

SHORT COMMUNICATION

Acyclic Aldehyde Sugars: 1,3-dimethyl-4,5-diamino Uracil as Recoverable Carbonyl Protecting Group[#]

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ARTICLE HISTORY

Received: March 16, 2023
Revised: July 07, 2023
Accepted: July 07, 2023

DOI:

10.2174/1570178620666230901101009



Abstract: 1,3-dimethyl-4,5-diaminouracil has been used as an efficient protecting group for the carbonyl moiety in sugars by the formation of the imine group. The protection reaction is carried out under mild conditions, the yields are quantitative in most of the cases, and the protecting group is completely recovered and reused. After *per*-acetylation, deprotection is accomplished at room temperature with aqueous formic acid to produce acyclic acetylated sugars in good global yield.

Keywords: Acyclic aldehyde sugars, carbonyl, uracil, thioacetals, butyllithium, organic synthesis.

1. INTRODUCTION

Protection and deprotection of carbonyl groups are two of the most important reactions in organic chemistry, and many methods have been developed for these reactions [1, 2]. They are mostly used in the protection of acetal or thioacetal groups [1]; the research is focused on the development of metal-free methodologies, avoiding the use of acids [3, 4]. In the case of thioacetals, efforts have been made towards the use of odorless and efficient thioacetalization reactions and the development of efficient mild ecofriendly cleaving reagents for deprotection of thioacetals and thioketals [5, 6]. However, although aldehyde sugars are important intermediates in natural product synthesis, no general methodology exists for the preparation of these acyclic sugars in which the carbonyl group is appropriately protected to avoid spontaneous lactonization. To date, only two methods have been reported for the preparation of aldehyde sugars, *i.e.*, methods that involve the hydrazone or oxime formation and both, and ozonolysis deprotection [7-10].

Imines have not been extensively used as a protecting group in organic synthesis due to their high reactivity [11]. They have been applied, for example, to the protection of aromatic aldehydes during the imine ortho-directed aromatic ring metallation with butyllithium [12, 13] or during the enantioselective alkylation of glycine [14].

We wish to report here that acetyl-protected acyclic sugar can be prepared on a multigram scale *via* the formation of an acyclic imine derivative of 1,3-dimethyl-4,5-diaminouracil (**1**) [15-17]. It is interesting that the protecting group can be quantitatively recovered and reused [18]. The availability of these sugar aldehydes will facilitate their use in organic synthesis.

2. RESULTS

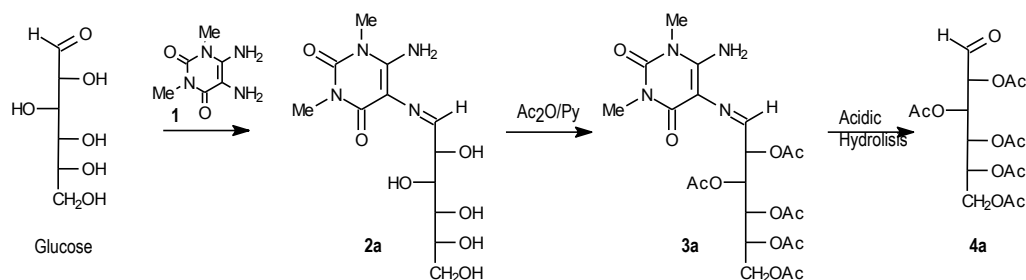
In this work, the aldehyde group of various sugars was converted to the corresponding Schiff base by sugar treatment with compound **1** in methanol at room temperature under an argon atmosphere [19, 20]. The detailed experimental is shown in the experimental section, and the results are shown in Table 1 (Scheme 1).

Yields of the reactions were almost quantitative in all cases and the protected compound **2a-g** was isolated by precipitation from the reaction mixture. In all cases, the imine derivative was purified by crystallization from ethanol. Only in the case of the imine of ribose (Table 1, entry 6), any attempt of purification was unsuccessful, and only decomposition products could be detected. Experimental data for the hydroxyl-free imines were found to be in accordance with their structures.

Hydroxyl acetylation in the protected sugars was carried out with acetic anhydride and pyridine at room temperature. Compounds **3a-g** were obtained in good yields. The results are shown in Table 1. Finally, by treating a solution of the acetylated imine **3a-g** in 10% aqueous formic acid for 2 h at room temperature, the aldehyde sugars (**4a-g**) were obtained

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[#]Dedicated to Professor Rico on the occasion of his retirement.



