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Short Communication

A Mild and Efficient Synthesis of Chiral Tetrahydroquinolino Pyranose Derivatives Catalyzed by Lanthanum(III) Nitrate Hexahydrate

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ABSTRACT: *A mild and highly efficient synthesis of chiral tetrahydroquinolino pyranose derivatives is described. The reaction of a chiral α,β-unsaturated aldehyde containing a hydroxyl group with different aryl amines using lanthanum(III) nitrate hexahydrate as a catalyst afforded corresponding chiral tetrahydroquinolinated pyranosides in excellent yields.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:429–433, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20441

INTRODUCTION

Tetrahydropyran moiety is present in many bioactive natural products, namely bryostatin-1, nerostatin-1, halichondrin-B, isohomohalichondrin-B, and several heterocyclics. The chemistry of tetrahydroquinoline derivatives is interesting to organic chemists owing to the presence of these scaffolds within the framework of numerous biologically interesting natural products and synthetic pharmaceutical agents [1,2]. The tetrahydroquinoline skeleton is present in many alkaloids [3–5], such as flindersine, orcine, and veprisine, and derivatives of these alkaloids possess a wide range of biological activities such as psychotropic, antiallergic, anti-inflammatory, and estrogenic activities [6–8]. Therefore, many synthetic methods have been developed for these classes of compounds. Most of the methods employed the hetero Diels–Alder method using different Lewis acids such as $BF_3{\cdot}OEt_2$ [9], $ZnCl_2$ [10], $BiCl_3$ [11], and $InCl_3$ [12,13] and Brönsted acids such as HBF_4, CF_3COOH, TsOH [14], and also mineral acids [15] to produce 2,3-tetrahydroquinolinated pyranose derivatives. Recently, Yadav et al. reported the synthesis of 2,4-tetrahydroquinolinated pyranose derivatives using $InBr_3$, $Bi(OTf)_3$, and $CeCl_3$/NaI [16–18]. Many of these methods having one or more disadvantages such as high acidity, long-reaction times, high reaction temperatures, use of stoichiometric amounts of reagents, difficulty in preparation of the catalyst, and most of these methods were conducted under moisture-free conditions. The use of either strongly acidic or basic conditions frequently leads to the formation of undesirable side products competing the reactions, such as polymerization, self-condensation, and rearrangements, which in turn decrease the purity and yields of the desired products. In view of current interest

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in catalytic processes, there is a merit to synthesize chiral tetrahydroquinolino pyranose derivatives using an inexpensive, mild, and nonpolluting reagent.

RESULTS AND DISCUSSION

The increasing demand of clean and efficient chemical reactions results in mild reaction conditions, which are areas of current great interest. On the other hand, organic reactions using a water-tolerant catalyst also received much attention in recent years, as they can be handled conveniently and removed from the reaction mixture, making the experimental procedure simple and ecofriendly. Recently, we explored $La(NO_3)_3{\cdot}6H_2O$ as a mild and efficient catalyst for the chemoselective tetrahydropyranylation of primary alcohols [19], chemoselective deprotection of acetonides [21], synthesis of quinazolinones [22], for acetylation of alcohols, phenols, and amines [20], synthesis of α-amino nitriles [23], *N*-benzyloxycarbonylation [24], *N*-tert-butoxycarbonylation of amines [25], thioacetylation of aldehydes [26], chemoselective protection of alcohols as their pivaloyl esters [27], and for efficient cleavage of cyclic and acyclic ethers [28]. In the above transformations, it has been observed that the substrates containing acid labile functional groups such as acetonides, TBDMS ethers, some isopropylidene-protected diols, and *N*-tert-Boc-protected amines were intact in the presence of $La(NO_3)_3{\cdot}6H_2O$. To continue our efforts to know the utility of $La(NO_3)_3{\cdot}6H_2O$, we found that it is an efficient and mild acid catalyst for the synthesis of chiral tetrahydroquinolino pyranose derivatives.

