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VILSMEIER-HAACK REACTION OF GLYCALS- A SHORT ROUTE TO C-2-FORMYL GLYCALS[#]

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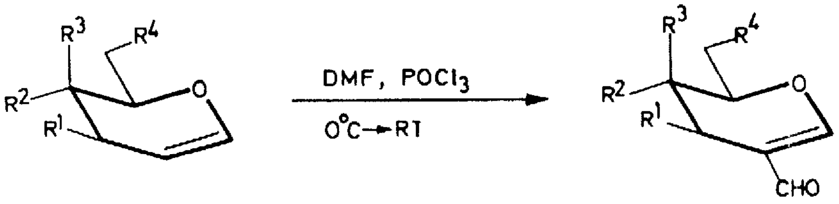
ABSTRACT : A short and straightforward route has been accomplished for the synthesis of C-2-formyl glycals by a Vilsmeier-Haack reaction of glycals.

Several methodologies[1] have been developed in recent years for the construction of a carbon-carbon bond at the anomeric centre of a sugar in view of the importance of C-glycosides[2]. In connection with one of our ongoing projects in this area, we were in search of a potential intermediate which would provide multiple avenues for the stereoselective introduction of carbon-carbon bond at the anomeric carbon and at the same time provide scope for subsequent functional group transformations so as to enable the synthesis of natural and unnatural C-glycosides. C-2-Formyl glycals appeared to be ideal intermediates. There are only two reports on the synthesis of C-2-formyl glycals, one being a dithiane based methodology[3] and the other involving acid hydrolysis of appropriate carbohydrate enol ethers[4]. In this communication we report a short and facile synthesis of 3,4,6-tri-O-alkyl-C-2-formyl glycals based on Vilsmeier-Haack formylation.

Treatment of a solution of 1,5-anhydro-2-deoxy-3,4,6-tri-O-methyl-D-arabino-hex-1-enitol (tri-O-methyl-D-glucal) (1a)[5] (1 mmol) in N,N-dimethylformamide (2 mL) with phosphorus oxychloride (3 mmol) at 0°C and at room temperature for 4h followed by base hydrolysis afforded 1,5-anhydro-2-deoxy-C-2-formyl-3,4,6-tri-O-methyl-D-arabino-hex-1-enitol (2a) as a viscous liquid in 60% yield ($[\alpha]_D^{23}$ = +89.5, c 0.26 in $CHCl_3$; M^+ = 216). The IR spectrum showed intense bands due to C=O and C=C at 1660 cm^{-1}, 1620 cm^{-1} respectively. The ^1H nmr and ^{13}C nmr data confirmed the structure of the compound (Table II).

[#] Dedicated to Dr. K. Nagarajan, Director, R & D, Searle (India) Ltd., Bombay on the occasion of his 60th birthday.

Another ether of glucal (1b)[6] and some ethers of galactal (1d-f)[7-9] also underwent this formylation affording the respective C-2-formyl glycals (Table I). In the case of the galactals, the reactions were quite facile and afforded the products in good yield (Entry 4,5,6; Table I). Particularly noteworthy is the stability of O-trityl group towards the electrophilic reagent and reaction conditions[11]. 1,5-anhydro-2-deoxy-3,4-di-O-methyl-6-O-triphenylmethyl-D-lyxo-hex-1-enitol (3,4-di-O-methyl-6-O-trityl-D-galactal) (1f) was prepared from D-galactal by standard methods[8,9]. However, the 1,5-anhydro-2-deoxy-4,6-O-isopropylidene-3-O-methyl-D-arabino-hex-1-enitol (4,6-O-isopropylidene-3-O-methyl-D-glucal) (1c)[10] was found to be quite unstable under the above conditions or even in the presence of added pyridine (Entry 3; Table I).



1

TABLE I

2

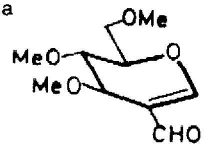
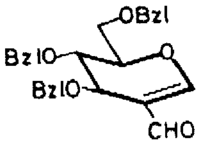
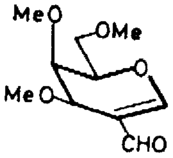
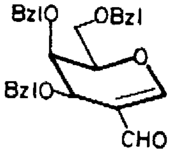
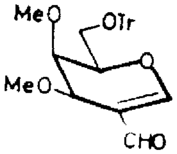
Entry	Substrate	R^1	R^2	R^4	R^3	Product	Reaction time (h)	Yield (%)
1	1a	OCH_3	OCH_3	OCH_3	H	2a	4	60
2	1b	OBzl	OBzl	OBzl	H	2b	8	55
3	1c	OCH_3	$(CH_3)_2C<^{O}_{O}$		H	--	-	--
4	1d	OCH_3	H	OCH_3	OCH_3	2d	8	80
5	1e	OBzl	H	OBzl	OBzl	2e	8-9	35
6	1f	OCH_3	H	OTr	OCH_3	2f	8-9	72

Bzl = benzyl; Tr = trityl (triphenylmethyl)

Though Vilsmeier-Haack reaction[12] has been recognised as one of the best methods for the formylation of active aromatic compounds, enolisable ketones and other active hydrogen compounds, strangely, its application for the synthesis of C-formyl glycals has not been explored[13]. The easy availability of various sugar glycals, mild reaction conditions and the modest to good yields of the products coupled with compatibility of groups like O-trityl, O-benzyl, make the present route an attractive one for the synthesis of C-2-formyl glycals over the existing methods[3,4].

