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An Efficient One-Pot Synthesis of β -Enamino Ketones from *Endo* Glucal via Hypervalent Iodine

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Abstract

β -Enamino ketones were successfully synthesized by reaction of *endo* glucals with primary or secondary amines in the presence of hypervalent iodine reagent in one pot. After the oxidation and protonation taking place on hypervalent iodine agent in acidic condition, *endo* glucals were effectively converted to the uncyclic β -alkoxyvinyl ketones. Further substitution of β -alkoxyvinyl ketones with primary or secondary amines provided the corresponding β -enamino ketone derivatives in 57–67% yields.

Introduction

(4*S*,5*R*)-1-Benzylanimo-5-hydroxy-4,6-*O*-dibenzyl-hex-1-en-3-one¹ **2** and (4*R*,5*R*)-1,4,6-tribenzyloxy-5-hydroxy-hex-1-en-3-one² **3** are important key precursors in the synthesis of Fagomine isomer **1** which is a quite specific and slightly more potent inhibitors of mammalian gut α -glucosidase and β -galactoside.³ (**1**, see Figure 1).

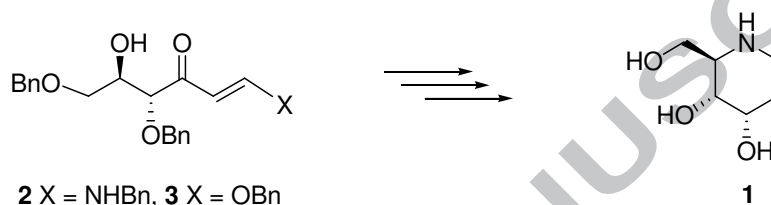


Figure 1.

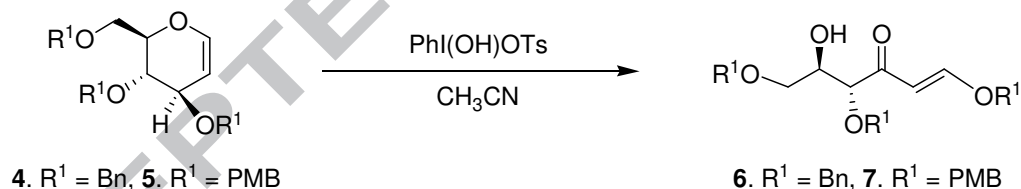
β -Enamino ketones⁴ were widely applied in the functional group transformation in the field of organic chemistry, including β -alkoxyvinyl ketones enamination,⁵ 1,2-aryl migration,⁶ 1,3-dicarbonyl enamination,⁷ dehydrogenation,⁸ lithiate enamine acylation,⁹ and Sonochemical Blaise reaction.¹⁰ Several methods for the synthesis of β -enamino ketones were reported by means of the condensation of acetylenes,¹¹ the Diels-Alder reaction,¹² the elimination reaction,^{13,14} the Friedel-Crafts acylation,¹⁵ the propiolate ester with amines,¹⁶ the oxidation reaction,¹⁷ and the retro-Nazarov reaction.¹⁸ However, few of the directed enamination methods were provided for the conversion of fully protected glycals to β -enamino ketones.¹⁹

In 1995, Kirschning et al. reported an efficient oxidation method to directly convert the fully protected glycals to 2,3-dihydro-4*H*-pyran-4-one derivatives via [hydroxy(tosyloxy)iodo]benzene.²¹ Since 2,3-dihydro-4*H*-pyran-4-ones are important precursors for the synthesis of 2-deoxyglycoside, we developed an efficient one-pot synthesis to prepare β -enamino ketones by oxidating *endo* glycals with [hydroxy(tosyloxy)iodo]benzene to give the intermediate β -alkoxyvinyl ketones, which

were substituted with amines to give the corresponding β -enamino ketones.