At the outset, enantiopure 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro-trans*-hex-2-enose was reacted with 2,4,5-tricloro aniline (Table 2, entry 1h) in the presence of 5 mol% of lanthanum(III) nitrate hexahydrate in acetonitrile at room temperature to yield the corresponding benzofused hetero bicycle (**3h**) in 89% yield. To optimize the reaction conditions, we carried out the above-mentioned reaction with different amounts of the catalysts varying from 5 mol% to 1 equivalent in different solvents, such as acetonitrile, chloroform, dichloromethane, 1,4 dioxane, and tetrahydrofuran at room temperature. We found that using 5 mol% of lanthanum(III) nitrate hexahydrate in acetonitrile gave the interesting results (Table 1, entry 5). Furthermore, increasing the amount of lanthanum(III) nitrate hexahydrate did not affect the rate of the reaction. Encouraged by these results, we carried out the reaction of several aryl amines with chiral acyclic α,β-unsaturated aldehydes containing γ-hydroxyl group, under similar conditions to yield corresponding sugar-derived tetrahydroquinolines in excellent yields (Table 2).

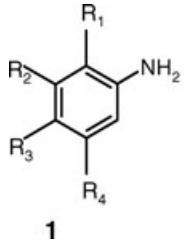
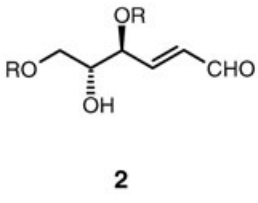
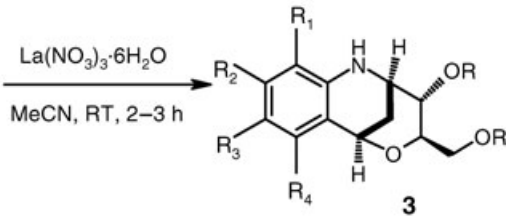
La(III) is highly oxophilic in nature and forms labile bonds with oxygen donor atoms and facilitates throughout the reaction. We believe that initially aryl amine attacks at β position of chiral α,β-unsaturated carbonyl compound followed by electrophilic substitution giving 4-hydroxy tetrahydroquinoline. Finally, it forms a tetrahydropyranose ring by losing of a water molecule (Scheme 2).

In conclusion, we described a mild and efficient protocol for the synthesis of tetrahydroquinolino pyranose derivatives from 4,6-di-*O*-acetyl-2,3-dideoxy-*aldehydo*-D-*erythro-trans*-hex-2-enose and aryl amines using catalytic amounts of lanthanum(III) nitrate hexahydrate. This method has following advantages: requires less reaction time, gives high yields and ecofriendly, does not need expensive reagents or special care to exclude moisture from the reaction medium, and catalytic amounts of reagent to form corresponding products in excellent yields, which makes it a useful and important addition to the present existing methods.

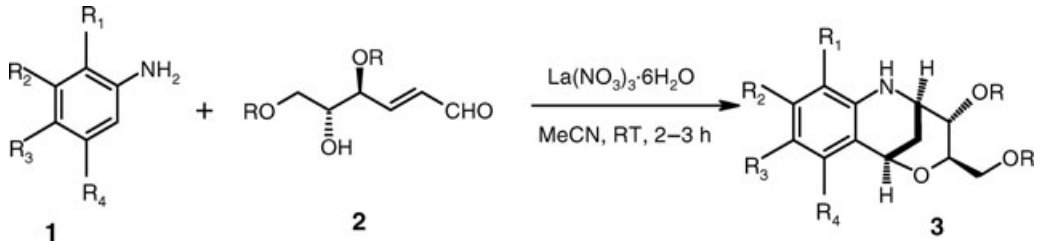
TABLE 1 Optimization of Reaction Conditions on the Reaction of 4,6-di-*O*-Acetyl-2,3-di-deoxy-*aldehydo*-D-*erythro-trans*-hex-2-enose with Aniline at Room Temperature

Entry	*$La(NO_3)_3{\cdot}6H_2O$*	*Solvent*	*Time (h)*	*Yield (%)*
1	1 equiv.	Acetonitrile	2	96
2	50 mol%	Acetonitrile	2	96
3	20 mol%	Acetonitrile	2	96
4	10 mol%	Acetonitrile	2	95
5	5 mol%	Acetonitrile	2	95
6	5 mol%	Chloroform	4	90
7	5 mol%	Dichloromethane	4	80
8	5 mol%	1,4 Dioxane	3	90
9	5 mol%	Tetrahydrofuran	4	89

