First Use of HEH in Oxazine Synthesis: Hydroxy-Substituted 2*H*-1,4-Benzoxazine Derivatives

Qing-yuan Meng, Qiang Liu,* Jing Li, Rui-Guang Xing, Xiao-Xia Shen, Bo Zhou

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. of China
Fax +86(931)8625657; E-mail: liuqiang@lzu.edu.cn
Received 29 July 2009

Abstract: The synthesis of 2*H*-1,4-benzoxazine derivatives from 1,2-epoxy-3-(2-nitroaryloxy)propanes in the presence of Hantzsch 1,4-dihydropyridine (HEH) and Pd/C as a catalyst was achieved. The nitro group was reduced before the epoxide functionality, leading to attack of the amino group on the epoxide moiety in a 6-*exo*-fashion. By introducing a methyl group at the 1-position, the 7-*endo* ring-closed product could also be formed.

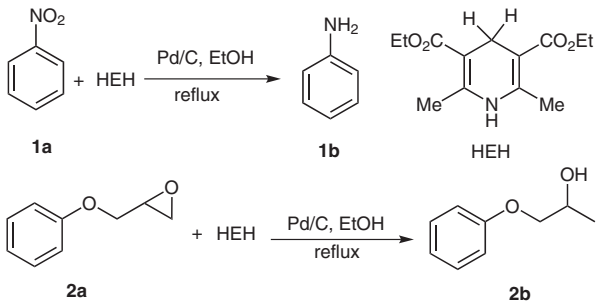
Key words: Hantzsch 1,4-dihydropyridine ester, organic reductant, hydrogen transfer, benzoxazine derivatives, domino reaction

The 2*H*-1,4-benzoxazine[1] scaffold is a structural subunit in many naturally occurring compounds. For example, various glycosides bearing a 2-hydroxy-2*H*-1,4-benzoxazine skeleton have been found in gramineous plants such as maize, wheat, and rice, and they have been suggested to act as plant resistance factors against microbial diseases and insects.[2] Derivatives of 2*H*-1,4-benzoxazine have shown interesting pharmaceutical properties, including potassium channel modulators,[3] antihypertensive agents,[4] or antirheumatic agents.[5] Hydroxy-substituted 1,4-benzoxazine is one of the most important intermediates for the construction of complex 1, 4-benzoxazine derivatives because the hydroxy group can be easily converted into the corresponding tosylate or amino compounds.[6]

Synthesis of hydroxy-substituted 1,4-benzoxazines was accomplished through the intermolecular ring-opening of epoxides with arylsulfonamides followed by cyclization of the corresponding hydroxysulfonamides,[7] or through the tandem reduction–oxirane ring-opening of substituted 2-nitrophenoxymethyloxiranes.[8] Obviously, the latter procedure is more advantageous because the reductive cyclization proceeded in a very simple and efficient way. However, there are still some limitations with the method. For instance, the need for metallic reducing agents and acidic reaction media restricts its use in further applications. In particular, the regioselectivity of the intramolecular ring-opening of epoxides was not known. It seems that the development of an efficient procedure that can address this issue could be of practical use.

Hantzsch 1,4-dihydropyridine (HEH) has been widely used as a model compound for the coenzyme NAD(P)H, which plays a pivotal role in biochemical redox processes. HEH is a safe and easy-to-handle reagent for the reduction of organic functional groups, and can be synthesized in a simple way.[9] We have found the reducibility of HEH was dramatically enhanced in the presence of Pd/C and even electron-rich olefins can be reduced to saturated alkanes.[10] Herein, we report the selective reduction of a nitro group in the presence of an epoxy group with HEH and Pd/C, to obtain hydroxy-substituted 2,3-dihydro-1,4-benzoxazine derivatives in one pot. In addition, this approach represents the first application of this coenzyme NAD(P)H model compound in the synthesis of oxazinic compounds.

