BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49(4), 1169—1170 (1976)

Branched-chain Sugars. VI. Reaction of Methylene Dimagnesium Bromide with Uloses[1]

Juji YOSHIMURA, Ken-ichi SATO, Hiroo WAKAI, and Masuo FUNABASHI

Laboratory of Chemistry for Natural Products, Faculty of Science, Tokyo Institute of Technology, Meguro-ku, Tokyo, 152

(Received December 5, 1975)

Synopsis Application of methylene dimagnesium bromide, instead of the Wittig reagent, to several uloses gave the corresponding methylene derivatives in nearly equal yields, when the hydroxyl groups vicinal to the carbonyl function are protected with alkaline-stable groups.

The Wittig reaction with uloses is widely used for synthesis of the corresponding substituted and unsubstituted methylene derivatives, which are useful intermediates for preparation of branched-chain sugars as well as for elongation of carbon-chain of monosaccharides.[2]

Bertini *et al.*[3] reported that methylene dimagnesium bromide prepared from dibromomethane and magnesium amalgam in ether–benzene (1 : 1), instead of magnesium turnings in ether only, easily reacts with aldehydes and ketones to afford the corresponding methylene derivatives in good yields. If this method is applicable to uloses, it might be rather easier than the Wittig reaction to handle a large amount of compounds. The present paper describes the results obtained by the reaction of methylene dimagnessium bromide with uloses in comparison with the Wittig reaction.

Results and Discussion

Examination of the conditions for preparation of methylene dimagnesium bromide disclosed that the addition of catalytic amount of iodine and mercuric chloride, instead of magnesium amalgam, easily activates magnesium turnings. (Method A). Moreover, preparation and concurrent reaction of methylene dimagnesium bromide with uloses, by the final addition of dibromomethane to a suspension of an ulose and activated magnesium turnings in tetrahydrofuran gave the best results both in the yield and in handling. (Method B). Such a concurrent preparation-reaction system may prevent the formation of unreactive species of methylene dimagnesium bromide[4], even though tetrahydrofuran was used as a solvent.[3]

As uloses, 1,2 : 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**)[5], 1,2-*O*-isopropylidene-3-*O*-methyl-6-*O*-trityl- (**2**)[6] and -6-*O*-benzyl-α-D-*xylo*-hexofuranos-5-ulose[6] (**3**), and methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranos-3-ulose[7] (**4**) were used. The yields of methylene derivatives are summarized in Table 1, together with that of the Wittig reaction reported in literatures. The structure of products were confirmed by elemental and spectrometric analyses and also by the melting point of admixture. In the case of **4**, only an intractable sirup was obtained both in the Grignard and Wittig reactions. These results indicate that methylene dimagnesium bromide is almost as useful as the corresponding Wittig reagent for preparation of methylene derivatives of uloses.

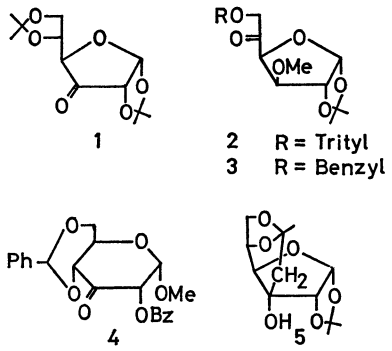

TABLE 1. COMPARISON OF YIELDS OF THE METHYLENE DERIVATIVES (**1**, **2** AND **3**)

Uloses	Yields (%)	
	Wittig reaction	Grignard reaction
1	55[9b], 60[1,9a]	60[a], 72[b]
2	50[6] c)	70[a]
3	85[6]	50[a], 60[b]

a) Method A, b) Method B, c) The yield was 80% in the case of the corresponding 3-*O*-benzyl derivative.[1]

Although the lack of reproducibility remained unexplained, a peculiar compound (**5**) was obtained in 86% yield, in the case of **1** in the method A without ether.

