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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* glycals 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 into 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.

1. Introduction

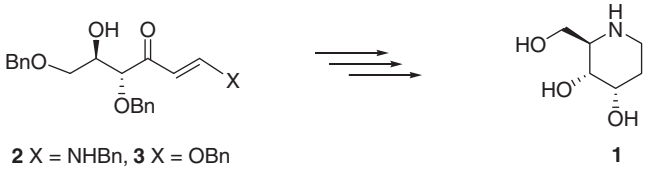
(4*S*,5*R*)-1-Benzylanimo-5-hydroxy-4,6-*O*-dibenzyl-hex-1-en-3-one[1] **2** and (4*R*,5*R*)-1,4,6-tribenzyloxy-5-hydroxy-hex-1-en-3-one[2] **3** are important key precursors in the synthesis of Fagomine isomer **1** which is a quite specific and slightly more potent inhibitor of mammalian gut α-glucosidase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

β-Enamino ketones[4] 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-dicarbon 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,[5h] the propiolate ester with amines,[15] the oxidation reaction,[16] and the retro-Nazarov reaction.[17] However, few of the directed enamination methods were provided for the conversion of fully protected glycals to β-enamino ketones.[18]

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]benzen.[20] 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]benzen to give the intermediate β-alkoxyvinyl ketones, which were substituted with amines to give the corresponding β-enamino ketones.

2. Result and discussion

The benzyl protected glycal **4** and *p*-methoxylbenzyl protected glycal **5** were prepared as the starting materials following the reported procedure.[19] On the other hand, the commercially available hypervalent iodine agent often acts as a mild oxidizing agent in organic synthesis.[20] In the newly developed glycal oxidation method, we treated the protected glycals **4–5** with 1 equiv of [hydroxy(tosyloxy)iodo]benzen in anhydrous CH_3CN at room temperature for 4 h. After the normal work-up and purification by column chromatography on silica gel, the corresponding oxidation



2 X = NHBn, **3** X = OBn

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Figure 1.

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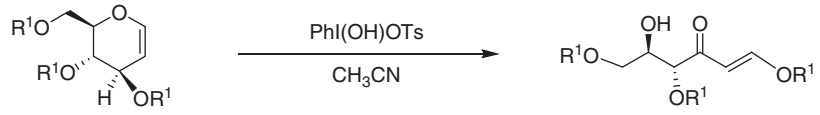


4. R^1 = Bn, **5**. R^1 = PMB

6. R^1 = Bn, **7**. R^1 = PMB

Scheme 1.

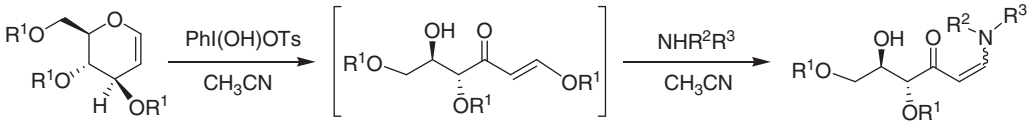
product β-alkoxyvinyl ketones **6–7** were isolated as a liquid oil in 65–70% yields (see Scheme 1). The subsequent amination step was performed with 2 equiv of benzylamine in MeOH from 0 °C to room temperature under N_2 for 2 h. The corresponding β-enamino ketones **8a** and **9a** were obtained in 60% and 63% yields, respectively.

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]benzen for oxidation. The resultant β-alkoxyvinyl ketones **6–7**, needless to be purified, were 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 peak at δ 6.81 (J = 7.2, 12.8 Hz) for the alkene proton on C_1, and a doublet at δ 5.40 (J = 7.2 Hz) for the alkene proton on C_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 ketones **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**.[20] 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 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 work-up 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.

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.



