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Efficient and Regioselective Synthesis of 5-Hydroxy-2-isoxazolines: Versatile Synthons for Isoxazoles, β-Lactams, and γ-Amino Alcohols

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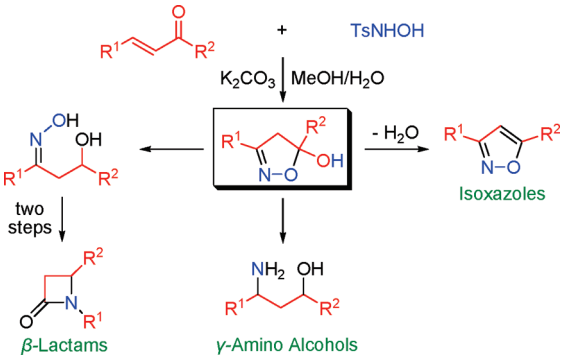

An efficient and highly regioselective protocol was developed for the preparation of 5-hydroxy-2-isoxazolines, which have been proved to be versatile synthons for isoxazles, β-hydroxy oximes, and γ-amino alcohols. β-Lactams, commonly embedded in the skeletons of bioactive natural products, were also synthesized in two steps from β-hydroxy oximes, providing a new strategy for the synthesis of this kind of compounds.

Introduction

2-Isoxazolines are important heterocycles in organic and medicinal chemistry,[1] which are frequently found in a diverse array of compounds, including biologically active natural products (e.g., cycloserin, acivicine) or drug candidates,[2] chiral ligands,[3] and intermediates in organic synthesis.[1,4] Particularly, due to their ability to undergo facile reductive ring-opening reactions, 2-isoxazolines are of interest as precursors

(1) (a) Lang, S. A.; Lin, Y.-I. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, UK, 1984; Vol. 6, pp 1−130. (b) Sutharchanadevi, M.; Muragan, R. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 3, pp 221−260. (c) Cicchi, S.; Cordero, F. M.; Giomi, D. *Prog. Heterocycl. Chem.* **2003**, *15*, 261.

(2) (a) Groutas, W. C.; Venkataraman, R.; Chong, L. S.; Yoder, J. E.; Epp, J. B.; Stanga, M. A.; Kim, E.-H. *Bioorg. Med. Chem.* **1995**, *3*, 125. (b) Xiang, Y.; Chen, J.; Schinazi, R. F.; Zhao, K. *Bioorg. Med. Chem.* **1996**, *6*, 1051. (c) Wityak, J.; Sielecki, T. M.; Pinto, D. J.; Emmett, G.; Sze, J. Y.; Liu, J.; Tobin, E.; Wang, S.; Jiang, B.; Ma, P.; Mousa, S. A.; Wexler, R. R.; Olson, R. E. *J. Med. Chem.* **1997**, *40*, 50. (d) Olson, R. E.; Sielecki, T. M.; Wityak, J.; Pinto, D. J.; Batt, D. G.; Frietze, W. E.; Liu, J.; Tobin, A. E.; Orwat, M. J.; Di Meo, S. V.; Houghton, G. C.; Lalka, G. K.; Mousa, S. A.; Racanelli, A. L.; Hausner, E. A.; Kapil, R. P.; Rabel, S. R.; Thoolen, M. J.; Reilly, T. M.; Anderson, P. S.; Wexler, R. R. *J. Med. Chem.* **1999**, *42*, 1178. (e) Antczak, C.; Bauvois, B.; Monneret, C.; Florent, J.-C. *Bioorg. Med. Chem.* **2001**, *9*, 2843. (f) Hwang, I. T.; Kim, H. R.; Jeon, D. J.; Hong, K. S.; Song, J. H.; Cho, K. Y. *J. Agric. Food Chem.* **2005**, *53*, 8639.

(3) (a) Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, *1*, 1795. (b) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907. (c) Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9274.

(4) (a) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (b) Smith, A. L.; Pitsinos, E. N.; Hwang, C. K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612. (c) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15. (d) Kambe, M.; Arai, E.; Suzuki, M.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2001**, *3*, 2575. (e) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410. (f) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764.

(5) (a) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. (b) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (c) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474. (d) Baraldi, P. G.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, P. *Synthesis* **1987**, 276. (e) Gothelf, K.; Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand.* **1992**, *46*, 494. (f) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587. (g) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. (h) Jiang, D.; Chen, Y. *J. Org. Chem.* **2008**, *73*, 9181.