At the outset, we realized that 1,2-epoxy-3-phenoxypropane (**2a**) could be reduced to the corresponding alcohol using HEH catalyzed by Pd/C (Scheme 1). At the same time, the same reductive reagents could also be used to reduce nitrobenzene (**1a**) to afford the corresponding anilines.[11]

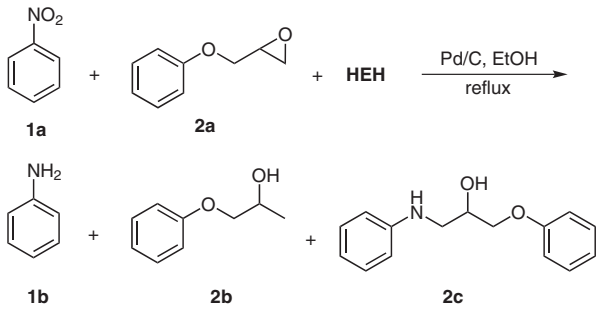


Scheme 1 Reactions of nitrobenzene and 1,2-epoxy-3-phenoxypropane with HEH and Pd/C

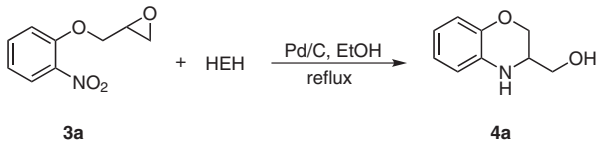
Interestingly, when we carried out the reduction in the presence of nitrobenzene (**1a**) and 1,2-epoxy-3-phenoxypropane (**2a**) together, aniline (**1b**) was obtained as the major product (Scheme 2). Most of the 1,2-epoxy-3-phenoxypropane was recovered unchanged. In addition, some epoxide ring-opening product **2c**,[12] formed from attack by the amino group on the epoxide ring, was found; the product ratio of **1b/2b/2c** was 73:6:21 (isolated yield).

With these results in mind, we decided to use 1,2-epoxy-3-(2-nitrophenoxy)propane (**3a**) as the starting material, with the expectation that reduction of the nitro group would occur first, to form the corresponding amino compound, which would be followed by ring-opening of the epoxide by the amino group in a domino process. Indeed,

SYNLETT 2009, No. 20, pp 3283–3286
Advanced online publication: 18.11.2009
DOI: 10.1055/s-0029-1218380; Art ID: W11909ST



Scheme 2 Reaction of nitrobenzene and 1,2-epoxy-3-phenoxypropane in the presence of HEH and Pd/C in one pot



Scheme 3 Synthesis of 2,3-dihydro-3-hydroxymethyl[1,4]benzoxazine

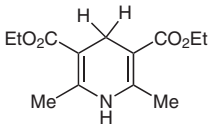
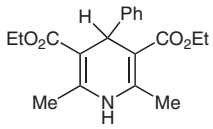
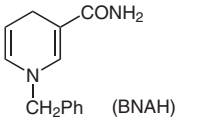
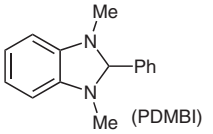
it was gratifying to observe that 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazine (**4a**) was formed (Scheme 3).

We then carried out the reduction using other NAD(P)H model compounds (Table 1). When a phenyl group was attached to the 4-position of HEH (entry 2), no reaction took place. BNAH also failed to serve as a reductive reagent (entry 3). On the other hand, PDMBI (entry 4) and 1,4-cyclohexadiene (entry 5) both gave the target product in moderate and poor yields, respectively. Obviously, HEH furnished the desired heterocycle in highest yield and was thus used for further study.

Further studies were performed to determine the substrate scope of this reaction (Table 2).[13] To our delight, substrates with electron-donating substituents at the 4-position of the aromatic ring could also undergo the reaction, to give the corresponding product in a high yield (entries 2–4). However, the presence of electron-withdrawing substituents at the 4-position of the substrate had a negative effect on the formation of the cyclization product. In this case, the nitro group was reduced to the amino group, but the epoxide moiety was also reduced at the same time. It seemed that the presence of the ethoxycarbonyl group retarded the rate of reduction of the nitro group to such an extent that the ring-opening of the epoxide then proceeded with a comparable rate to give the alcohol compound that could not be cyclized (entry 5). Nevertheless, the reaction proceeded satisfactorily when the 5-position of the aromatic ring was substituted by a methyl group (entry 6), or when the ethoxycarbonyl group was substituted at the 3-position (entry 7).

