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A Divergent and Selective Synthesis of Isomeric Benzoxazoles from a Single N–Cl Imine

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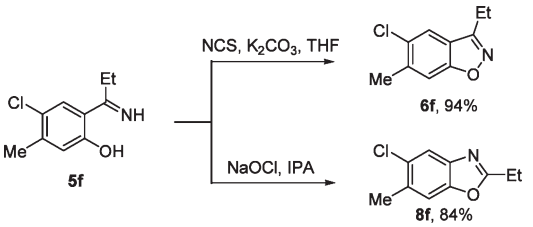
ABSTRACT



A divergent and regioselective synthesis of either 3-substituted benzisoxazoles or 2-substituted benzoxazoles from readily accessible *ortho*-hydroxyaryl N–H ketimines is described. The reaction proceeds in two distinct pathways through a common N–Cl imine intermediate: (a) N–O bond formation to form benzisoxazole under anhydrous conditions and (b) NaOCl mediated Beckmann-type rearrangement to form benzoxazole, respectively. The reaction path also depends on the electronic nature of the aromatic ring, with the electron-rich aromatic rings favoring the rearrangement and the electron-deficient rings favoring the N–O bond formation. A Beckmann-type rearrangement mechanism *via* net [1,2]-aryl migration for the formation of 2-substituted benzoxazole is proposed.

The isomeric benzisoxazole and benzoxazole heterocycles are ubiquitous in the realms of pharmacologically active agents and natural products (Figure 1). For example, benzisoxazole serves as a starting material for the synthesis of more elaborate structures with bioactive properties. Three important pharmaceutical drugs (the antipsychotic risperidone[1] and its hydroxyl analogue, paliperidone,[2] and the anticonvulsant zonisamide) were discovered based on the benzisoxazole core.[3] Benoxaprofen and flunoxaprofen, both containing benzoxazole cores, are chiral nonsteroidal anti-inflammatory drugs once approved for improving the symptoms of osteoarthritis and rheumatoid arthritis.[4] Additionally, the benzoxazole ring occurs in a number of natural products such as salvianen and its regioisomer, pseudosalvianen.[5] Given the importance of this class of heterocycles, the pursuit of a general and efficient synthesis of both benzisoxazole and benzoxazole that controls the formation of heterocycles in a regioselective fashion is of great importance. Many existing approaches to either benzisoxazole[6] or benzoxazole[7] have been reported. The efficient synthesis of either benzisoxazoles or benzoxazoles from the same substrate, however, remains elusive and would have great advantages over existing protocols. Herein, we report a divergent and regioselective synthesis of either

(1) Risperidone was approved by the United States Food and Drug Administration (FDA) in 1993 for the treatment of schizophrenia. For reviews on risperidone, see: (a) Swainston, H. T.; Goa, K. L. *CNS Drugs* **2004**, *18*, 113. (b) Deeks, E. D. *Drugs* **2010**, *70*, 1001 and references cited therein.

(2) Paliperidone was commercialized recently as an improved drug compared to its parent, risperidone; see: (a) Yang, L. P. H.; Plosker, G. L. *CNS Drugs* **2007**, *21*, 417. (b) Ivo, C. L.; Joris, B. In *Bipolar Psychopharmacotherapy: Caring for the Patient*, 2nd ed.; Akiskal, H., Mauricio, T., Eds.; Wiley: 2011, p 153.

(3) Zonisamide, widely prescribed as an antiepileptic drug, was developed by Dianippon of Japan. For reviews on zonisamide in the treatment of epilepsy, see: (a) Andreas, S.-B. *Expert Opin. Pharmaco.* **2010**, *11*, 115. (b) Wroe, S. J. *Zonisamide. Treatment of Epilepsy*, 3rd ed.; Wiley: 2009; p 713.

(4) (a) Dunwell, D. W.; Evans, D. *J. Med. Chem.* **1977**, *20*, 791. (b) Hopkins, S. J. *Drugs Today* **1980**, *16*, 281. (c) Dong, J. Q.; Liu, J.; Smith, P. C. *Biochem. Pharmacol.* **2005**, *70*, 937.