C-2-Formyl glycals and C-2-vinyl glycals have received greater attention recently for their behaviour in Diels-Alder reactions particularly from the view point of π-facial selectivity[14,15]. Our method provides a quick access for these aldehydes, from which the corresponding C-2-vinyl glycals can also be prepared.

TABLE II

Compound No. & Structure*	Specific rotation	^1H nmr δ (ppm)	^{13}C nmr (ppm)
2a 	$[\alpha]_D^{23}$ = +89.5 (c 0.26 in $CHCl_3$)	9.40(s,1H,CHO) 7.38(s,1H,H_1) 4.70(m,1H) 4.19(m,1H) 3.50-3.80(m,3H) 3.40(s,6H,2CH_3) 3.35(s,3H,CH_3)	190.33(d); 164.16(d) 117.36(s); 78.73(d) 73.24(d); 70.72(t) 66.28(d); 59.10(q,q) 57.57(q).
2b 	$[\alpha]_D^{25}$ = +6.8 (c 0.34 in $CHCl_3$)	9.39(s,1H,CHO) 7.20-7.50(m,16H) 4.40-4.70(m,8H) 3.50-3.90(m,3H)	190.40(d); 164.34(d) 138.11(s); 137.58(s) 137.17(s); 128.55(d) 128.44(d); 128.35(d) 128.05(d); 127.89(d) 127.83(d); 127.76(d,d) 127.71(d); 117.69(s) 79.34(d); 73.36(t) 72.43(t); 71.63(t) 71.29(d); 68.39(t) 65.22(d).
2d 	$[\alpha]_D^{26}$ = +68.7 (c 0.50 in CCl_4)	9.36(s,1H,CHO) 7.28(s,1H,H_1) 4.65-4.70(m,1H) 4.45(m,1H) 3.50-3.85(m,3H) 3.35-3.50(3s,9H)	189.41(d); 164.56(d) 118 71(s); 78.33(d) 75.53(d); 70.33(t) 65.52(d); 59.15(q) 59.02(q); 57.78(q)
2e 	$[\alpha]_D^{25}$ = + 5.6 (c 0.45 in CCl_4)	9.30(s,1H,CHO) 7.20-7.40(m,16H) 4.50-4.80(m,8H) 3.80-4.00(m,3H)	189.38(d); 164.38(d) 138.70(s); 137.90(s) 137.37(s); 128.53(d) 128.39(d); 126.15(d) 128.02(d); 127.88(d) 127.73(d); 127.67(d) 127.61(d); 127.41(d) 119.23(s); 78.76(d) 73.67(t); 73.40(t) 73.07(t); 71.50(d) 68.44(t); 64.67(d)
2f 	$[\alpha]_D^{27}$ = +97.4 (c 0.45 in CCl_4)	9.25(s,1H,CHO) 7.20-7.50(m,15H) 7.10(s,1H,H_1) 4.60(m,1H) 4.30(m,1H) 3.42-3.70(m,3H) 3.40(s,3H,CH_3) 3.20(s,3H,CH_3)	189.34(d); 164.64(d) 143.94(s); 128.76(d) 127 77(d), 127.00(d) 118.42(s); 86.93(s) 78.59(d), 75.54(d) 65.72(d); 61.93(t) 58.50(q); 58.04(q)

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* All the compounds exhibited intense bands in the IR spectrum at 1660 cm^{-1} and 1620 cm^{-1} due to C=O and C=C stretching frequencies respectively and showed satisfactory elemental analysis.

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9. 1,5-anhydro-2-deoxy-6-O-triphenylmethyl-D-lyxo-hex-1-enitol (6-O-trityl-D-galactal) was prepared as per reference **8** which was then methylated using NaH and CH_3I in dry DMF.
10. 1,5-anhydro-2-deoxy-4,6-O-isopropylidene-D-arabino-hex-1-enitol (4,6-O-isopropylidene-D-glucal) was prepared according to reference **8**. It was methylated using NaH and CH_3I in dry DMF.
11. A slightly modified procedure was followed for compound 1f. Dry pyridine (3 equiv) was added to Vilsmeier complex (3 equiv) at 0°C prior to the addition of the compound (1 equiv).
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