Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5787-5790, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01226-9

Stereospecific Addition of Formaldehyde Dialkylhydrazones to Sugar Aldehydes. Synthesis of Cyanohydrins and α-Hydroxy Aldehydes.

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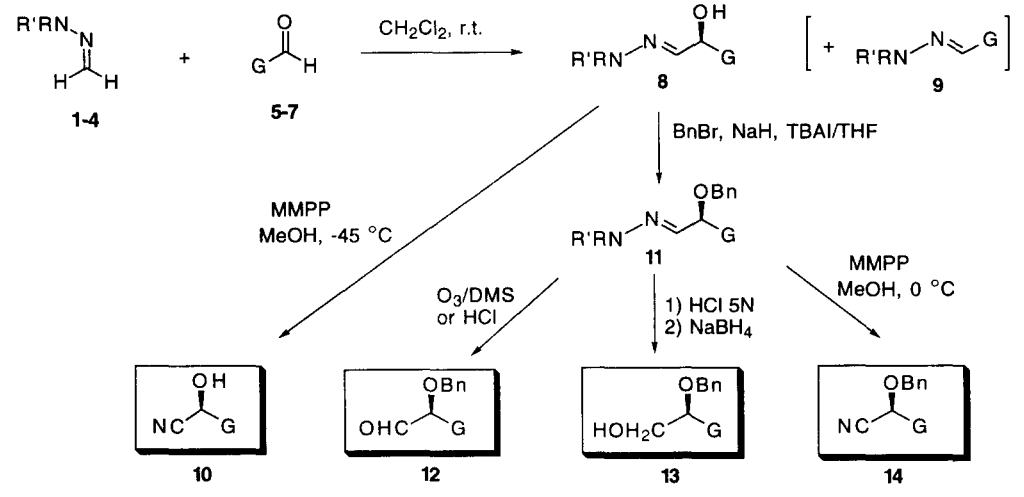
Abstract: Formaldehyde dialkylhydrazones smoothly add to sugar aldehydes without any need of promoter or catalyst. α-Hydroxy dialkylhydrazones, which are obtained in good yields and high stereoselectivities, have been successfully transformed in cyanohydrins by treatment with magnesium monoperoxyphtalate (MMPP) and in *O*-protected α-hydroxy aldehydes by ozonolysis or HCl mediated hydrolysis. No racemization was observed in the cleavage of the dialkylhydrazone group.

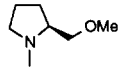
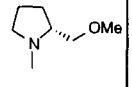
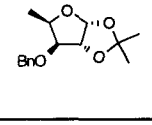
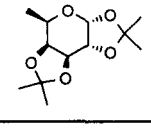
Monosaccharides and derivatives are often employed as chiral synthons or templates for stereospecific synthesis of several types of compounds with multiple asymmetric centers.[1] Among the various means with which a carbohydrate unit can be assembled, methodologies involving as a key operation carbon-carbon bond formation between an enantiopure precursor and a homologative manipulable reactant constitute a leading subject in modern synthetic chemistry.[1,2]

We have recently reported on the use of formaldehyde dialkylhydrazones as neutral formyl anion and cyanide equivalents through Michael addition to conjugated nitroalkenes[3] and enones.[4] We now wish to describe the first results of the extension of this methodology for the stereospecific one-carbon homologation of aldoses and dialdoses leading to cyanohydrins and α-hydroxy aldehydes. Both class of compounds are of great interest due to their synthetic potential. Cyanohydrins can be easily converted to α-hydroxycarboxylic acids, esters, ketones, aldehydes, β-hydroxy amines as well as amino acids without racemization.[5] On the other hand, the synthesis of protected α-hydroxy aldehydes illustrates the possibilities of this methodology as an alternative of the few existing methods[2] for the stereospecific side-chain elongation of aldoses towards long-chain polyhydroxylated aldehydes of interest for natural product synthesis.[1,6]

The addition of formaldehyde dialkylhydrazones **1-4** to sugar derived aldehydes **5-7** proceeded in dichloromethane at room temperature without any need of promoter or catalyst,[7] with the yields and stereoselectivities indicated in Table 1. *O*-Protected α-D-xylodialdofuranose **5** and α-D-galactodialdopyranose **6** afforded esentially one single diastereoisomer of the corresponding adducts **8**, except for the case of the 'mismatched' pairs leading to **8h**. In the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (**7**) with hydrazone **2**, diastereomerically pure hydrazones *anti*-**8i** and *syn*-**8i** could be separated by column chromatography. Efforts to improve the yields or to shorten the reaction times by changing the solvent (MeOH, Et_2O, THF) or by adding different catalysts [$BF_3{\cdot}OEt_2$, dimethylthexylsilyl triflate (TDSOTf), *p*-TsOH, $ZnBr_2$, $ZnCl_2$, etc.] favored the formation of hydrazones **9**, isolated as by products in the non catalyzed addition reaction (Table 1). The formation of these compounds can be explained considering a mechanism involving subsequent direct and

retro [2+2] cycloaddition processes[8] (Scheme 2), in agreement with the known catalysis by Lewis acids in related hetero cycloaddition reactions.