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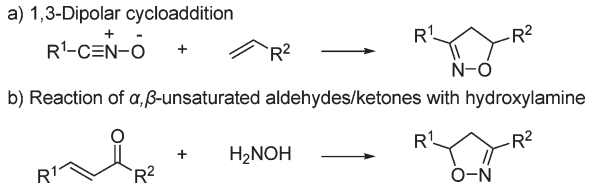
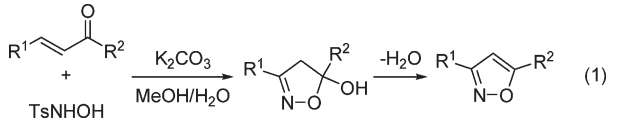
SCHEME 1. Conventional Synthesis of the 2-Isoxazolines



for β-hydroxy ketones,[5] β-hydroxy nitriles,[6] β-amino acids,[7] and γ-amino alcohols,[8] etc. Therefore, numerous synthetic methods have been developed to produce 2-isoxazolines of which the 1,3-dipolar cycloaddition of nitrile oxides to alkenes[9] (Scheme 1, reaction a) and the reaction of α,β-unsaturated carbonyl compounds with hydroxylamine are the most important[1] (Scheme 1, reaction b). Although these transformations are widely used, some challenges still remain especially for regio- and stereoselectivities.[10,11]

Recently, we reported an efficient and regioselective approach for the preparation of a series of 3-substituted and 3,5-disubstituted isoxazoles (eq 1).[12] In this transformation, it was proposed that the



isoxazoles were formed via dehydration of 5-hydroxy-2-isoxazolines. Herein, we provide a full account of our work on the reaction of *N*-hydroxy-4-toluenesulfonamide **1** (TsNHOH)[13] with α,β-unsaturated aldehydes/ketones, providing a very facile and highly regioselective tactic to 5-hydroxy-2-isoxazolines, which would be versatile synthons for isoxazoles **12** (Figure 1, path a),[14] β-hydroxy oximes **13**,[15] β-lactams **15** (Figure 1, path b),[16] and γ-amino alcohols **2**,[17] especially chiral 3-amino-3-phenylpropan-1-ol **2a**, a valuable intermediate for the synthesis of (*S*)-dapoxetine (Figure 1, path c).[18,19]

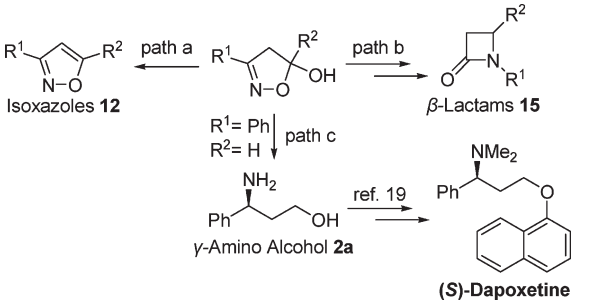


FIGURE 1. 5-Hydroxy-2-isoxazolines as versatile synthons.

Results and Discussion

Synthesis of 5-Hydroxy-2-isoxazolines. 5-Hydroxy-2-isoxazolines were commonly obtained as intermediates in the synthesis of isoxazoles from 1,3-dicarbonyl compounds and hydroxylamine.[14b] However, this approach was usually hard to control, leading to low regioselectivity.[20] While the 1,3-cycloaddition of nitrile oxides with enolates appeared to be an especially versatile route to the 5-hydroxy-2-isoxazolines, this method bore some disadvantages due to the high reactivity of reactants and harsh reaction conditions.[9,21] Thus, the development of facile and regioselective methods for the synthesis of 5-hydroxy-2-isoxazolines is desirable. We envisioned that condensation between hydroxylamine **1**[13] with a leaving group (Ts) and α,β-unsaturated aldehydes/ketones would be a suitable strategy to achieve this goal (Scheme 2).

