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Tetrahedron Letters 45 (2004) 9533–9536
Tetrahedron Letters

A simple, efficient alternative for highly stereoselective iodoacetoxylation of protected glycals

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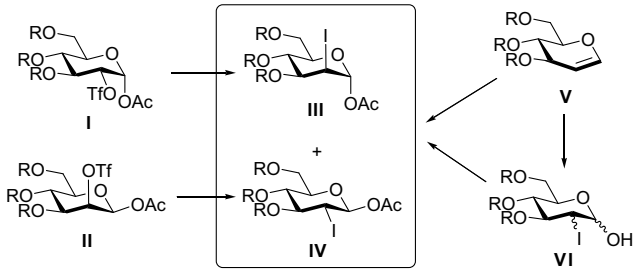
Received 29 September 2004; revised 22 October 2004; accepted 28 October 2004

Abstract—Protected glycals are converted in high yields and selectivities in less than 2 h at low temperatures to 2-deoxy-2-iodoglycosyl acetates using the simple, inexpensive reagent mixture of ammonium iodide, hydrogen peroxide and acetic anhydride/acetic acid in acetonitrile. The corresponding 2-deoxy-2-bromoglycosyl acetates are obtained using ammonium bromide instead of the iodide, although longer reaction times are required and selectivities are inferior.

The preparation of 2-deoxy-2-iodoglycopyranosyl acetates in the stereoselective synthesis of 2-deoxyglycosides continues to attract attention.[1–3] Glycosyl acetates are easily activated as glycosyl donors, and the iodo substituent provides stereo-directing anchimeric assistance in the glycosylation step and is readily amenable to radical-induced reductive cleavage to give 2-deoxyglycosides. As a radical precursor it also provides the basis for introduction of alkenyl substituents, and it was our work in this context[4] together with our interest in developing environmentally benign synthetic protocols,[5] which prompted an investigation of alternative methodologies for the preparation of 2-deoxy-2-iodoglycopyranosyl acetates from protected glycals.

The existing synthetic approaches to these 2-deoxy-2-iodoglycopyranosyl acetates can be divided into three categories, summarized for the gluco- and manno- cases in Scheme 1. The first, involving displacement of 2-triflates from otherwise protected glycosyl acetates (**I** and **II**)[6] provides access in good yields to the desired products **III** and **IV**, but relies on selective preparation and careful handling of the moderately stable 2-triflates. The second category (exemplified in Ref. 1) proceeds via formation of iodohydrins **VI** from glucals **V**



Scheme 1. Summary of the synthetic routes to 2-iodomannosyl- and 2-iodoglucosyl acetates.

followed by acetylation to give mixtures, which include iodoacetates **III** and **IV**. In most cases this is limited by the low diastereoselectivity of the iodohydrin formation, although in one instance[7] the exclusive formation of 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodomannose has been reported. The third category provides direct access to the iodoacetates **III** and **IV** from glucals **V** using, in most cases, a source of electrophilic iodine together with acetic acid as solvent or co-solvent.[2,3] Yields are generally good to excellent, and product selectivities range from a modest ~2:1 to the synthetically useful ~11:1 in favour of the α-*manno*-configuration, achieved with the CAN/NaI/AcOH procedure.[2] Selectivity in favour of the *gluco*-isomer results when *tert*-butyldimethylsilyl protecting groups are used, and has been explained[8] in terms of the preference in this glycal for the $^{5}H_{4}$

Keywords: Glycals; 2-Izodoglycosides; Iodoacetates.
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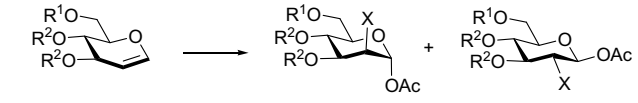
doi:10.1016/j.tetlet.2004.10.166

conformation, which minimizes significant steric interactions of the bulky silyl groups but also restricts access of the electrophile to the β-face of the glucal.