(5) (a) Don, M.-J.; Shen, C.-C.; Lin, Y.-L.; Syu, W., Jr.; Ding, Y.-H.; Sun, C.-M. *J. Nat. Prod.* **2005**, *68*, 1066. (b) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452.

(6) For recent reviews of the synthesis of benzisoxazoles, see: (a) Hartinger, S. *Sci. Syn., Knowl. Upd.* **2010**, *1*, 133. (b) Smalley, R. K. *Sci. Syn.*, Schaumann, E., Ed.; Thieme: Stuttgart, 2002, 11, 289.

(7) For recent reviews of the synthesis of benzoxazoles, see: (a) Schnürch, M.; Hämmerle, J.; Stanetty, P. *Sci. Syn., Knowl. Upd.* **2010**, *1*, 153. (b) Boyd, G. V. *Sci. Syn.* **2002**, *11*, 481.

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benzisoxazoles or benzoxazoles from a single, readily accessible substrate, *ortho*-hydroxyaryl N−H ketimines.

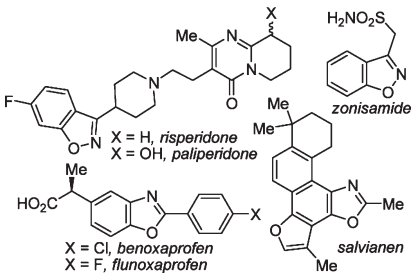
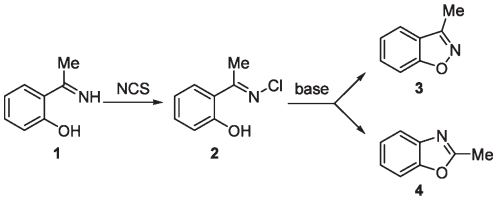


Figure 1. Benzisoxazoles and benzoxazoles as medicinal agents and natural products.

The *ortho*-hydroxyaryl N−H ketimines readily prepared from the *ortho*-hydroxyaryl ketones have surprisingly found limited application in organic synthesis.[8] These unsubstituted imines are stable species largely due to a strong intramolecular H-bond between the OH and imino nitrogen. In an effort to explore the utilization of these ketimines in the synthesis of heterocycles, we envisioned that an activation of the imino nitrogen followed by intramolecular N−O bond formation would lead to effective construction of benzisoxazole rings. We were delighted to find that this conceptually simple approach worked well when N−H ketimine **1** was treated with NCS in the presence of DABCO to afford benzisoxazole **3** in 89% yield (Table 1, entry 1). We subsequently found that treatment of N−H ketimines in various organic solvents with 10% aqueous NaOCl led to smooth formation of benzoxazoles (Figure 3, *vide infra*). This preliminary lead prompted us to develop a versatile method for direct access to both isomeric heterocycles, benzisoxazole, and benzoxazole, under different reaction conditions.

We further explored the generality of the controlled synthesis of 3-substituted benzisoxazoles by using NCS as a chlorinating agent to activate N−H ketimine. Treatment of N−H ketimine with NCS in several solvents afforded a new species N−Cl imine (**2**).[9] The N−Cl imine was not isolated, but rather it was treated with bases to facilitate the N−O bond formation. As shown in Table 1, a brief survey of bases for effective N−O formation indicates that an inexpensive inorganic base such as K_2CO_3 is superior to others, though potassium *tert*-butoxide and DABCO also gave satisfactory results for this substrate. Other bases were ineffective for the N−O bond formation (Table 1, entries 2−9). Furthermore, it was not necessary to form the N−Cl imine first prior to the introduction of the base. The activation and ring closure can be run in one pot by mixing an N−H ketimine, base, and NCS in a solvent at ambient temperature. Alternative chlorinating agents such as *tert*-BuOCl and trichloroisocyanic acid were less effective than NCS, generating a messy reaction profile.