Result and Discussion

The benzyl protected glycal **4** and *p*-methoxybenzyl protected glycal **5** were prepared as the starting materials following the reported procedure.²⁰ On the other hand, the commercially available hypervalent iodine agent often acts as a mild oxidizing agent in organic synthesis.²¹ In the newly developed glycal oxidation method, we treated the protected glycals **4–5** with one equivalent of [hydroxy(tosyloxy)iodo]benzen in anhydrous CH₃CN at room temperature for 4 h. After the normal work-up and purification by column chromatography on silica gel, the corresponding oxidation product β -alkoxyvinyl ketones **6–7** were isolated as the liquid oil in 65%–70% yields (see Scheme 1). The subsequent amination step was performed with two equivalent of benzylamine in MeOH from 0 °C to room temperature under N₂ for 2 h. The corresponding β -enamino ketones **8a** and **9a** were obtained in 60 and 63% yields respectively.



Scheme 1.

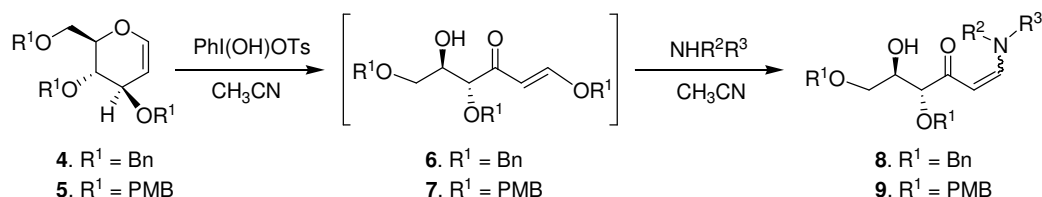
Table 1. The results for synthesis of β -Enamino Ketones **8** and **9**

Entry	Glucals 4 and 5		β -Enamino Ketones 8 and 9 ^a			
	S.M.	R ¹	Products	R ²	R ³	Yields (%)
1	4	Bn	8a	H	Bn	63
2	4	Bn	8b	H	<i>n</i> -Bu	66
3	4	Bn	8c	H	<i>n</i> -Oct	67
4	4	Bn	8d	H	Ph	62

5	4	Bn	8e	Et	Et	63
6	4	Bn	8f	-CH ₂ (CH ₂) ₂ CH ₂ -		61
7	5	PMB	9a	H	Bn	60
8	5	PMB	9b	H	<i>n</i> -Bu	61
9	5	PMB	9c	H	<i>n</i> -Oct	62
10	5	PMB	9d	H	Ph	59
11	5	PMB	9e	Et	Et	58
12	5	PMB	9f	-CH ₂ (CH ₂) ₂ CH ₂ -		57

The standard procedure of one-pot synthesis of β -enamino ketones was carried out in CH₃CN solution at room temperature for 4 h. After the starting material was consumed, the amine substrate was added into the reaction mixture and stirred at room temperature for 2 h.