(6) Wade, E A.; Bereznak, J. E; Palfey, B. A.; Carroll, P. J.; Dailey, W. E; Sivasubramanian, S. *J. Org. Chem.* **1990**, *55*, 3045.
(7) (a) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846. (b) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376.
(8) (a) Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101. (b) Auricchio, S.; Ricca, A. *Tetrahedron* **1987**, *43*, 3983. (c) Jäger, V.; Schroter, D. *Synthesis* **1990**, 556. (d) Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727. (e) Scott, J. P.; Oliver, S. F.; Brands, K. M. J.; Brewer, S. E.; Davies, A. J.; Gibb, A. D.; Hands, D.; Keen, S. P.; Sheen, F. J.; Reamer, R. A.; Wilson, R. D.; Dolling, U. *J. Org. Chem.* **2006**, *71*, 3086. (f) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 17066.
(9) (a) Huisgen, R.; Christl, M. *Chem. Ber.* **1973**, *106*, 3291. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (c) Padwa, A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 4, 1069−1168. (d) Easton, C. J.; Hughes, C.; Merricc, M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261. (e) Namboothiri, I. N. N.; Rastogi, N. *Top. Heterocycl. Chem.* **2008**, 1.
(10) (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Lohse-Fraefel, N.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 2011. (c) Serizawa, M.; Ukaji, Y.; Inomata, K. *Tetrahedron: Asymmetry* **2006**, *17*, 3075. (d) Lee, C. K. Y.; Herlt, A. J.; Simpson, G. W.; Willis, A. C.; Easton, C. J. *J. Org. Chem.* **2006**, *71*, 3221. (e) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665. (f) Norman, A. L.; Mosher, M. D. *Tetrahedron Lett.* **2008**, *49*, 4153.
(11) For recent synthesis of 2-isoxazolines, see: (a) Pennicott, L.; Lindell, S. *Synlett* **2006**, 0463. (b) Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kündig, E. P. *Tetrahedron* **2007**, *63*, 8413. (c) Qazi, N. A.; Singh, P. P.; Jan, S.; Kumar, H. M. S. *Synlett* **2007**, 1449. (d) Jiang, D.; Peng, J.; Chen, Y. *Org. Lett.* **2008**, *10*, 1695. (e) Pohjakallio, A.; Pihko, P. M. *Synlett* **2008**, 0827. (f) Pohjakallio, A.; Pihko, P. M. *Chem.—Eur. J.* **2009**, *15*, 3960. (g) Guo, J.; Gaudette, J.; Cheng, J. F. *Tetrahedron Lett.* **2009**, *50*, 933.
(12) Tang, S.; He, J.; Sun, Y.; He, L.; She, X. *Org. Lett.* **2009**, *11*, 3982.
(13) (a) Hassner, A.; Wiederkehr, R.; Kascheres, A. J. *J. Org. Chem.* **1970**, *35*, 1962. (b) Böhma, S.; Exner, O. *Org. Biomol. Chem.* **2003**, *1*, 1176. (c) Porcheddu, A.; Giacomelli, G. *J. Org. Chem.* **2006**, *71*, 7057.
(14) For recent reviews, see: (a) Wakefield, B. J. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2001; Vol. 11, pp 229−288. (b) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925. (c) Carlsen, L.; Döpp, D.; Döpp, H.; Duus, F.; Hartmann, H.; Lang-Fugmann, S.; Schulze, B.; Smalley, R. K.; Wakefield, B. J. In *Houben-Weyl Methods in Organic Chemistry*; Schaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1992; Vol. E8a, pp 45−204. (d) Sperry, J.; Wright, D. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723.
(15) For a review, see: Yamane, M.; Narasaka, K. In *Science of Synthesis*; Padwa, A., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2004; Vol. 27, pp 605−647.
(16) (a) *The Chemistry of β-lactams*; Page, M. I., Ed.; Chapman and Hall: London, UK, 1992. For reviews on β-lactam antibiotics see: (b) Dürkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180. (c) *Chemistry and Biology of β-lactam antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, NY, 1982; Vols. 1−3. (d) Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lucaks, G., Ed.; Springer: Berlin, Germany, 1993; Vol. 2, p 621. (e) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417.
(17) (a) Santana, L.; Teijeira, M.; Uriarte, E.; Balzarini, J.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1349. (b) Vilaplana, M. J.; Molina, P.; Arques, A.; Andrés, C.; Pedrosa, R. *Tetrahedron: Asymmetry* **2002**, *13*, 5. (c) Gais, H. J.; Griebel, C.; Buschmann, H. *Tetrahedron: Asymmetry* **2000**, *11*, 917. (d) Wang, G.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1873.
(18) Sorbera, L. A.; Castañer, J.; Castañer, R. M. *Drugs Future* **2004**, *29*, 1201.
(19) (a) Siddiqui, S. A.; Srinivasan, K. V. *Tetrahedron: Asymmetry* **2007**, *18*, 2099. (b) Chincholkar, P. M.; Kale, A. S.; Gumaste, V. K.; Deshmukh, A. R. A.S. *Tetrahedron* **2009**, *65*, 2605. (c) Kang, S.; Lee, H.-K. *J. Org. Chem.* **2010**, *75*, 237.
(20) (a) Wünsch, K.-H.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1967**, *8*, 277. (b) Grünanger, P.; Vita-Finzi, P. *The Chemistry of Heterocyclic Compounds*, Isoxazoles, Part 1, Weissenberg, A., Taylor, E. C., Eds.; Wiley-Interscience, New York, 1991.
(21) (a) Di Nunno, L.; Scilimati, A. *Tetrahedron* **1987**, *43*, 2181. (b) Di Nunno, L.; Scilimati, A.; Vitale, P. *Tetrahedron* **2002**, *58*, 2659. (c) Kai, H.; Tomida, M.; Nakai, T.; Takase, A. *Heterocycles* **2002**, *57*, 2299.