4. R^1 = Bn
5. R^1 = PMB

6. R^1 = Bn
7. R^1 = PMB

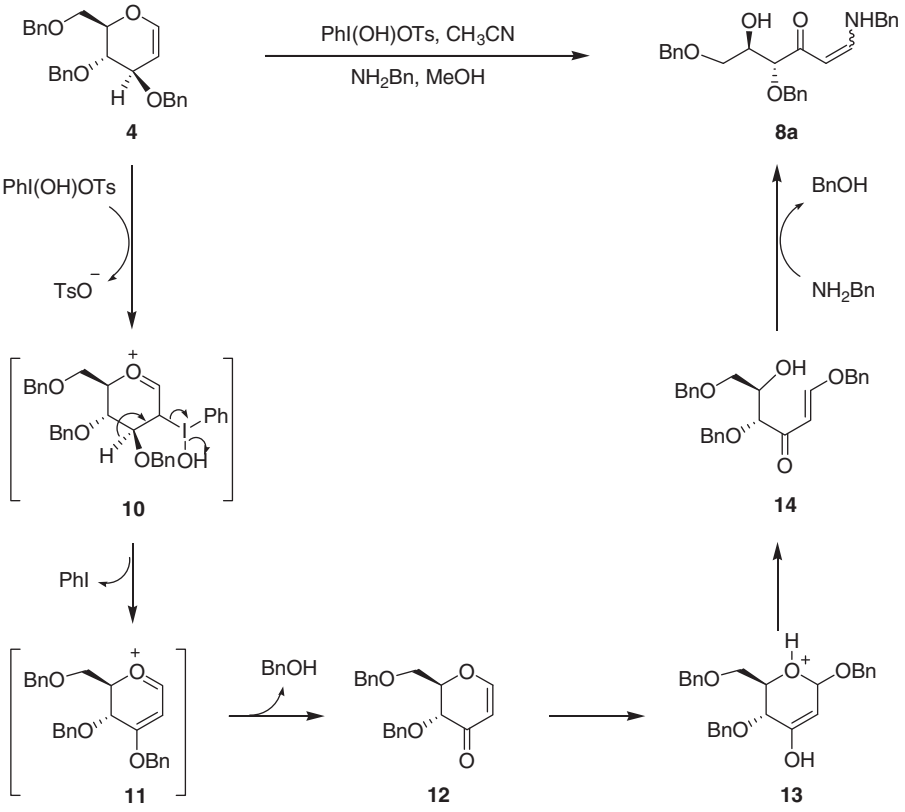
8. R^1 = Bn
9. R^1 = PMB

Scheme 2.

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	*n*-Bu	66
3	**4**	Bn	**8c**	H	*n*-Oct	67
4	**4**	Bn	**8d**	H	Ph	62
5	**4**	Bn	**8e**	Et	Et	63
6	**4**	Bn	**8f**	$-CH_2(CH_2)_2CH_2-$		61
7	**5**	PMB	**9a**	H	Bn	60
8	**5**	PMB	**9b**	H	*n*-Bu	61
9	**5**	PMB	**9c**	H	*n*-Oct	62
10	**5**	PMB	**9d**	H	Ph	59
11	**5**	PMB	**9e**	Et	Et	58
12	**5**	PMB	**9f**	$-CH_2(CH_2)_2CH_2-$		57

[a] The standard produre of one-pot synthesis of β-enamino ketones was carried out in CH_3CN solution at room temperature for 4.0 h. After the starting material was consumed, the amine substrate was added into the reaction mixture and stirred at room temperature for 2 h.



Scheme 3.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.019.