Scheme 1. Protection, acetylation, and deprotection sequence.

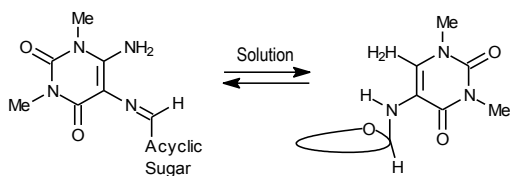
Table 1. Protection, acetylation, and deprotection yields.

Entry	Sugar	Imine (2) Yield, %	Acetylation (3) Yield, %	Aldehyde (4) Yield, %
1	D-glucose, a	94	81	90
2	D-galactose, b	88	89	81
3	D-mannose, c	90	92	93
4	D-arabinose, d	91	92	85
5	L-arabinose, e	89	85	77
6	D-ribose, f	94	96	95
7	D-xylose, g	97	82	96

in almost quantitative yield. These results have also been summarized in Table 1.

3. DISCUSSION

The regioselectivity of the reaction of compound **1**, where the amine group in position 5 was the reactive group, could be attributed to the non-basic character of the amine in position 4. The synthesized acyclic imines **2a-g** existed in a facile equilibrium, as observed in the $^1\text{H-NMR}$ spectra, between the acyclic imine group ($^1\text{H-NMR}$ for H-1' *ca.* d 8 ppm) and cyclic lactam ($^1\text{H-NMR}$ for H-1' *ca.* d 4 ppm). The cyclic isomer was observed in CDCl_3 , Py-d_6 , or DMSO-d_6 , suggesting a fast equilibrium with this compound as the dominant species (Scheme 2).



Scheme 2. Equilibrium in solution of protected sugars.

Hydroxyl acetylation in the protected sugars was achieved in good yields by treating the imines **2a-g** with a mixture of acetic acid anhydride and pyridine at room temperature by following the standard methods for this reaction [15, 17].

Deprotection of the carbonyl group was accomplished by treatment of Schiff's bases under acidic conditions at room temperature (Ar atmosphere to avoid spontaneous oxidation of compound **1**). Several acids were studied, including acetic acid, oxalic acid, hydrochloric acid, sulfuric acid, and formic acid at concentrations between 10% and 50%. Best yields and smooth conditions were obtained with aqueous formic acid. This reaction time (2 h) was enough to completely deprotect the carbonyl group. The crude aldehydes were isolated in greater than 90% purity by extraction with chloroform, followed by evaporation of the solvents under vacuum, and then purified by crystallization. The aqueous layer was concentrated to dryness under vacuum to quantitatively recover the protecting group (**1**).

4. METHODS

General procedure for carbonyl protection. A solution of sugar (0.26 mol), compound **1** (45.0 g, 0.26 mol), and acetic acid (10 mL) in dry methanol (1000 mL) was stirred at 22°C for 12 h under the Ar atmosphere. During this period, a white solid appeared. The solid was filtered off and washed with cold methanol to give imine **2a-g**.

General procedure for carbonyl deprotection. Imine **3a-g** (0.033 mol) was stirred in a solution of 1 M aqueous formic acid (500 mL) for 2 h 15 min. The solution mixture was extracted with CHCl_3 (2 x 100 mL), washed with water (1 x 100 mL), and concentrated under vacuum to dryness. Crystallization from ethanol gave pure per-acetylated acyclic sugars **4a-g**. Recovery of compound **1** was accomplished by

concentration under vacuum to achieve dryness of the aqueous phase.

CONCLUSION

In conclusion, we have developed a mild and efficient method for the protection of the carbonyl moiety in sugars. Acetylation and deprotection lead to the per-acetylated acyclic sugars. Also, the reactions can be carried out on a multi-gram scale. This method avoids more complicated reaction and elaboration conditions needed in the ozonolysis deprotection and the use of non-environmentally safe reagents.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

FQM397 and UMA20-FEDERJA84 projects provided the financial support for this study (Grant no. 8.06/5.81.5984).

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

We thank Junta de Andalucía the financial support.