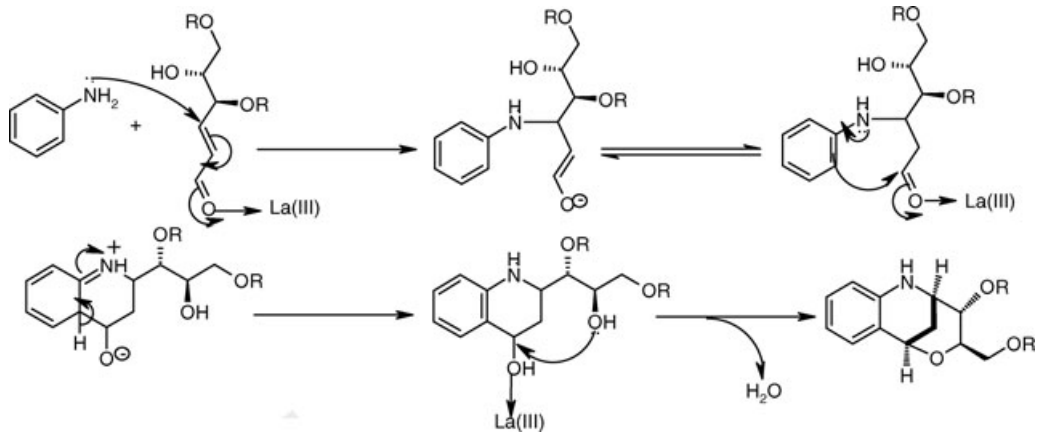
TABLE 2 Synthesis of Sugar-Derived Chiral Tetrahydroquinolino Pyranose Derivatives from Hydroxy-α,β-unsaturated Aldehydes and Aryl Amines Using Lanthanum(III) Nitrate Hexahydrate as a Catalyst

Entry	*Aryl Amine*	*α,β−Unsaturated Aldehyde*	*Product*[a]	*Reaction Time (h)*	*Yield*[b] *(%)*
	 **1**	 **2**	 **3**		
1a	$R_1 = R_2 = R_3 = R_4 = H$	R = Ac	**3a**	2	95
1b	$R_1 = R_2 = R_4 = H$, $R_3 = F$	R = Ac	**3b**	3	90
1c	$R_1 = F$, $R_2 = R_3 = R_4 = H$	R = Ac	**3c**	2.5	92
1d	$R_1 = Cl$, $R_2 = R_3 = R_4 = H$	R = Ac	**3d**	3	90
1e	$R_1 = Me$, $R_2 = R_3 = R_4 = H$	R = Ac	**3e**	2	92
1f	$R_2 = Cl$, $R_1 = R_3 = R_4 = H$	R = Ac	**3f**	3	90
1g	$R_3 = Me$, $R_1 = R_2 = R_4 = H$	R = Ac	**3g**	2	89
1h	$R_1 = R_3 = R_4 = Cl$, $R_2 = H$	R = Ac	**3h**	3	89
1i	$R_1 = R_4 = H$, $R_2 = R_3 = F$	R = Ac	**3i**	2.5	90
1j	$R_2 = Me$, $R_1 = R_3 = R_4 = H$	R = Ac	**3j**	3	94
1k	$R_1 = R_3 = Cl$, $R_2 = R_4 = H$	R = Ac	**3k**	3	93
1l	$R_3 = OAc$, $R_1 = R_2 = R_4 = H$	R = Ac	**3l**	2.5	92
1m	$R_1 = R_2 = R_3 = R_4 = H$	R = Bn	**3m**	2	89
1n	$R_1 = R_2 = R_4 = H$, $R_3 = F$	R = Bn	**3n**	2	79
1o	$R_1 = R_2 = R_3 = R_4 = H$	R = Me	**3o**	2	76
1p	$R_1 = R_2 = R_4 = H$, $R_3 = F$	R = Me	**3p**	2	94

[a]All the products was characterized by ^1H NMR, ^{13}C NMR, IR, and mass spectral analysis.
[b]Yields refers to isolated pure compound yield after column chromatography.