References and notes

1. Sugiyama, M.; Hong, Z.; Liang, P. H.; Dean, S. M.; Whalen, L. J.; Greenberg, W. A.; Wong, C. H. *J. Am. Chem. Soc.* **2007**, *129*, 14811–14817.
2. Squarcia, A.; Vivolo, F.; Weinig, H. G.; Passacantilli, P.; Piancatelli, G. *Tetrahedron Lett.* **2002**, *43*, 4653–4655.
3. Kato, A.; Asano, N.; Kizu, H.; Matsui, K. *J. Nat. Prod.* **1997**, *60*, 312–314.
4. (a) Howes, P. D.; Smith, P. W. *Tetrahedron Lett.* **1996**, *37*, 6595–6598; (b) Kozmin, S. A.; Janey, J. M.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 3039–3052; (c) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Org. Biomol. Chem.* **2005**, *3*, 2140–2144; (d) Hayman, C. M.; Larsen, D. S.; Simpson, J.; Bailey, K. B.; Gill, G. S. *Org. Biomol. Chem.* **2006**, *4*, 2794–2800; (e) Maingot, L.; Vu, N. Q.; Collet, S.; Guingant, A.; Martel, A.; Dujardin, G. *Eur. J. Org. Chem.* **2009**, 412–422.
5. (a) Bonacorso, H. G.; Martins, M. A. P.; Bittencourt, S. R. T.; Lourega, R. V.; Zanatta, N.; Flores, A. F. C. *J. Fluorine Chem.* **1999**, *99*, 177–182; (b) Martins, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293–297; (c) Bonacorso, H. G.; Lourega, R. V.; Wastowski, A. D.; Flores, A. F. C.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2002**, *43*, 9315–9318; (d) Bonacorso, H. G.; Lewandowski, H.; Drekener, R. L.; Costa, M. B.; Pereira, C. M. P.; Wastowski, A. D.; Peppe, C.; Martins, M. A. P.; Zanatta, N. *J. Fluorine Chem.* **2003**, *122*, 159–163; (e) Zanatta, N.; Borchhardt, D. M.; Alves, S. H.; Coelho, H. S.; Squizani, A. M. C.; Marchi, T. M.; Bonacorsoa, H. G.; Martinsa, M. A. P. *Bioorg. Med. Chem.* **2006**, *14*, 3174–3184; (f) McLaughlin, M.; Rubio, S. G.; Tilstam, U.; Antunes, O. A. C.; Laird, T.; Yadav, G. D.; Zlota, A. *Org. Process Res. Dev.* **2006**, *10*, 168–183; (g) Druzhinin, S. V.; Balenkova, E. S.; Nenajdenko, V. G. *Tetrahedron* **2007**, *63*, 7753–7808; (h) Fang, X.; Chen, Y.; He, D.; Yang, X.; Wu, F. *J. Fluorine Chem.* **2008**, *129*, 1167–1172.
6. Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989–2992.
7. (a) Rechsteiner, B.; Texier-Boullet, F.; Hamelin, J. *Tetrahedron Lett.* **1993**, *34*, 5071–5074; (b) Braibante, M. E. F.; Braibante, H. S.; Missio, L.; Andricopulo, A. *Synthesis* **1994**, 898–900; (c) Amougay, A.; Letsch, O.; Pete, J.-P.; Piva, O. *Tetrahedron* **1996**, *52*, 2405–2420; (d) Calvet, S.; David, O.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M. C.; Lhommet, G. *Tetrahedron* **2003**, *59*, 6333–6339; (e) Brandt, C. A.; de Silva, A. C. M. P.; Pancote, P. C. G.; Brito, C. L.; de Silveira, M. A. B. *Synthesis* **2004**, 1557–1559; (f) Giuseppe, B.; Marcella, B.; Manuela, L.; Enrico, M.; Paolo, M.; Letizia, S. *Synlett* **2004**, 239–242; (g) Khodaei, M. M.; Khosropour, A. R.; Kookhazadeh, M. *Synlett* **2004**, 1980–1984; (h) Khosropour, A. R.; Khodaei, M. M.; Kookhazadeh, M. *Tetrahedron Lett.* **2004**, *45*, 1725–1728; (i) Gogoi, S.; Bhuyan, R.; Barua, N. C. *Synth. Commun.