NMR spectrum of **5** showed the appearance of a quartet of isolated methylene group and a very broad signal of a hydroxyl proton, and the disappearance of one methyl signal of isopropylidene group.

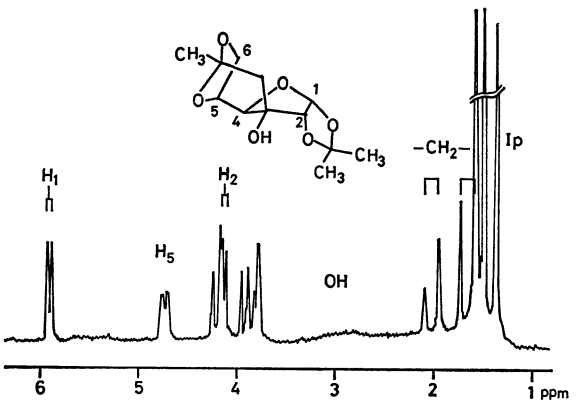

Fig. 1. NMR spectrum of **5**.

From this fact, in addition to the disappearance of the absorption of carbonyl group in IR spectrum, and elemental analysis, the structure **5** was tentatively determined to be 1,2-*O*-isopropylidene-3-*C*-(2′-oxopropyl)-α-D-allofuranose-(2′-*C*, 5-*O*, 6-*O*)-ketal. Examination of the structure with Dreiding model indicates no steric hindrance in this fused-ring system, and a similar structure is known in 1,2-*O*-isopropylidene-[3-*C*, 5-*O*, 6-*O*-(methylmethylidyne)]-α-D-allofuranose.[8]

Experimental

Optical rotations were measured in a 0.5 dm tube with a Carl Zeiss LEP-Al polarimeter. IR spectra were measured with a Hitachi Model EPI-G2 spectrometer. NMR spectra were taken with JEOL 4H-100 spectrometer in deuteriochloroform containing TMS as an internal refernce. Chemical shifts and coupling constants were recorded in δ and Hz units, and IR in cm^{-1}.

Reaction of Uloses with Methylene Dimagnesium Bromide. *Method A.* A suspension of magnesium turning (1.46 g, 60 m atom), catalytic amount of iodine and mercuric chloride in benzene (40 ml) and ether (40 ml) was refluxed for the activation of magnesium, and then the addition of dibromomethane (4.35 g, 25 mmol) to the above suspension with stirring, under cooling if necessary, to form methylene dimagnesium bromide. A solution of uloses (5 mmol) in benzene was added dropwise into the Grignard solution with stirring at room temperature, and the mixture was poured into saturated ammonium chloride after stirring for 1 h. The resulting solution was filtered, and the filtrate was concentrated into a half volume, extracted with chloroform. Concentration of the extracts gave the corresponding methylene derivatives, which were purified by the methods reported in the literatures and identified with authentic specimens.

Method B. To a suspension of magnesium activated as mentioned in method A in tetrahydrofuran, was added, in turn, a solution of uloses in THF and dibromomethane with stirring, under cooling if necessary. The reaction mixture was treated in the same way as above.

1,2-O-Isopropylidene-3-C-(2′-oxopropyl)-α-D-allofuranose-(2′-C, 5-O,6-O)-ketal (5). As an example, methylene dimagnesium bromide (the same scale as method A) was prepared in benzene only. 1,2 : 5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose was then added to the Grignard solution. The work-up of the reaction mixture gave crude crystals which were recrystallized from benzene to give needles having mp 139—140° and $[\alpha]_D^{22}$ −2.8° (*c* 1.1, $CHCl_3$). IR: 3500 (OH), NMR: 5.91 (H_1; d, $J_{1,2}$=3.75), 4.74 (H_5; q), 4.13 (H_2; d), 4.3—3.7 (H_3, H_4, H_6, H_6'; m), 2.02 and 1.66 (CH_2; q, J_{gem}=17.5), 1.60, 1.50 and 1.38 (3×CH_3).

Found: C, 55.66; H, 7.14%. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03%.

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