In view of the limited number of efficient approaches to these iodoacetates we felt there was scope for developing alternatives, which exploit the simplicity and cost effectiveness of the oxidation of iodide salts to provide iodonium ion equivalents. The synthetic possibilities of iodination of organic substrates with halide salts in the presence of hydrogen peroxide and a catalyst have recently been highlighted,[1,9,10] and in our first attempts at direct oxidative halogenation we treated tri-*O*-acetyl-D-glucal **1** and tri-*O*-benzyl-D-glucal **2** with NH_4I and 50% aqueous H_2O_2 in acetic acid, using conditions reported to achieve easy iodination of phenol.[11,12] The desired 2-iodoacetates were formed but were accompanied by significant amounts of the corresponding iodohydrins. However, addition of acetic anhydride to the reaction mixture, ideally to intercept water present in the reaction, ensured clean and selective conversion to the iodoacetates, while the further modification of introducing acetonitrile as solvent with concomitant reduction of the amounts of Ac_2O and AcOH, allowed for lowering of the reaction temperature without the solution freezing. These modifications were in consideration that low temperatures generally favour high stereoselectivities, while in addition, the proposed method is optimized with regard to the atom efficient use of the reagents, with close to equivalent amounts of both iodide and H_2O_2 required to realize full conversion in most instances.

Treatment of variously protected glucals and galactals in this way[13] (Scheme 2 and Table 1) provided efficient and selective access to the desired 2-deoxy-2-iodoglycosylacetates. In all cases complete conversion of the starting glycal was achieved, and products were identified by ^1H and ^{13}C NMR spectroscopy after chromatographic separation.[14] Only the 1,2-*trans* addition products were



	R^1	R^2
1	Ac	Ac
2	Bn	Bn
5	TBDPS	Ac
6	TBDPS	Bn
7	TBDPS	TBDPS

	R^1	R^2	X
9a,b	Ac	Ac	I
10a,b	Bn	Bn	I
11a,b	TBDPS	Ac	I
12a,b	TBDPS	Bn	I
13a,b	TBDPS	TBDPS	I
14a,b	Ac	Ac	Br
15a,b	Bn	Bn	Br

Scheme 2. Haloacetoxylation of protected glucals.

Table 1. Yields and selectivities in the iodoacetoxylation of protected glucals (see Schemes 2 and 3)

Entry	Substrate	Products	Yield (%)	Ratio[a]
1	**1**	**9a,b**	85	83:17
2	**2**	**10a,b**	100	91:9
3	**5**	**11a,b**	100	93:7
4	**6**	**12a,b**	95	93:7
5	**7**	**13a,b**	94	17:83
6	**1**	**14a,b**	82	3:2
7	**2**	**15a,b**	88	2:1
8	**8**	**16a–c**	96	15:1:4

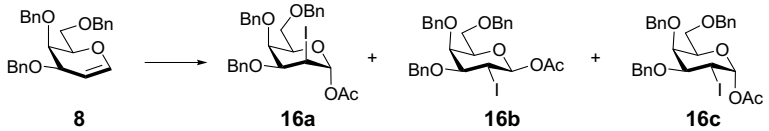
[a] Determined from ^1H NMR of the reaction products before separation.

detected in reactions of protected glucals, and in accordance with previous findings the α-manno products predominated except in the case of the per-*O*-silylated derivatives. The product distribution in the reaction of benzylated galactal **8** was similar to previously reported results with the *talo*-isomer **16a** as the major product, and a significant proportion of α-*gluco*-isomer **16c** resulting from 1,2-*cis* addition (Scheme 3).

The selectivities and yields compare very favourably with reported methods, with those obtained with benzyl or silyl protecting groups being the best yet reported, and the reaction conditions are tolerant of a range of protecting groups. The selectivity towards 2-deoxy-2-iodomannopyranosyl acetate increases noticeably from entries 1–3, corresponding inter alia to changes in the substituent at C-6 from acetyl to benzyl to *tert*-butyldiphenylsilyl. Interestingly, formation of **13b** using NIS in AcOH required heating at 100 °C for 10 min[8] whereas the reaction proceeds at room temperature within 2 h using our method. In general we observed that selectivities were dependent on temperature, with lower temperatures favouring α-*manno* selectivity, although cooling below 0 °C led to unacceptably slow reactions.

The possibility of using this methodology for bromoacetoxylation reactions was demonstrated by replacement of NH_4I with NH_4Br in reactions of acetylated and benzylated glucals **1** and **2** (Scheme 2 and Table 1, entries 6 and 7), albeit that the bromoacetoxylation is less stereoselective. NaI was also evaluated as an iodide source instead of NH_4I in the conversion of acetylated glucal **1** to **9a** and **9b**. In this instance an improved stereoselectivity of 7:1 in favour of **9a** was observed but the yield (64% overall) was inferior and the ^1H NMR spectrum of the reaction products provided evidence for inseparable, hitherto unidentified products.