Table 1. Survey on the Bases[a]



entry	base	solvent	**2**[b]	**3**[b]	**4**[b]
1	DABCO	CH_2Cl_2	0	**92**	8
2	Et_3N	CH_3CN	52	38	10
3	pyridine	CH_2Cl_2	**100**	0	0
4	*i*-PrNEt_2	CH_3CN	45	39	16
5	DBU	CH_3CN	35	48	17
6	DBU	CH_2Cl_2	45	42	13
7	DIPA	CH_3CN	52	28	20
8	K_2CO_3	THF−H_2O[c]	30	50	20
9	NaOAc	THF	61	32	7
10	K_2CO_3	THF	0	**93**	7
11	KO*t*-Bu	THF	0	**94**	6

[a] N−H ketimine (0.50 mmol), NCS (0.75 mol), and base (1.0 mmol) were mixed in solvent (1.0 mL) at room temperature for 12 h. [b] Regioisomeric ratio was determined by reverse HPLC and reported as area percentage. [c] THF/H_2O = 1:1.

A variety of *ortho*-hydroxyaryl N−H ketimines were subjected to the previously identified conditions (Table 1, entry 10) for the N−O bond formation. As shown in Figure 2, the reaction is quite general for various substrates (ketimines **5a**−**o**). A wide variety of 3-substituted benzisoxazoles (**6a**−**o**) were readily prepared in good to excellent yields (76−99% yield) under these milder conditions. The N−O bond formation is independent of the substituents (R) attached to the hydroxy aromatic ketone, as substrates with R = Me, Et, $PhCH_2CH_2$, and aryl all gave benzisoxazoles. Moreover, it was noted that the N−O bond formation of the substrates bearing electron-deficient groups was extremely facile compared to the others as shown in examples **6j** and **6k**; both were formed quantitatively. The N−O bond formation can be readily applied to the preparation of 3-aryl benzisoxazoles **6l**−**n** in good yields and 3-(4′-pyridinyl)-benzisoxazole (**6o**) in 97% yield.

Having successfully prepared a range of 3-substituted benzoisoxazoles **6a**−**o** from *ortho*-hydroxyaryl N−H ketimines **5a**−**o** employing NCS as an activating agent, we next decided to explore the NaOCl mediated rearrangement of ketimines for the preparation of 2-substituted benzoxazoles. Delightfully, this reaction is also general as a wide array of 2-substituted benzoxazoles can be readily

(8) (a) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Barkov, A. Y.; Matochkina, E. G.; Kodess, M. *Tetrahedron* **2008**, *64*, 5055. (b) Enantioselective reduction of *ortho*-hydroxyaryl alkyl N-H ketimines was reported; see: Nguyen, T. B.; Bousserouel, H.; Wang, Q.; Guéritte, F. *Org. Lett.* **2010**, *12*, 4705. (c) Crecente-Campo, J.; Pilar Vazquez-Tato, M.; Seijas, J. A. *Eur. J. Org. Chem.* **2010**, *21*, 4130.

(9) The structure elucidation of N−Cl imine **2** was carried out by NMR spectroscopic techniques. For details, see Supporting Information.