SCHEME 2. Our Strategy for Synthesis of 5-Hydroxy-2-isoxazolines

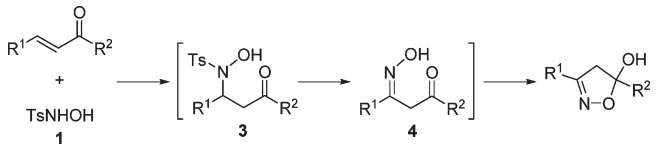
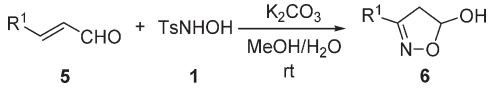


TABLE 1. Synthesis of 3-Substituted 5-Hydroxy-2-isoxazolines[a]



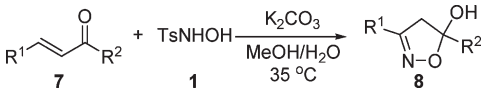
entry	substrate	product	yield (%)[b]
1	**5a**, R^1 = Ph	**6a**	92
2[c]	**5b**, R^1 = 4-NO_2-C_6H_4	**6b**	91
3	**5c**, R^1 = 2-NO_2-C_6H_4	**6c**	87
4	**5d**, R^1 = 4-MeO-C_6H_4	**6d**	83
5	**5e**, R^1 = 4-Cl-C_6H_4	**6e**	91
6	**5f**, R^1 = 2-Cl-C_6H_4	**6f**	84
7	**5g**, R^1 = 4-Br-C_6H_4	**6g**	88
8	**5h**, R^1 = 2-Br-C_6H_4	**6h**	78
9	**5i**, R^1 = 4-Me-C_6H_4	**6i**	85
10	**5j**, R^1 = 2-Me-C_6H_4	**6j**	76
11[d]	**5k**, R^1 = 4-Me_2N-C_6H_4	**6k**	74
12	**5l**, R^1 = 2-furyl	**6l**	85
13[d]	**5m**, R^1 = styryl	**6m**	70
14[e]	**5n**, R^1 = MeO_2C	**6n**	76

[a]General reaction conditions: **5** (0.2 mmol), **1** (0.8 mmol), and base (1.0 mmol) in 2 mL of solvent at rt, 10 h. [b]Isolated yield. [c]1 h. [d]35 °C, 2 days. [e]**1** (0.3 mmol) and base (0.4 mmol) in 2 mL of EtOH at 0 °C, 2 h.

Intermediate **3** would be generated in high regioselectivity via the conjugate addition, then extrusion of the leaving group to produce 3-carbonyl oxime **4** following cyclization would lead to the desired product. With this idea in mind, we successfully obtained 5-hydroxy-2-isoxazolines under the treatment of **1** with enals/enones.[12] The most efficient set of conditions were to employ 1.0 equiv of enal **5**, 4.0 equiv of **1**, and 5.0 equiv of K_2CO_3 in MeOH/H_2O at room temperature. Under the optimal experimental conditions, the scope of this method was extensively evaluated (Tables 1 and 2 and Scheme 3).

As shown in Table 1, a series of 3-substituted 5-hydroxy-2-isoxazolines **6** were readily obtained in good to excellent yields from enals **5** and **1** under the optimal conditions. In general, substrates containing an electron-withdrawing group were more active to offer higher yields (entries 2, 5, and 7) and ortho-substituted aromatic substrates resulted in lower yields due to their lower reactivity (entries 3, 6, 8, and 10). This result implied that electron density at the aromatic ring played an important role in this process. Heteroaromatic substituted enal was also tolerable in this procedure to give good yield (entry 12). Moreover, under modified conditions, 3-vinyl and 3-ester acroleins were also suitable reactants, giving the desired products **6m** and **6n** in good yields (entries 13 and 14). As confirmed in earlier studies[12] that an unsaturated carbon substituent attached to the 3-position of the substrates is necessary, 3-alkyl-substituted enals such as crotonaldehyde were not competent reactants for this protocol.