To further evaluate the scope of this reaction, a variety of substituted epoxides were employed. To our surprise, when 2,3-epoxy-1-(2-nitrophenoxy)butane (**3h**) was used as substrate, both 6-*exo* (**4i**) and 7-*endo* (**4j**) products were obtained (entry 8). Adding an additional methyl group to

Table 1 Effect of Different Organic Reductive Reagents on the Synthesis of 2,3-Dihydro-3-hydroxymethyl-1,4-benzoxazine[a]

Entry	Hydrogen donor	Yield (%)[b]
1		84
2		N.R[c]
3	 (BNAH)	N.R[c,d]
4	 (PDMBI)	44[d]
5		30

[a] Reaction conditions: **3a** (0.5 mmol), hydrogen donor (1.85 mmol), 10% Pd/C (5% wt of hydrogen donor), reflux, 12 h under N_2.
[b] Isolated yields.
[c] No reaction.
[d] Hydrogen donor (3.7 mmol).

the epoxide led only to the 6-*exo* product (**4k**). It seemed that the 6-*exo* mode of attack was more facile because of the hindrance of the two methyl groups (entry 9). However, 7-*endo* attack could be achieved by controlling the position of the substituent. Hence, 1,2-epoxy-2-methyl-3-(2-nitrophenoxy)propane (**3j**) afforded the seven-membered heterocycle **4l** in good yield (entry 10). A good result was also achieved when cyclohexene oxide was used. However, cyclopentene oxide gave the corresponding oxazine in a low yield (entry 12).

In summary, we have successfully developed a domino reaction in which benzoxazine derivatives were obtained from 1,2-epoxy-3-(2-nitroaryloxy)propanes using the organic reductive reagent HEH in the presence of Pd/C. Selective reduction of the nitro group was observed, followed by a 6-*exo* attack on the epoxide ring. However, the 7-*endo* mode of attack could be obtained through substitution at the epoxide position. This novel catalytic system not only provides an efficient method with which to prepare various benzoxazine derivatives, but may also inspire other uses for the combination of HEH and Pd/C in reductive chemistry.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 The Synthesis of 2,3-Dihydro-1,4-benzoxazine Derivatives[a]

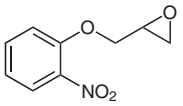
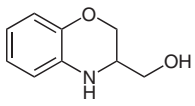
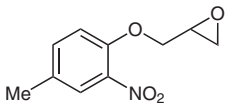
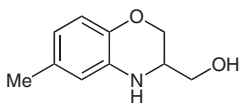
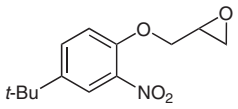
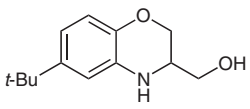
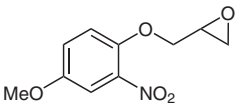
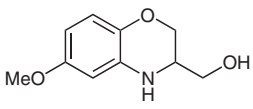
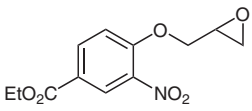
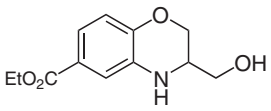
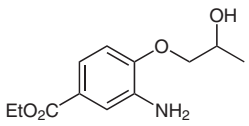
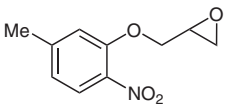
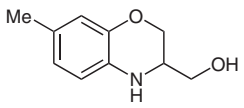
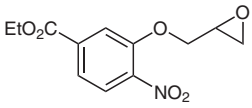
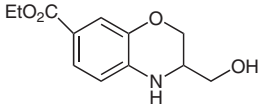
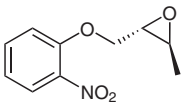
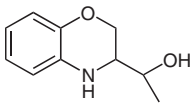
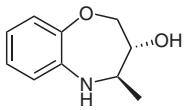
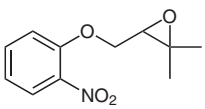
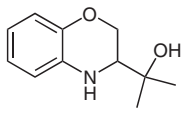
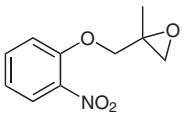
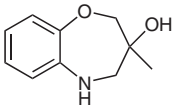
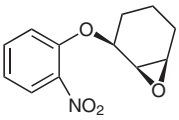
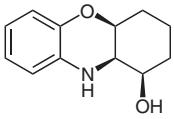
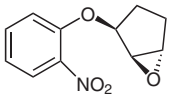
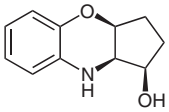
Entry	Substrate	Product	Yield (%)[b]
1	 **3a**	 **4a**	84
2	 **3b**	 **4b**	87
3	 **3c**	 **4c**	83
4	 **3d**	 **4d**	90
5	 **3e**	 **4e**	59
		 **4f**	22
6	 **3f**	 **4g**	80
7	 **3g**	 **4h**	74
8	 **3h**	 **4i**	33
		 **4j**	57[c]
9	 **3i**	 **4k**	86