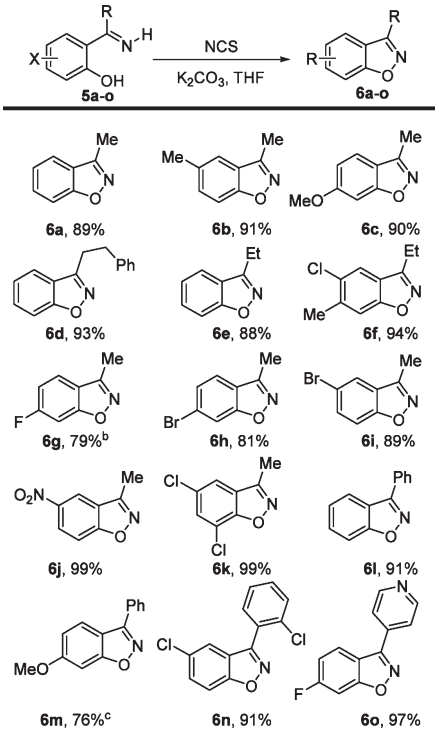


Figure 2. Synthesis of 3-substituted benzoisoxazole **6** from *ortho*-hydroxyaryl N−H ketimines. All the reactions were carried out in THF at ambient temperature for 12 h employing 1.0 equiv of *ortho*-hydroxyaryl N−H ketimine, 1.5 equiv of NCS, and 2 equiv of K_2CO_3. Yields refer to isolated material based on ketimines **5**. For **6g**, Me−THF was used and the yield was based on NMR spectra. For **6m**, the regiosiomer, 2-phenyl benzoxazole, was isolated in 19% yield.

prepared from the *ortho*-hydroxyaryl ketimines as summarized in Figure 3. The same substrates used in the NCS-mediated N−O bond formation (Figure 2, **6a**−**g**) were subjected to the NaOCl-mediated rearrangement, affording products **8a**−**g** in good to excellent yields. Experimentally, the NaOCl-mediated rearrangement of N−H ketimine to benzoxazole was carried out by adding 3 equiv of 10% aqueous NaOCl to N−H ketimine in IPA at ambient temperature. The reaction is almost instantaneous as indicated by the fading of the yellow color of N−H ketimine in IPA upon addition of the NaOCl. The simplicity and high efficiency of this protocol render it attractive when compared to the others reported in the literature.[7] Further examination of a few more substrates (**5j**, **5k**, **5l**, and **5o**) revealed that substrates bearing electron-donating groups in the hydroxy aromatic ring are more prone to the rearrangement whereas those with electron-withdrawing groups failed. For example, N−H ketimines **5j** (X = NO_2) and **5k** (X = dichloro) afforded benzisoxazole (**6j** and **6k**) quantitatively upon treatment with NaOCl. Ketimines bearing aromatic substituents (R = Ar, **5l**, **5o**) formed corresponding benzisoxazoles in good yields, rather than their regioisomers, benzoxazoles, upon treatment with NaOCl. On the other hand, benzoxazoles (**8h** and **8i**) can be readily prepared in quantitative yields from the corresponding electronic-rich aromatic N−H ketimines. Treatment of ketimine **7j** (X = 4-F) with NaOCl afforded benzoxazole **8j** in 88% yield. Finally, a new heterocycle, quinoline fused oxazole **8k**, was obtained uneventfully in 91% yield.

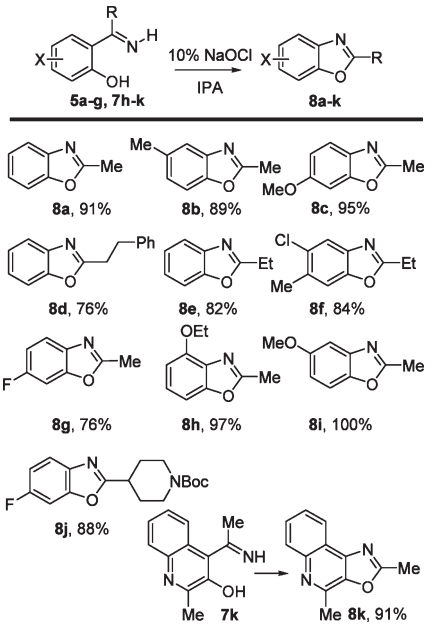


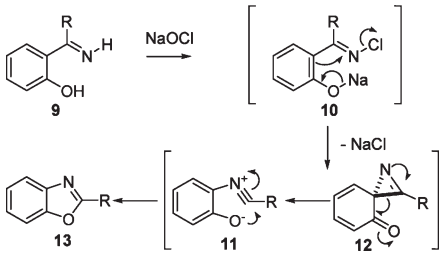
Figure 3. Synthesis of 2-substituted benzoxazole **8** from *ortho*-hydroxyaryl N−H ketimines. All the reactions were carried out in IPA at ambient temperature for 10−30 min employing 1.0 equiv of *ortho*-hydroxyaryl N−H ketimines and 3.0 equiv of 10% aq NaOCl. Yields refer to isolated material based on N−H ketimines **5** and **7**. Benzisoxazole regioisomers of **8d**, **8e**, and **8f** were obtained in 19%, 12%, and 11% yield, respectively.