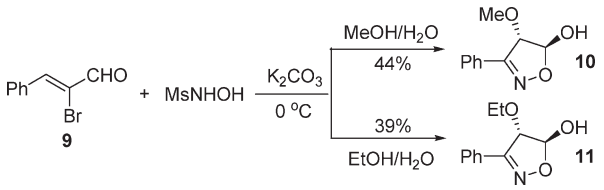
TABLE 2. Synthesis of 3,5-Disubstituted 5-Hydroxy-2-isoxazolines[a]



entry	substrate	product	yield (%)[b]
1[c]	**7a**, R^1 = Ph, R^2 = Me	**8a**	74
2[c]	**7b**, R^1 = 4-Me-C_6H_4, R^2 = Me	**8b**	58
3	**7c**, R^1 = 4-NO_2-C_6H_4, R^2 = Me	**8c**	90
4	**7d**, R^1 = 4-Cl-C_6H_4, R^2 = Me	**8d**	78
5	**7e**, R^1 = 4-Br-C_6H_4, R^2 = Me	**8e**	69
6[c]	**7f**, R^1 = Ph, R^2 = Ph	**8f**	77
7[c]	**7g**, R^1 = 4-MeO-C_6H_4, R^2 = Ph	**8g**	72
8[c]	**7h**, R^1 = 4-Cl-C_6H_4, R^2 = Ph	**8h**	62
9[c]	**7i**, R^1 = 4-Br-C_6H_4, R^2 = Ph	**8i**	50
10[d]	**7j**, R^1 = Ph, R^2 = 4-NO_2-C_6H_4	**8j**	89
11[d]	**7k**, R^1 = 4-Cl-C_6H_4, R^2 = 4-NO_2-C_6H_4	**8k**	92
12[c]	**7l**, R^1 = 2-furyl, R^2 = Ph	**8l**	62
13[c,e]	**7m**, R^1 = styryl, R^2 = Ph	**8m**	57

[a]General reaction conditions: **7** (0.2 mmol), **1** (1.5 mmol), and base (1.6 mmol) in 2 mL of solvent at 35 °C, 24 h. [b]Isolated yield. [c]Some of the starting material was recovered, and yield was based on recovered material; for details see the Supporting Information. [d]10 h. [e]MeONa as base (2.0 mmol) in 2 mL of MeOH for 2 days.

SCHEME 3. Synthesis of 3,4-Disubstituted 5-Hydroxy-2-isoxazolines



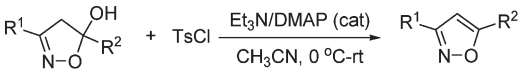
We then evaluated the scope of enones **7** for the synthesis of 3,5-disubstituted 5-hydroxy-2-isoxazolines **8** and ascertained that this method could be applied to various enones as well (Table 2). However, the activities of enones **7** were usually lower compared to those of enals **5**, so the preparation of 5-hydroxy-2-isoxazolines from **7** required relatively higher temperature and longer reaction time than from **5**.[22] By using this protocol, 3,5-diaryl-substituted 5-hydroxy-2-isoxazolines could be prepared conveniently (entries 6−12), which were easy to dehydrate to give diaryl-substituted isoxazoles in the literature.[20a,23] Heteroaromatic substituted chalcones and 3-styryl-substituted enones **7l**/**7m** were also shown as suitable substrates in this process (entries 12 and 13).

To further expand the scope of this strategy, 2-bromo-3-phenylacrylaldehyde **9** was used as a potential substrate. A significant exception was noted: when **9** was subjected to the above-mentioned conditions, only 4-methoxyl-3-phenyl-5-hydroxy-2-isoxazoline **10** was isolated in low yield. Under modified conditions, using *N*-hydroxylmethanesulfonamide (MsNHOH) as hydroxylamine component at 0 °C for 4 h, 2-isoxazoline **10** was isolated in 44% yield (Scheme 3). The

(22) Substrates could not be full consumed in some cases (Table 2, entries 1−2, 6−10, and 14), for details see the Supporting Information.

(23) (a) Kidwai, M.; Kukreja, S.; Thakur, R. *Lett. Org. Chem.* **2006**, *3*, 135. (b) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 6787.

SCHEME 4. Synthesis of Isoxazoles



6/8

12a: R^1 = Ph, R^2 = H, 93% yield
12b: R^1 = 4-NO_2-C_6H_4, R^2 = H, 91% yield
12c: R^1 = 2-furyl, R^2 = H, 85% yield
12d: R^1 = Ph, R^2 = CH_3, 91% yield
12e: R^1 = Ph, R^2 = Ph, 94% yield

relative stereochemistry of **10** was assigned as *anti* by NOE experiments. We postulated that after the formation of normal product 4-bromo-3-phenyl-5-hydroxy-2-isoxazoline, the S_N2 substituted reaction of nucleophile MeOH occurred to give thermodynamically stable product **10**. This hypothesis was proved when ethanol was used as a solvent: *anti*-4-ethoxyl-3-phenyl-5-hydroxy-2-isoxazoline **11** was obtained in 39% yield (Scheme 3). Several non-nucleophilic solvents such as DCM, THF, and CH_3CN have been used for this reaction, but no products occurred besides some decomposed starting materials. The results obtained have shown nonprotic solvents are not suitable solvents for this reaction.[12] Therefore, 3,4-disubstituted 5-hydroxy-2-isoxazolines were also prepared by this protocol.