SCHEME 1



SCHEME 2

EXPERIMENTAL SECTION

Typical Experimental Procedure for the Synthesis of Chiral Tetrahydroquinolino Pyranose Derivatives

To a solution of aryl amine (1 mmol) and 4,6-di-*O*-acetyl-2,3-di-deoxy-*aldehydo*-D-*erythro*-*trans*-hex-2-enose (1 mmol) in acetonitrile (25 mL) was added lanthanum(III) nitrate hexahydrate (5 mol%). The reaction was stirred at room temperature for an appropriate time (Table 2). After completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure, water was added (10 mL), and the product was extracted into ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum to give crude product, which was purified on a silica gel column to yield corresponding sugar-derived chiral tetrahydroquinolino pyranose derivatives in good yields. Spectral data for selective compounds as follows:

3b: Oily liquid, $[a]_D^{27} = 67.1$ ($c = 0.75$, $CHCl_3$), IR (KBr): υ_{max}: 3356, 2961, 1733, 1505, 1260, 1040, 809 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.75–6.89 (m, 2H), 6.4–6.48 (m, 1H), 4.76 (dd, $J = 3.1$, 10.5 Hz, 1H), 4.65 (dd, $J = 1.8$, 3.8 Hz, 1H), 4.25 (brs, 1H, NH), 4.15 (dd, $J = 4.2$, 12.0 Hz, 1H), 3.85 (dd, $J = 2.1$, 12.0 Hz, 1H), 3.75 (ddd, $J = 2.5$, 3.1, 4.5 Hz, 1H), 3.5 (ddd, $J = 2.1$, 4.2, 10.3 Hz, 1H), 2.2 (ddd, $J = 2.5$, 3.8, 13.1 Hz, 1H), 2.1 (s, 3H), 2.0 (s, 3H), 1.95 (ddd, $J = 1.8$, 4.5, 13.1 Hz, 1H). ^{13}C NMR (proton decoupled, 75 MHz, $CDCl_3$): δ 170.2, 169.5, 156.7, 141, 119.4, 117.2, 116.5, 113.7, 71.7, 68.1, 67.7, 62.6, 46.7, 27.9, 21, 20.8. FAB mass: 323 (M^+) 267, 221, 191, 147, 133, 73.

3c: Solid, mp 116–118°C; $[\alpha]_D^{25} + 41.6$ ($c = 2.0$, $CHCl_3$); IR (KBr) γ_{max}: 3378, 2866, 2858, 1707, 1626, 1488, 1244, 998, 824, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 6.80–6.90 (m, 2H), 6.5–6.55 (m, 1H), 4.74 (dd, $J = 3.1$, 9.8 Hz, 1H), 4.66 (dd, $J = 1.8$, 3.8 Hz, 1H), 4.35 (brs, 1H, NH), 4.13 (1H, ddd, $J = 12.08$, 6.70, 4.53 Hz), 3.93 (1H, dd, $J = 12.08$, 2.27 Hz), 3.80 (1H, ddd, $J = 4.7$, 3.3, 2.1 Hz), 3.46–3.52 (1H, m), 2.27 (1H, ddd, $J = 13.6$, 3.6, 2.4 Hz), 2.07 (3H, s), 2.04 (3H, s), 1.86–1.90 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 164.6, 142.0, 129.4, 126.6, 119.2, 119.0, 113.6, 69.9, 68.0, 67.3, 63.1, 46.8, 27.5, 21.0, 20.7; EI mass *m/z*: 321 (M^+), 148, 141, 97, 71, 58, 44.

3h: IR (KBr) γ_{max}: 3417, 2926, 1739, 1620, 1584, 1464, 1369, 1230, 1064, 816, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.98 (1H, s), 4.86 (1H, dd, $J = 10.8$, 3.6 Hz), 4.72 (1H, dd, $J = 4.1$, 2.0 Hz), 4.38 (1H, br s, NH), 4.23 (1H, dd, $J = 12.2$, 4.2 Hz), 4.0 (1H, dd, $J = 12.2$, 1.8 Hz), 3.76 (1H, ddd, $J = 4.5$, 3.2, 2.5 Hz), 3.61 (1H, ddd, $J = 10.2$, 4.2, 2.1 Hz), 2.24 (1H, m), 2.12 (3H, s), 2.04 (3H, s), 1.98 (1H, m); FAB mass *m/z*: 409 ($M^+ + H$), 339, 333, 292, 220, 281, 194, 166, 153, 128, 97, 84, 44.

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