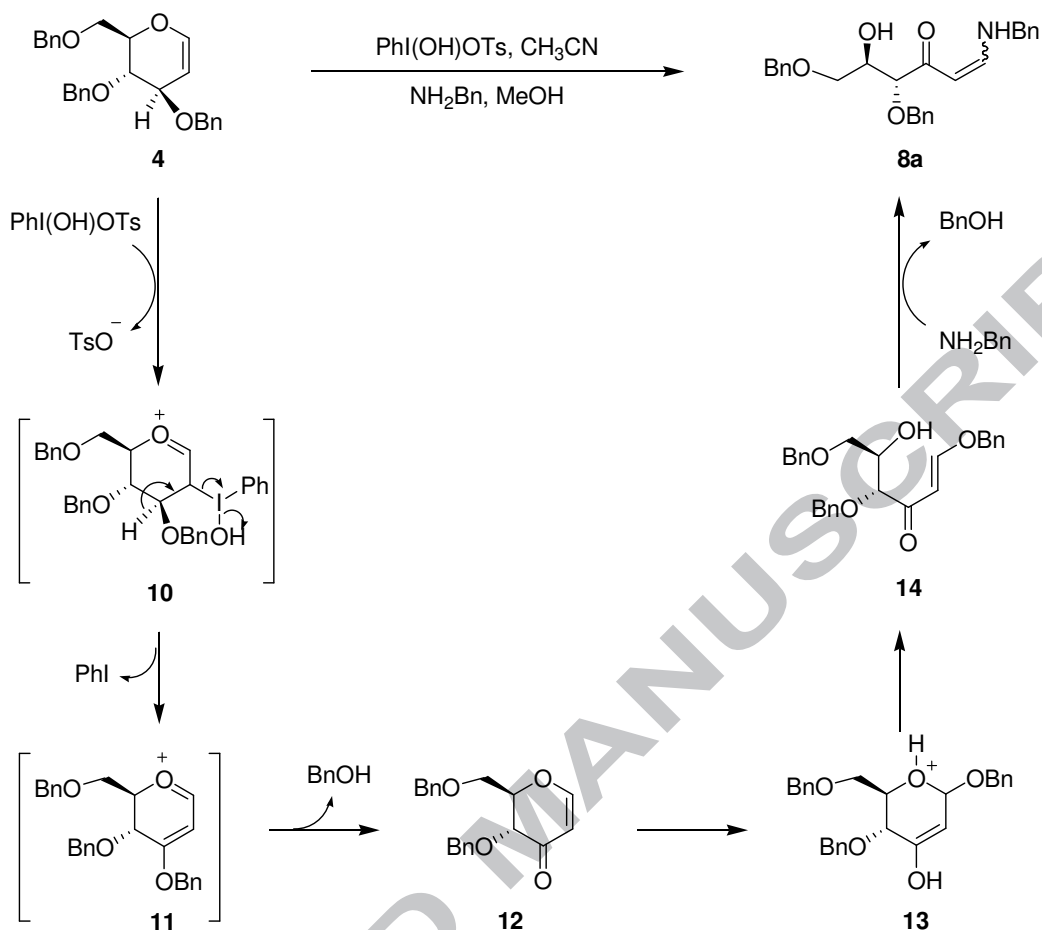
To develop a better synthetic methodology for the expansion of the structural variation of β -enamino ketones **8** and **9**, we tried to combine the two-step process as an efficient and convenient “one-pot” method. The protected glycals **4–5** was allowed to react with [hydroxy(tosyloxy)iodo]benzene for oxidation. The resultant β -alkoxyvinyl ketones **6–7**, needless to be purified, was subjected to amination to generate model β -enamino ketone products **8a** and **9a** (Scheme 2 and Table 1). The structures of β -enamino ketone **8a** and **9a** were determined by DEPT, NOESY and other spectroscopic methods. For example, compound **8a** possessed a characteristic broad singlet peak at δ 10.28 for the amino proton, a doublet doublet peak at δ 6.81 ($J = 7.2, 12.8$ Hz) for the alkene proton on C₁, and a doublet at δ 5.40 ($J = 7.2$ Hz) for the alkene proton on C₂.



Scheme 2.

We then tried to apply this new method to synthesize β -enamino ketone derivatives by using different primary amines including *n*-butylamine, *n*-octylamine, and aniline, and secondary amines (diethylamine and pyrrole) as the amination agents (see Scheme 2 and Table 1). The corresponding β -enamino ketone **8b–8f** and **9b–9f** could be obtained in 57–67% yields (Table 1).

We proposed a plausible mechanism for the one-pot reaction of β -enamino ketones **8–9** as shown in Scheme 3. In the first step of the conversion, the molding benzyl protected glycal **4** was oxidized with [hydroxy(tosyloxy)iodo]benzen to give the intermediate **12** through an oxinium ion **10** and **11**.²¹ After further substitution with the by-product BnOH, the intermediate **12** was fast converted to the Michael adduct **13**. Following the consequent ring-opening step, the stable β -alkoxyvinyl ketone **14** was generated. The subsequent amination step was carried out by reaction of **14** with benzylamine to provide the corresponding β -enamino ketone **8a**. To demonstrate the our proposed mechanism, we prepared the intermediated hex-1-en-3-ulose **12** as a reactant to react with BnOH, TSOH, and PhI under the same condition. After workup and normal purification, the ring-opening product β -alkoxyvinyl ketone **14** was isolated as a major product. As a result, the data would be supported to our proposed mechanism.



Scheme 3.

In conclusion, a newly efficient “one-pot” method was developed to synthesize β -enamino ketones by means of the mild oxidation of *endo* glycals with hypervalent iodine agent and the amination with primary or secondary amines.

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