Synthesis of Isoxazoles. Isoxazoles are important constituents of biologically active natural products (e.g, muscimol), pharmaceutical agents (e.g, isoxicam, eflunomide), and valuable precursors to such structures as 1,3-dicarbonyl compounds.[14] On the basis of our previous studies,[12] we found that 5-hydroxy-2-isoxazolines can be easily transformed to isoxazoles **12** in excellent yields by using 1.5 equiv of TsCl, 2.0 equiv of Et_3N, and catalytic DMAP in CH_3CN at 0 °C−rt for 4 h (Scheme 4). This transformation provided a high-yield route to isoxazoles under very mild reaction conditions. Earlier reports on the synthesis of isoxazole by dehydration of 5-hydroxy-2-isoxazoline usually required high temperature under either basic or acidic conditions.[12,21,24]

Synthesis of β-Hydroxy Oximes, β-Hydroxy Aryl Amides, and *N*-Aryl-β-lactams. To prepare multifunctional open-chain products, various reductive ring-opening reactions of 5-hydroxy isoxazolines were explored. $NaBH_4$, $NaBH_4$/$NiCl_2 \cdot (H_2O)_6$, Pd/C hydrogenation in MeOH were employed and proved to be ineffective in this reaction.[25] When **6a** was treated with 2.0 equiv of $LiAlH_4$ in THF at 0 °C for 2 h, we were pleased to find that the *E* isomer of β-hydroxy oxime **13a**[26] was obtained in excellent yield. To the best of our knowledge, there was no literature precedent for this type of transformation. The product oxime is a very useful functional group for organic synthesis, which would act as the precursors for other important functionalities such as amines, nitriles, amides, nitrile oxides, etc.[27] The utility of oxime was exhibited by Beckmann rearrangement of **13a**, using White's protocol.[28] The desired product β-hydroxy aryl amide **14a** was obtained in 82% yield under mild conditions.

To investigate the scope and limitations of this novel transformation, a number of 5-hydroxy-2-isoxazolines were subjected to the reaction conditions. As evidenced from the results shown in Table 3, various oximes **13** and β-hydroxy amides **14** were obtained in good yields. Such functional groups as chloro (entry 3), nitro, and bromo were tolerated under these conditions.[29] 5-Hydroxy-3-styryl-2-isoxazoline **6m** led to allylic β-hydroxy oxime **13d** and *N*-styryl β-hydroxy amide **14d**, respectively (entry 4). This result provided a novel pathway to prepare enamide, which may be difficult to be obtained by other means. 3,5-Disubstituted 5-hydroxy-2-isoxazolines **8a**/**8f** were also suitable substrates for this protocol to give desired oximes **13e**/**13f** and amides **14e**/**14f** (entries 5 and 6), showing that the two-step sequence is versatile.

It was known that *N*-aryl-β-lactams can be prepared conveniently by an intramolecular Mitsunobu reaction[30]of β-hydroxy aryl amide.[31] Under the influence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP), β-lactams **15** were smoothly obtained in moderate yield (Scheme 5). Therefore, a three-step procedure for the synthesis of β-lactams[16] **15** which represent an important species of biologically active molecules was developed from readily available 5-hydroxy-2-isoxazolines.

Synthesis of γ-Amino Alcohols. γ-Amino alcohols, especially optically active forms, have found important applications in synthetic and medicinal chemistry.[17] As stated in the introduction, 2-isoxazolines are potential synthons for the preparation of γ-amino alcohols.[8] To develop the approach, our initial efforts were directed toward the synthesis of racemic amino alcohol using **6a** as a model substrate. When 4.0 equiv of $BH_3 \cdot THF$ was used, we observed that the conversion to the desired product 3-amino-3-phenylpropan-1-ol **2a** was of 91% yield (Scheme 6).[32] Similarly, products **2b** and **2c** were also isolated in good yields under the same conditions.[8a,b]

Chiral γ-amino alcohol **2a** was the key intermediate[19,33] for the synthesis of the selective serotonin reuptake inhibitor (*S*)-dapoxetine from Eli Lilly and Company (Figure 1).[18] We then attempted the synthesis of the optically active **2a** according to the procedure developed by Ortiz-Marciales' group.[34]

(24) (a) Rosa, F. A.; Machado, P.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **2008**, *45*, 879. (b) Di Nunno, L.; Vitale, P.; Scilimati, A. *Tetrahedron* **2008**, *64*, 11198.