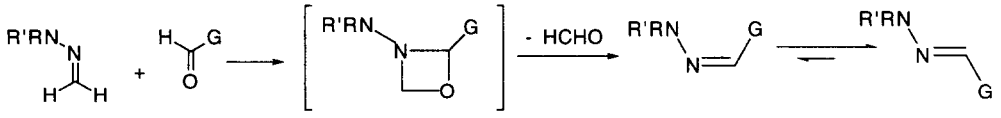
Comp.	1	2	3	4	Comp.	5	6	7
NRR'	NMe_2				G			

Scheme 1

Table 1. Synthesis of Compounds 8-14.[9]

R'RN=CH 2	GCHO	Time	Yield of **8** (%)[a]	de (%)[b]	Yield of **9**	Yield of **10**	Yield of **11**	Yield of **12** (%)[a]	Yield of **13**	Yield of **14**
1	**5**	14 d	**8a**, 38	>95	**9a**, 51					
2	**5**	20 h	**8b**, 73	>95	Traces	**10b**, 86	**11b**, 85	**12b**, 74[c]	**13b**, 71	**14b**, 89
3	**5**	6 d	**8c**, 80	>95	Traces					
4	**5**	3 d	**8d**, 65[e]	93	Traces					
1	**6**	6 d	**8e**, 45	>95	**9e**, 38					
2	**6**	15 h	**8f**, 68	>95	**9f**, 20	**10f**, 73	**11f**, 84	**12f**, 61[d]	**13f**, 65	**14f**, 93
3	**6**	3 d	**8g**, 60	>95	**9g**, 11					
4	**6**	8 h	**8h**, 42[e]	78	Traces					
2	**7**	10 h	**8i**, 70	57	Traces					
			anti-**8i**, 54			**10i**, 71	**11i**, 83	**12i**, 64[d]		**14i**, 88
			syn-**8i**, 7							
3	**7**	46 h	**8j**, 68[e]	75	**9j**, 16					

[a]Of isolated pure product. [b]Determined by ^1H and ^{13}C NMR spectroscopy. [c]By HCl mediated hydrolysis. [d]By ozonolysis. [e]Inseparable mixture of diastereoisomers.



Scheme 2

The easily available and economically prepared pyrrolidine derived hydrazone **2** appears to be the most convenient choice. The higher reactivity of **2** indicates a more effective delocalization of the pyrrolidine nitrogen lone-pair electrons into the π-system, which implies an increased nucleophilic character of the azomethine carbon, in accordance with that observed in the corresponding related enamines.[10] Formaldehyde dimethylhydrazone (**1**) was less reactive, affording higher **9**:**8** ratios, whereas the use of the chiral formaldehyde (*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP or RAMP) hydrazones (**3** or **4**) did not imply better diastereoselectivities or different stereochemical results, indicating that the diastereofacial selectivity of the sugar aldehyde is far superior to that of the chiral hydrazones.[11]

α-Hydroxy hydrazones **8** are of special interest, owing to pronounced versatility due to the presence of both the hydrazone group and suitable protected hydroxy functionality in the molecules. Moreover, adducts **8c**,**d**,**f**,**g**, containing an additional chiral center, are interesting substrates for further asymmetric transformations, i.e. the well established highly diastereoselective, nucleophilic 1,2-addition of organometallic reagents to the C=N bond of chiral SAMP hydrazones to give optically active amines.[12]

The actual equivalence of the pyrrolidinehydrazone moiety with the cyano group was demonstrated through efficient deprotection by oxidative cleavage with MMPP[13] affording cyanohydrins **10** in high yields. The usual synthetic route to optically pure cyanohydrines involves the diastereoselective addition of trimethylsilyl cyanide and related cyanide-transfer agents to chiral aldehydes, and the enantioselective addition of trimethylsilyl cyanide to aldehydes in the presence of chiral catalysts.[5,14] The simplicity of our procedure coupled with the use of inexpensive reagents are important advantages over previous methods.

As the second class of title compounds, the diastereoselective synthesis of *O*-protected α-hydroxy aldehydes **12** was carried out without racemization (^{13}C NMR) either by ozonolysis or HCl mediated hydrolysis of the corresponding α-benzyloxy hydrazones **11**. During ozonolysis the reaction medium remains neutral from the beginning of the reaction until workup, being of special interest to all those carbonyl compounds having additional base- or acid-sensitive groups. Moreover, our use of ozone or diluted acid is preferably to mercury reagents, thermolysis, or strong reducing agents.

Additionally, α-benzyloxy hydrazones **11** were converted into further important and useful derivatives bearing a great synthetic potential (Scheme 1). Acid hydrolysis and subsequent 'one-pot' reduction with $NaBH_4$ led to the monoprotected diols **13**. The MMPP cleavage of **11** gave the protected cyanohydrins **14** in excellent yield. The results of these transformations are collected in Table 1.

The stereochemistry of the newly created stereogenic center of **8** has been demonstrated by comparison with the literature data of the derived α-benzyloxy aldehydes **12b**, **12f** and **12i**,[2] and in all cases is consistent with *anti*-diastereoface selection, according to the Felkin-Ahn open-chain model for nucleophilic addition to chiral carbonyl compounds.[15]

The mildness of the reaction conditions, the operational simplicity, and versatility attributable to the foregoing homologation procedure are particularly noteworthy. These factors, considered in light of the demonstrated synthetic utility of intermediates possessing the dialkylhydrazone moiety, strongly suggest that

this method will be a valuable addition to existing literature procedures for the one-carbon homologation of carbonyl compounds into cyanohydrins and α-hydroxy aldehydes. The addition of formaldehyde SAMP and RAMP hydrazones to simple aliphatic and aromatic aldehydes for the enantioselective synthesis of more complex natural products is now under study in our laboratory.

ACKNOWLEDGMENTS: We thank the Dirección General de Investigación Científica y Técnica for financial support (grant no. PB94-1429) and the Ministerio de Educación y Ciencia for a fellowship to E.M.-Z.

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(*Received in UK* 22 *April* 1996; *revised* 14 *June* 1996; *accepted* 21 *June* 1996)