REFERENCES

- [1] Wuts, P.G.M. John Wiley & Sons: New York, **2014**.
- [2] Fernandes, R.A. John Wiley & Sons: New York, **2018**.
<http://dx.doi.org/10.1002/9781119295266>
- [3] Terlizzi, L.D.; Galathri, E.M.; Protti, S.; Kokotos, C.G.; Fagnoni, M. **2023**, *16*, e202201998.
<http://dx.doi.org/10.1002/cssc.202201998> PMID: 36427248
- [4] Steuernagel, D.; Wagenknecht, H.A. *Chemistry*, **2023**, *29*(13), e202203767.
<http://dx.doi.org/10.1002/chem.202203767> PMID: 36524858
- [5] Yu, H-F.; Liao, P-Q. *Chem. J. Chin. Univ.*, **2012**, *33*, 1969-1972.
- [6] Ganguly, N.C.; Nayek, S.; Barik, S.K. *J. Indian Chem. Soc.*, **2011**, *88*, 251-256.
- [7] Spencer, R.P.; Bae Yu, H.K.; Cavallaro, C.L.; Schwartz, J. *J. Org. Chem.*, **1997**, *62*(13), 4507-4509.
<http://dx.doi.org/10.1021/jo970067d> PMID: 11671783
- [8] Weitz, D.J.; Bednarski, M.D. *J. Org. Chem.*, **1989**, *54*(20), 4957-4959.
<http://dx.doi.org/10.1021/jo00281a046>
- [9] Bález-Sanz, J.M.; López-Sastre, J.A.; Patiño-Molina, M.R.; Santacana-Gómez, T.; Romero-Ávila, C. *J. Carbohydr. Chem.*, **1999**, *18*, 403417.
- [10] Sarabia, F.; Chammas, S.; López Herrera, F.J. *Tetrahedron*, **2001**, *57*(52), 10271-10279.
[http://dx.doi.org/10.1016/S0040-4020\(01\)01074-2](http://dx.doi.org/10.1016/S0040-4020(01)01074-2)
- [11] Bekhit, A.A.; El-Sayed, O.A.; Aboul-Enein, H.Y.; Siddiqui, Y.M.; Al-Ahdal, M.N. *J. Enzyme Inhib. Med. Chem.*, **2004**, *19*(1), 33-38.
<http://dx.doi.org/10.1080/14756360310001650219> PMID: 15202490
- [12] Kende, A.S.; Curran, D.P. *J. Am. Chem. Soc.*, **1979**, *101*(7), 1857-1864.
<http://dx.doi.org/10.1021/ja00501a036>
- [13] Keay, B.A.; Rodrigo, R. *J. Am. Chem. Soc.*, **1982**, *104*(17), 4725-4727.
<http://dx.doi.org/10.1021/ja00381a059>
- [14] Respondek, T.; Cueny, E.; Kodanko, J.J. *Org. Lett.*, **2012**, *14*(1), 150-153.
<http://dx.doi.org/10.1021/ol202939g> PMID: 22149572
- [15] patent US5510484A, **1994**.
- [16] Wawzonek, S. *J. Org. Chem.*, **1976**, *41*(2), 310-313.
<http://dx.doi.org/10.1021/jo00864a027> PMID: 1245906
- [17] Blicke, F.F.; Godt, H.C., Jr. *J. Am. Chem. Soc.*, **1954**, *76*(10), 2798-2800.
<http://dx.doi.org/10.1021/ja01639a058>
- [18] Benavente, J.; García, M.E.; Urbano, N.; López-Romero, J.M.; Contreras-Cáceres, R.C.; Casado-Rodríguez, M.A.; Moscoso, A.; Hierrezuelo, J. *Int. J. Biol. Macromol.*, **2017**, *103*, 758-763.
<http://dx.doi.org/10.1016/j.ijbiomac.2017.05.133> PMID: 28545964
- [19] Rico-Gómez, R.; Rodríguez-González, A.; Ríos-Ruiz, J.; Nájera, F.; López-Romero, J.M. *Eur. J. Org. Chem.*, **2003**, *2003*(20), 4023-4032.
<http://dx.doi.org/10.1002/ejoc.200300377>
- [20] Rico-Gómez, R.; López-Romero, J.M.; Hierrezuelo, J.; Brea, J.; Loza, M.I.; Pérez-González, M. *Carbohydr. Res.*, **2008**, *343*(5), 855-864.
<http://dx.doi.org/10.1016/j.carres.2008.01.011>

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