HETEROCYCLES, Vol. 61, 2003, pp. 101 - 104
Received, 29th August, 2003, Accepted, 8th October, 2003, Published online, 20th October, 2003

A NEW BISMUTH NITRATE-INDUCED STEREOSPECIFIC GLYCOSYLATION OF ALCOHOLS↑

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↑On the occasion of the 30th Anniversary of Heterocycles, Volume 61

Abstract - Bismuth nitrate-catalyzed stereospecific glycosylation of alcohol with glycal has been developed.

The glycosylation of alcohols is a fascinating area of research because of the biological activities of O-glycosides.[1] Therefore, methods to develop effective glycosylation are in demand.[2] Although discovered many years ago, Ferrier rearrangement[3] is still one of the most attractive methods for this purpose. Several Lewis acids[4] and acidic-support[5] have been utilized to accomplish this transformation. The main shortcomings of these processes are the non-stereoselectivity of the reaction and as a result mixtures of α- and β-glysosides are generally formed in varying proportion. Attempts have been made to improve the stereoselectivty and some successful realization of this target towards better α-isomer is also achieved.[6]
We have been working on metal or its salt-mediated reactions on a projected route towards the development of several biologically active compounds including anticancer agents[7] and β-lactams.[8] Our exploration in this field culminated a convenient method for the stereoselective synthesis of β-glycosides in moderate yield by the reaction of alcohols and acetobromoglucose in the presence of indium.[9] During this course of study, we became interested in developing the synthesis of several α-glycosides *via* Ferrier rearrangement using eco-friendly reaction conditions. This paper describes a stereospecific glycosylation mediated by bismuth nitrate in good yield. We believe this is the first stereoselctive and chiral resolution method of alcohols *via* glycosylation by bismuth nitrate.
We reported the use of bismuth nitrate in several organic transformations.[10, 11] For example, nitration of aromatic hydrocarbons, phenolic compounds and β-lactams were realized in excellent yield.[10] A facile Michael reaction of indoles and carbamates with unsaturated ketones was also worked well with bismuth nitrate.[11] These reactions, in principle, require the presence of mineral acids or Lewis acids. The

mechanism of these bismuth nitrate reactions is not fully explored. However, involvement of catalytic amounts of nitric acid is speculated. There are unique advantages of using bismuth salts: the non-toxicity and mildness are the main criteria. Since Ferrier rearrangement is an acid-mediated process, we envision that bismuth nitrate might be a good catalyst in the glycosylation of alcohols in the presence of glycal. We are delighted to disclose our findings that bismuth nitrate actually proves to be effective in catalyzing a Ferrier type of rearrangement and the results are presented below.

Scheme 1

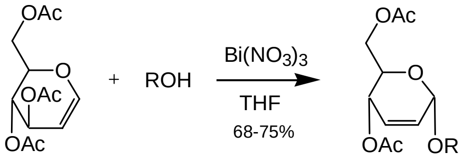
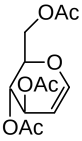
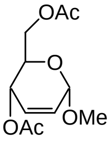
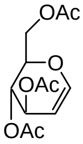
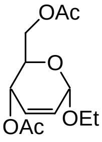
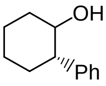
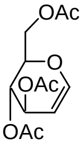
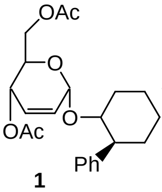
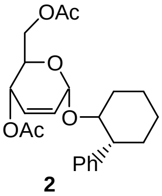
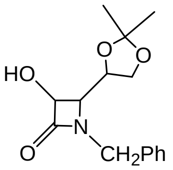
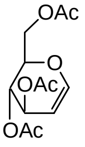
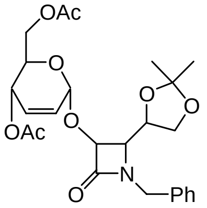
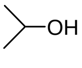
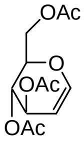
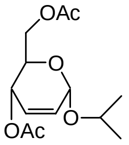
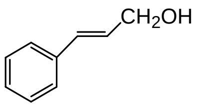
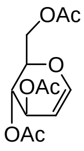
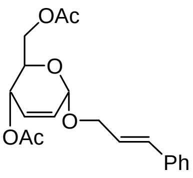