(25) These reagents were usually used to reductive ring opening of 2-isoxazolines in the literature which were mentioned in refs 5−8.

(26) The *E* configuration of **13a** was assigned by NMR analysis and then proved by Beckmann rearrangement. Previously, β-hydroxy oxime **13a** was prepared by cobalt-catalyzed reaction of nitric oxide or ethyl nitrite with aryl-substituted olefins in the presence of BH_4^- ion in low yield; see: Okamoto, T.; Kobayashi, K.; Oka, S.; Tanimoto, S. *J. Org. Chem.* **1987**, *52*, 508; **1988**, *53*, 4897.

(27) For a review, see: Yamane, M.; Narasaka, K. In *Science of Synthesis*; Padwa, A., Ed.; Georg Thieme Verlag: Stuttgart Germany, 2004; Vol. 27, pp 605−647.

(28) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373.

(29) The reduction product oximes of **6b** and **8e** were obtained in 85% yield and 92% yield, respectively. Copies of ^1H NMR spectra of oximes have been provided in the Supporting Information.

(30) (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. (b) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (c) Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679. (d) Mitsunobu, O. *Synthesis* **1981**, 1.

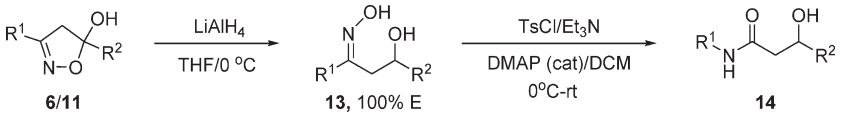
(31) (a) Bose, A. K.; Sahu, D. P.; Manhas, M. S. *J. Org. Chem.* **1981**, *46*, 1229. (b) Bose, A. K.; Manhas, M. S.; Sahu, D. P.; Hegde, V. R. *Can. J. Chem.* **1984**, *62*, 2498.

(32) Uncuta, C.; Caraman, G. B.; Tanase, C. I.; Bartha, E.; Kravtsov, V. CH.; Simonov, Y. A.; Lipkowski, J.; Vanthuyne, N.; Roussel, C. *Chirality* **2005**, *17*, 63.

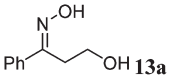
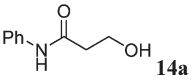
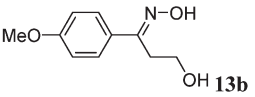
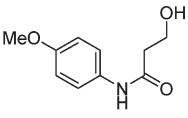
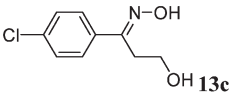
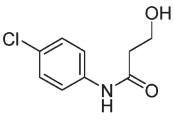
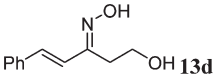
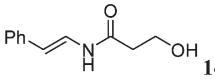
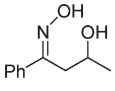
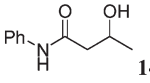
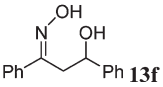
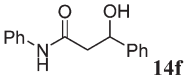
(33) This intermediate can also be prepared by two novel organocatalytic mannich reactions of acetaldehyde with *N*-protected-imine; see: (a) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453. (b) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem.* **2008**, *120*, 2112. *Angew. Chem., Int. Ed.* **2008**, *47*, 2082.

(34) (a) Huang, X. G.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F. G.; Ayala, A. M.; Correa, W.; De-Jesús, M. *Org. Lett.* **2007**, *9*, 1793. (b) Huang, K.; Ortiz-Marciales, M.; Merced, F. G.; Meléndez, H. J.; Correa, W.; De Jesús, M. *J. Org. Chem.* **2008**, *73*, 4017. (c) Huang, K.; Ortiz-Marciales, M.; Stepanenko, V.; De Jesús, M.; Correa, W. *J. Org. Chem.* **2008**, *73*, 6928.

TABLE 3. Synthesis of β-Hydroxy Oximes and β-Hydroxy Aryl Amide[a]

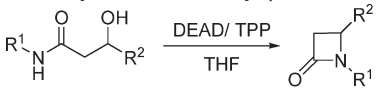


6/11 — 13, 100% E — 14

entry	6/8	13	yield (%)[b]	14	yield (%)[b]
1	6a	 13a	91	 14a	82
2	6d	 13b	76	 14b	60
3	6e	 13c	83	 14c	78
4	6m	 13d	84	 14d	71
5	8a	 13e	86	 14e	77
6	8f	 13f	75	 14f	70

[a]Reaction conditions: see the Supporting Information. [b]Isolated yield.