Concerning the proposed mechanism of the reaction, the appearance of a brown/yellow colour in the reaction



Scheme 3. Iodoacetoxylation of protected galactals.

solutions upon addition of H_2O_2 to the other reactants suggests the presence of molecular I_2, formed either by reaction of I^- with H_2O_2 under acidic conditions[17,18] or by reaction of I^- with peracetic acid, generated upon addition of H_2O_2 to acetic anhydride in the presence of acetic acid.[19] It is possible that an initial and rapid formation of a π-complex between the olefin and I_2 is followed by a rate-determining abstraction of I^- by the peracetic acid.[19] The high degree of stereoselectivity in solvolysis of the resulting iodonium species and the fact that in the absence of acetic anhydride the iodoacetates predominate over iodohydrins suggests that acetic acid attacks the iodonium species directly. The presence of an excess of acetic anhydride ensures that the concentration of water in the reaction mixture is minimized, allowing for successful addition of the acetate or acetic acid to the cyclic iodonium species.

In summary, we have shown that the simple, cost effective and environmentally benign combination of NH_4I (or NH_4Br), 50% aq H_2O_2 and Ac_2O/AcOH in CH_3CN at low temperatures achieves efficient and highly stereoselective haloacetoxylation of protected glycals. The application of this methodology to a wider range of olefins is currently being investigated, together with its compatibility with a wider array of protecting groups, and will be reported later in full.

Acknowledgements

We thank the NRF (South Africa) and the Ministry of the Flemish Community (Flanders, Belgium) for financial support for this research under the RSA-Flemish Community bilateral agreement.