Table 1: Glycosylation of Alcohols with 3, 4, 5-tri-*O*-acetoxy Glucal

Entry	Alcohol	Sugar	Glycoside	Yield (%)
1	MeOH			75
2	EtOH			75
3			 **1** +  **2**	68
4				70
5				70
6				70

Reaction of methanol, ethanol and isopropanol and other alcohols with 3, 4, 5-tri-*O*-acetyl D-glucal in the presence of bismuth nitrate (10-30 mol%) produced a single glycoside in each case in 68-75% yield. The anomeric stereochemistry of these glycosides was determined as α- from the coupling constant of the anomeric hydrogen (8-10 Hz) of a reduced isomer prepared by a hydrogenation experiment (**Scheme 1** and **Table** 1).

To improve the scope of this method, glycosylation reaction was then performed on racemic alcohol with two chiral centers with the hope of their optical resolution. Thus, reaction of 2-phenylcyclohexanol under identical conditions produced two diastereomeric α-glycosides which were separated by column chromatography (Entry 3). The individual glycosides (**1**) and (**2**) then converted to the optically active *trans* phenyl cyclohexanols (**3**) and (**4**) of opposite stereostructures by acid-mediated cleavage reaction (**Scheme 2**).

Scheme 2

The present glycosylation method was then extended to optically active hydroxy β-lactams (Entry 4). A single isomer in good yield was obtained and the stereochemistry of the glycoside bond was deduced to be α. The exclusive formation of the α-glycoside deserves some special comments. Reaction of simpler alcohols with nitric acid was attempted, but a complex mixture of products was obtained. Separation of pure glycosides from this mixture was practically impossible. We believe this is due to the high strength of nitric acid. Attempts to obtain glycosides by using varying concentration of nitric acid proved very difficult: in some cases reactions were sluggish and in some cases complex mixtures of products were formed. In order to confirm the critical role of bismuth nitrate in this reaction, other metal salts were tested. For example, ferric nitrate and zinc nitrate gave poor yield of glycosides. However, copper sulfate, sodium nitrate and ferric chloride proved to be ineffective completely indicating the precise role of bismuth nitrate in this reaction.

The complexation role of bismuth nitrate with the unsaturated bond of the glycal is ruled out since the reaction does not proceed at all in the presence of solid potassium carbonate (20 mol%). Alternatively, an allylic isomerization of glucal to a 2, 3-dehydro sugar and subsequent S_N1 reaction might be the route in the presence of bismuth nitrate.

The formation of a single isomer and successful resolution of racemic alcohol can open further possibilities of research with this inexpensive reagent. The glycosylation reaction conducted with environmentally benign reagent bismuth nitrate can be used for increasing the hydrophilicity of hydroxy compounds and for providing access to additional functional groups by modification of the carbohydrate moiety.

ACKNOWLEDGMENTS

We gratefully acknowledge the funding support received for this research project from the University of Texas M. D. Anderson Cancer Center for the partial support of this research. We are thankful to NIH Cancer Center Support Grant, 5-P30-CA16672-25, in particular the shared resources of the Pharmacology and Analytical Center Facility.

[a:] Undergraduate research participant

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12. A representative procedure: A mixture of methanol (1 mL), glycal (1.5 mmol), bismuth nitrate pentahydrate (0.2 mmol) was stirred at room temperature for overnight. The progress of the reaction was monitored by TLC. After the reaction, dichloromethane (20 mL) was added to it and then it was washed with saturated sodium bicarbonate (5 mL), brine (5 mL) and dried with sodium sulfate. The solvent was evaporated in vacuo and directly subjected to column chromatography using silica gel (230-400 mesh, 20% ethyl acetate-80% hexane) to afford the pure product. The reaction was performed with 1 mmol of alcohols and THF was used as the reaction media in Entries 3, 4 and 6.