.

The bromide **12d** also reacted with sodium acetate (200 mol%; boiling MeCN) (Scheme 4) in a time-dependent manner. Thus, after 5.5 h, a 17:67:16 mixture of compounds **16d**, **17d** and **18d** was present; after 22 h, the ratio was 22:60:18.[7]

In conclusion, we consider our findings to be of synthetic and mechanistic note. Compounds of type **12** appear to be the first representatives of α-bromomethyl β-oxy α,β-unsaturated carbonyl compounds to be described and their formation provides an opening insight into the regiochemical behaviour of 2-acyl-1-oxyallyl radicals. The substitution reactions, involving a new class of allylic bromides, highlight the contrasting behaviour of soft/borderline nucleophiles (*i.e.* $EtOCS_2^-$, NCS^-/N_3^-) compared with hard nucleophiles (*i.e.* AcO^-) [10] and contribute to an understanding of ambident allylic reactivity [11]. Finally, the methodology makes compounds of types **12–15**, of notable synthetic potential, accessible by practical routes.

[8]For a 6:1 mixture of **17a** and **18a**: λ_{max} (EtOH)/nm 210 (ε 8900); ν_{max} (Nujol)/cm^{-1} 1750 and 1735 (ester C=O), and 1675 (enone C=O); δ (300 MHz; $CDCl_3$) 2.00, 2.01, 2.02, 2.03, 2.04, 2.08, 2.10 and 2.11 (0.42, 3, 2.58, 0.42, 2.58, 5.16, 0.42 and 0.42 H, each s, 5 x $MeCO_2$), 2.34 and 2.35 (0.42 and 2.58 H, each s, 1-H_3), 3.66 and 3.72 [0.14 and 0.86 H, dt (*J* 10 and 3 Hz) and ddd (*J* 2.5, 5 and 10 Hz), 5'-H], 4.09, 4.13–4.15 and 4.27 [0.86, 0.28 and 0.86 H, dd (*J* 2.5 and 12.5 Hz), m and dd (*J* 5 and 12.5 Hz), 6'-H_2], 4.89 and 4.96 [0.86 and 0.14 H, each d (*J* 8 Hz), 1'-H], 5.00–5.10 (2 H, m, 2'- and 4'-H), 5.22 (1 H, t, *J* 9.5 Hz, 3'-H), 6.23, 6.30, 6.33 and 6.38 (0.14, 0.86, 0.14 and 0.86 H, each s, C:CH_2), and 6.79 and 6.85 (0.86 and 0.14 H, each s, 4-H); *m/z* (FAB) 511 (MNa^+, 7%), 331 ($C_{14}H_{19}O_9^+$, 60) and 169 (100).

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