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13. A representative procedure is as follows: To a solution of glucal **1** (100 mg, 0.37 mmol) in AcOH/CH_3CN (1:1, 2 mL) was added NH_4I (64 mg, 0.44 mmol), and Ac_2O (0.5 mL) and the resulting mixture cooled to 0 °C. H_2O_2 (25 μL of a 50% aqueous solution in water, 0.44 mmol) was added and the solution stirred for 1 h at 0 °C, when TLC showed the reaction was complete. A 0.1 M solution of sodium thiosulfate was then added until the brownish colour disappeared, and the solution was cooled in an ice-water bath before adding cold 10% aq NaOH until the solution became slightly basic. The resultant mixture was extracted with ethyl acetate, and the combined organic phases washed once with brine, then dried ($MgSO_4$) and concentrated. Separation of the product mixture by chromatography on silica gel yielded the pure isomers **9a** (144 mg, 70%) and **9b** (30 mg, 15%).
14. Analytical data for known compounds **9a**, **9b**, **10a**, **10b**, **13a**, **13b**, **14a**, **14b**, **15a**, **15b**, **16a**, **16b** and **16c** were consistent with published data (Refs. 5, 7, 14, 15 and 16); data for new compounds is as follows. **11a**: mp 153–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–7.34 (m, 10H, 2 × Ph), 6.45 (d, 1H, J = 1.5 Hz, H-1), 5.63 (t, 1H, J = 9.6 Hz, H-4), 4.60 (dd, 1H, J = 4.2, 9.6 Hz, H-3), 4.52 (dd, 1H, J = 1.5, 4.2 Hz, H-2), 3.98–3.92 (m, 1H, H-5), 3.72 (d, 2H, J = 2.7 Hz, H-6_a and H-6_b), 2.12, 2.09, 1.93 (3s, 9H, 3 × CH_3CO_2), 1.08 (s, 9H, Me_3C–Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.0, 168.2 (3 × CH_3CO_2), 135.8, 135.7, 133.2, 133.1, 129.7, 129.6, 127.6 (2 × Ph), 95.0 (C-1), 74.0 (C-5), 69.2 (C-3), 67.1 (C-4), 62.0 (C-6), 27.3 (C-2), 26.7 (Me_3C–Si), 20.9, 20.8, 20.5 (3 × CH_3CO_2), 19.2 (Me_3C–Si). IR (cm^{-1}): 3004, 2933, 2859, 2346, 1751, 1473, 1429, 1371, 1299, 1240, 1220, 1142, 1112, 1062, 1008, 977, 942. Anal. Calcd for $C_{28}H_{35}IO_8Si$: C, 51.38; H, 5.39. Found: C, 51.42; H, 5.31.
11b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67–7.33 (m, 10H, 2 × Ph), 5.87 (d, 1H, J = 9.3 Hz, H-1), 5.30 (dd, 1H, J = 9.3, 11.2 Hz, H-4), 5.12 (t, 1H, J = 9.3 Hz, H-3), 3.98 (dd, 1H, J = 9.3, 11 Hz, H-2), 3.80–3.65 (m, 3H, H-5, H-6_a and H-6_b), 2.18, 2.09, 1.89 (3s, 9H, 3 × CH_3CO_2), 1.04 (s, 9H, Me_3C–Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 169.3, 168.4 (3 × CH_3CO_2), 136.0, 135.6, 133.1, 133.0, 129.7, 129.6, 127.7, 127.6, 127.5 (2 × Ph), 94.0 (C-1), 75.7, 75.4 (C-3 and C-5), 68.8 (C-4), 62.2 (C-6), 29.7 (C-2), 26.7 (Me_3C–Si), 20.7, 20.6, 20.5 (3 × CH_3CO_2), 19.2 (Me_3C–Si). IR (cm^{-1}): 3075, 2995, 2930, 2857, 2346, 1759, 1464, 1428, 1366, 1271, 1267, 1263, 1260, 1238, 1217, 1113, 1058, 1007, 904, 889. Anal. Calcd for $C_{28}H_{35}IO_8Si$: C, 51.38; H, 5.39. Found: C, 51.50; H, 5.55.
12a: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.18 (m, 20H, 4 × Ph), 6.45 (d, 1H, J = 1.6 Hz, H-1), 4.97 (d, 1H, J = 10.4 Hz, CH_2Ph), 4.74 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.65 (d, 1H, J = 10.4 Hz, CH_2Ph), 4.57 (d, 1H, J = 11.6 Hz, CH_2Ph), 4.48 (dd, 1H, J = 1.6, 4.4 Hz, H-2), 4.26 (t, 1H, J = 9.4 Hz, H-4), 4.00 (dd, 1H, J = 3.2, 11.6 Hz, H-6_a), 3.88–3.82 (m, 2H, H-5 and H-6_b), 3.25 (m, 1H, H-3), 2.01 (s, 3H, CH_3CO_2), 1.11 (s, 9H, Me_3C–Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5 (CH_3CO_2), 135.9, 135.7, 129.6, 129.5, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5 (4 × Ph), 95.8 (C-1), 75.5, 75.5, 75.1 (C-3, C-4, C-5, CH_2Ph), 71.2 (CH_2Ph), 62.2 (C-6), 31.1 (C-2), 26.9 (Me_3C–Si), 20.8 (CH_3CO_2), 19.3 (Me_3C–Si). IR (cm^{-1}): 3071, 3033, 3000, 2933, 2860, 2585, 2346, 1750, 1589, 1497, 1473, 1455, 1428, 1371, 1295, 1272, 1269, 1265, 1261, 1259, 1219, 1143, 1112, 1028, 1000, 937, 868. Anal. Calcd for $C_{38}H_{43}IO_6Si$: C, 60.79; H, 5.77. Found: C, 61.14; H, 5.94.
12b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.21 (m, 20H, 4 × Ph), 5,84 (d, 1H, J = 9.6 Hz, H-1), 4.98 (d, 1H, J = 10 Hz, CH_2Ph), 4.91 (d, 1H, J = 4 Hz, CH_2Ph), 4.89 (d, 1H, J = 4.4 Hz, CH_2Ph), 4.77 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.00 (dd, 1H, J = 9.6, 10.4 Hz, H-2), 3.95 (m, 2H, H-6_a and H-6_b), 3.87 (t, 1H, J = 9 Hz, H-4), 3.78 (dd, 1H,

$J = 9$, 10.4 Hz, H-3), 3.53–3.49 (m, 1H, H-5), 2.19 (s, 3H, CH_3CO_2), 1.05 (s, 9H, Me_3C–Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (CH_3CO_2), 135.9, 135.5, 129.6, 126.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5 (4 × Ph), 94.4 (C-1), 85.4 (C-3), 78.9 (C-4), 76.6 (C-5), 75.8 (C_2Ph), 75.1 (CH_2Ph), 62.0 (C-6), 30.5 (C-2), 26.8 (Me_3C–Si), 20.7 (CH_3CO_2), 19.3 (Me_3C–Si). IR (cm^{-1}): 3073, 3033, 2999, 2931, 2858, 2670, 2349, 1760, 1589, 1497, 1472, 1455, 1428, 1362, 1310, 1271, 1267, 1263, 1260, 1222, 1152, 1112, 1068, 1048, 1029, 1013, 889. Anal. Calcd for $C_{38}H_{43}IO_6Si$: C, 60.79; H, 5.77. Found: C, 61.18; H, 5.75.

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