* **2005**, *35*, 2811–2818; (j) Zhao, Y.; Zhao, J.; Zhou, Y.; Lei, Z.; Li, L.; Zhang, H. *New J. Chem.* **2005**, *29*, 769–772; (k) Dalpozzo, R.; Nino, A.; Nardi, M.; Russo, B.; Procopio, A. *Synthesis* **2006**, *7*, 1127–1132; (l) Bhosale, R. S.; Suryawanshi, P. A.; Ingle, S. A.; Lokhande, M. N.; More, S. P.; Mane, S. B.; Bhosale, S. V.; Pawar, R. P. *Synlett* **2006**, 933–935; (m) Zhang, Z. H.; Yin, L.; Wang, Y.-M. *Adv. Synth. Catal.* **2006**, *348*, 184–190; (n) Epifano, F.; Genovese, S.; Curini, M. *Tetrahedron Lett.* **2007**, *48*, 2717–2720; (o) Sridharan, V.; Avendano, C.; Menendez, J. C. *Synlett* **2007**, 881–884; (p) Hebbache, H.; Hank, Z.; Boutamine, S.; Meklati, M. h.; Bruneau, C.; Renaud, J. L. *C. R. Chimie* **2008**, *11*, 612–619.
8. Fustero, S.; Pina, B.; de la Torre, M. G.; Navarro, A.; de Arellano, C. R.; Simón, A. *Org. Lett.* **1999**, *1*, 977–980.
9. Bartoli, G.; Cimarelli, C.; Dalpozzo, R.; Palmieri, G. *Tetrahedron* **1995**, *51*, 8613–8622.
10. Lee, A. S. Y.; Cheng, R. Y.; Pan, O. G. *Tetrahedron Lett.* **1997**, *38*, 443–446.
11. Croxall, B. W.; Schneider, H. J. *J. Am. Chem. Soc.* **1949**, *71*, 1257–1260.
12. Danishefsky, S.; Webb, R. R. *J. Org. Chem.* **1984**, *49*, 1955–1958.
13. Hudlicky, T.; Olivo, H. F.; Natchus, M. G. *J. Org. Chem.* **1990**, *55*, 4767–4770.
14. (a) Tiecco, M.; Testaferri, L.; Tingoli, M.; Marini, F. *J. Org. Chem.* **1993**, *58*, 1349–1354; (b) Royals, E. E.; Brannock, K. *J. Am. Chem. Soc.* **1954**, *76*, 3041–3042.
15. (a) Berlin, S.; Ericsson, C.; Engman, L. *J. Org. Chem.* **2003**, *68*, 8386–8396; (b) Arcadi, A.; Alfonsi, M.; Marinelli, F. *Tetrahedron Lett.* **2009**, *50*, 2060–2064.
16. Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269–1274.
17. Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328–14329.
18. Lin, Z. P.; Lin, H. C.; Wu, H. H.; Chou, H. W.; Chen, K. L.; Sung, K. C.; Wong, F. F. *Tetrahedron Lett.* **2009**, *50*, 5120–5122.
19. (a) Beau, J. M.; Sinaÿ, P. *Tetrahedron Lett.* **1985**, *26*, 6185–6188; (b) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758–8762.
20. (a) Lichtenthaler, F. W.; Ronninger, S.; Jarglis, P. *Liebigs Ann. Chem.* **1989**, 1153–1161; (b) Bovonsombat, P.; Djuardi, E.; Mc Nelis, E. *Tetrahedron Lett.* **1994**, *35*,

2841–2844; (c) Kirschning, A. *J. Org. Chem.* **1995**, *60*, 1228–1232; (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178; (e) Hirt, U. H.; Spingler, B.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 7674–7679; (f) Muraki, T.; Togo, H.; Yokoyama, M. *J. Org. Chem.* **1999**, *64*, 2883–2889; (g) Prakash, O.; Kaur, H.; Batra, H.; Rani, N.; Singh, S. P.; Moriarty, R. M. *J. Org. Chem.* **2001**, *66*, 2019–2023; (h) Zhdankin, V. V. *Chem. Rev.* **2002**, *102*, 2523–2584; (i) Nabana, T.; Togo, H. *J. Org. Chem.* **2002**, *67*, 4362–4365; (j) Ueno, M.; Nabana, T.; Togo, H. *J. Org. Chem.* **2003**, *68*, 6424–6426; (k) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903; (l) Justik, M. W. *Tetrahedron Lett.* **2007**, *48*, 3003–3007.