Table 2 The Synthesis of 2,3-Dihydro-1,4-benzoxazine Derivatives[a] (continued)

Entry	Substrate	Product	Yield (%)[b]
10	 **3j**	 **4l**	86
11	 **3k**	 **4m**	92[c]
12	 **3l**	 **4n**	52[c]

[a] Reaction conditions: **3a** (0.5 mmol), HEH (1.85 mmol), 10% Pd/C (5% wt of HEH), reflux, EtOH (30 mL), 12 h under N_2.
[b] Isolated yield.
[c] The relative stereostructure of compounds was determined by NOSEY NMR spectrum.

Acknowledgment

We thank the National Natural Science Foundation of China (Grant No. 20702023 and 20621091), the 111 Project and Program for New Century Excellent Talents in University (NCET-06-0906) and the Special Fund for Doctoral Program from the Ministry of Education of China (Grant No. 20070730040) for financial support.

References and Notes

(1) (a) Sainsbury, M. *Thiazines and Their Benzoderivatives,* In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford, **1984**, 995–1038. (b) Ellis, G. P. *Synthesis of Fused Heterocycles*; John Wiley and Sons: New York, **1987**, 55–57.
(2) Niemeyer, H. M. *Phytochemistry* **1988**, *27*, 3349.
(3) (a) Empfield, J. R.; Russell, K. *Annu. Rep. Med. Chem.* **1995**, *30*, 81. (b) Caliendo, G.; Grieco, P.; Perissutti, E.; Santagada, V.; Santini, A.; Alberizio, S.; Fattorusso, C.; Pinto, A.; Sorrentino, R. *Eur. J. Med. Chem.* **1998**, *33*, 957. (c) Sebille, S.; De Tullio, P.; Boverie, S.; Antoine, M. H.; Lebrun, P.; Pirotte, B. *Curr. Med. Chem.* **2004**, *11*, 1213.
(4) Touzeau, F.; Arrault, A.; Guillaumet, G.; Scalbert, E.; Pfeiffer, B.; Rettori, M.; Renard, P.; Mérour, J.-Y. *J. Med. Chem.* **2003**, *46*, 1962.
(5) Matsuoka, H.; Ohi, N.; Mihara, M.; Suzuki, H.; Miyamoto, K.; Maruyama, N.; Tsuji, K.; Kato, N.; Akimoto, T.; Takeda, Y.; Yano, K.; Kuroki, T. *J. Med. Chem.* **1997**, *40*, 105.
(6) Zhou, D. H.; Harrison, B. L.; Shah, U.; Andree, T. H.; Hornby, G. A.; Scerni, R.; Schechter, L. E.; Smith, D. L.; Sullivan, K. M.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1338.
(7) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Ind. Eng. Chem. Res.* **2003**, *42*, 680.
(8) Jiao, P.-F.; Zhao, B.-X.; Wang, W.-W.; He, Q.-X.; Wan, M.-S.; Shin, D.-S.; Miao, J.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2862.
(9) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827.
(10) (a) Shen, X.-X.; Liu, Q.; Xing, R.-G.; Zhou, B. *Catal. Lett.* **2008**, *126*, 361. (b) Liu, Q.; Li, J.; Shen, X.-X.; Xing, R.-G.; Yang, J.; Liu, Z.-G.; Zhou, B. *Tetrahedron Lett.* **2009**, *50*, 1026.
(11) Niu, X. Q.; Liu, Z. G.; Yu, W.; Wu, L. M. *Chin. J. Org. Chem.* **2009**, *29*, 229.
(12) (a) Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939. (b) De, A.; Ghosh, S.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 8379. (c) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319. (d) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287.
(13) **General procedure for the synthesis of 2,3-dihydro-1,4-benzoxazine derivatives:** To a stirred solution of substrate (0.5 mmol) in ethanol (30 mL) was added HEH (0.468 g, 1.85 mmol), and 10% Pd/C (18 mg), and the reaction mixture was refluxed for 12 h under N_2. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel to give the corresponding product.