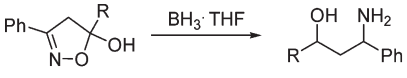
SCHEME 5. Synthesis of *N*-Aryl-β-lactams



14

15a: R^1 = Ph, R^2 = H, 67% yield
15b: R^1 = Ph, R^2 = Ph, 75% yield

SCHEME 6. Synthesis of γ-Amino Alcohols



6/8

2a: R = H, 91% yield
2b: R = CH_3, 79% yield
2c: R = Ph, 70% yield

The optically active **2a** was obtained by the spiroborate-catalyzed borane reduction of **6a**. However, the preliminary results were not satisfactory (see the Supporting Information), and we will extensively study this matter later.

Conclusion

In conclusion, an efficient approach for the highly regioselective synthesis of a diverse array of 5-hydroxy-2-isoxazolines was developed, in which TsNHOH was employed as an effective reactant for the conjugate addition to α,β-unsaturated carbonyl compounds and subsequent extrusion of sulfinate followed by the cyclization to afford the desired products. This methodology tolerates a wide variety of functional groups, including 3-heterocycle, 3-styryl, and 3-ester enals/enones. Furthermore, 5-hydroxy-2-isoxazolines were demonstrated as versatile synthons for the syntheses of isoxazoles, β-hydroxy oximes, and *N*-aryl-β-lactams. In addition, preparation of optically active γ-amino alcohols via asymmetric reductive ring-opening reactions was also attempted. Further investigations toward the chiral synthesis of 2-isoxazolines and relative nitrogen-containing bioactive compounds are currently underway in our laboratory and will be reported in due course.

Experimental Section

General Procedure for the Preparation of 5-Hydroxy-2-isoxazolines (Compound 6a). To a solution of 150 mg (0.8 mmol) of *N*-hydroxyl-4-toluenesulfonamide **1** in 1.4 mL of methanol/water (v:v = 6:1) was added 140 mg (1.0 mmol) of K_2CO_3 in portions. Then 0.2 mmol of enal **5a** dissolved in 0.6 mL of methanol was added, and the reaction mixture was stirred 10 h at rt and monitored by TLC to determine that all of the starting material was consumed. On completion, the reaction mixture was diluted with EtOAc (40 mL). Then the mixture was washed with water (5 mL) and brine (5 mL). The organic extracts were dried over sodium sulfate and filtered. Concentration of the solution by rotary evaporation under reduced pressure gave a residue, which was purified by flash column chromatography to

afford 30 mg (92%) of the product **6a** as a white solid. The characterization data obtained are identical with those previously reported.[12]

Procedure for the Preparation of 10/11. A round-bottomed flask was charged with 134 mg (1.2 mmol) of *N*-hydroxylmethanesulfonamide (MsNHOH) in 3.0 mL of methanol/water or ethanol/water (v:v = 9: 1), and 208 mg (1.5 mmol) of K_2CO_3 was added in portions. Then 63 mg (0.3 mmol) 2-bromo-3-phenylacrylaldehyde **9** was slowly added at 0 °C. The reaction mixture was stirred about 4 h and monitored by TLC to determine that all of the starting material was consumed. On completion, the reaction mixture was diluted with EtOAc (40 mL) and the mixture was washed with water (5 mL) and brine (5 mL). The organic extracts were dried over sodium sulfate and filtered. Concentration of the solution by rotary evaporation under reduced pressure gave a residue, which was purified by flash column chromatography to afford the product **10** in 44% yield and the product **11** in 39% yield, respectively. **10**: white solid, mp 132−134 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56−7.79 (m, 2H), 7.46−7.49 (m, 3H), 6.39 (d, J = 7.2 Hz, 1H), 5.32 (s, 1H), 5.13 (d, J = 7.2 Hz, 1H), 3.41 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.1, 130.3, 128.9, 127.9, 127.0, 109.3, 80.3, 55.3; HRMS calcd for $C_{10}H_{11}NO_3$ $[M]^+$ 193.0733, found 193.0730. **11**: white solid, mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.81 (m, 2H), 7.35−7.45 (m, 3H), 5.43 (dd, J = 5.1, 0.6 Hz, 1H), 5.18 (d, J = 0.6 Hz, 1H), 3.86−3.96 (m, 1H), 3.61−3.71 (m, 1H), 2.25 (br s, 1H), 1.23 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.8, 129.1, 128.3, 127.4, 108.6, 82.1, 64.8, 15.1; HRMS calcd for $C_{11}H_{13}NO_3$ $[M]^+$ 207.0890, found 207.0886.

Acknowledgment. We are grateful for the generous financial support by the NSFC (QT program, 20872054 and 20732002).

Supporting Information Available: General experimental details, details of the synthesis of optically active **2a**, procedures for the preparation of **12**, **13**, **14**, **15**, and **2**, compound characterization, and copies of spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.