We propose that the formation of benzoxazole proceeds with a Beckmann-type rearrangement[10] *via* a spiro enone intermediate (**12**, Scheme 1).[11] The generation of a phenoxide intermediate (**10**) using NaOCl and an electron-rich aromatic ring appears to facilitate the rearrangement. We speculate that the hydrogen bond to the phenoxide in aqueous media weakens the nucleophilicity of the phenoxides, and hence the species favors the rearrangement *via* net [1,2]-aryl migration instead of the N−O bond formation.[12,13] It should be noted that the conventional Beckmann rearrangement generally proceeds under strongly acidic and dehydrating media at high reaction temperature.[14] The current anionic protocol for the benzoxazole formation, however, is a very mild yet rapid process run at ambient temperature.

(10) For reviews on Beckmann rearrangement, see: (a) Gawley, R. E. *Org. React.* **1988**, *35*, 1 and references cited therein. (b) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons: New York, 2001; p 1415 and references cited therein.

(11) A spiro enone intermediate was proposed in the pyrolysis of 3-phenyl benzisoxazole to 2-phenyl benzoxazole; see: (a) Aldous, G. L.; Bowie, J. H.; Thompson, M. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 16. (b) Davies, K.; Storr, R. C.; Whittle, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 9.

Scheme 1. Proposed Rearrangement Mechanism *via* Net [1,2]-Aryl Migration for the Formation of Benzoxazole



In summary, we have discovered and developed a versatile method for the divergent and regioselective synthesis of either 3-substituted benzisoxazoles or 2-substituted benzoxazoles from a single *ortho*-hydroxyaryl N−H ketimine starting material. The reaction proceeds *via* a facile N−O bond formation from an N−Cl imine intermediate to form benzisoxazoles under anhydrous conditions. The reaction mediated by NaOCl, on the other hand, likely goes through an alkoxide intermediate *via* net [1,2]-aryl rearrangement to form the corresponding 2-substituted benzoxazoles. The methods demonstrated here allow easy access to a wide array of two isomeric heterocycles tolerant of various substitution patterns. They provide rapid access to a variety of structurally useful benzoxazoles and, hence, could serve as a versatile tool for the modular synthesis of benzoxazole containing medicinal agents. We also hope this work will prompt others to explore application of *ortho*-hydroxyaryl N−H ketimines in organic synthesis.

Acknowledgment. The authors would like to thank our colleagues at Merck Research Laboratories, NJ, USA, Dr. Charles W. Ross for the HRMS work as well as Dr. Robert T. Williamson and Lisa Dimichele for the structural elucidation work using NMR.

Supporting Information Available. Experimental procedure, spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For our work on the syntheses of benzofuran and indole *via* net [1,2]-aryl migration, see: (a) Pei, T.; Chen, C.-y.; Dimichele, L.; Davies, I. W. *Org. Lett.* **2010**, *12*, 4972. (b) Pei, T.; Tellers, D. M.; Streckfuss, E. C.; Chen, C.-y.; Davies, I. W. *Tetrahedron* **2009**, *65*, 3285. (c) Pei, T.; Chen, C.-y.; Dormer, P. G.; Davies, I. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4231.

(13) Formation of amides *via* the migration of the R group was not observed for all the runs in Figure 3. Furthermore, we proved that the formation of benzoxazole **4** was not derived from the initially formed benzisoxazole **3** as **3** remains intact upon treatment with 10% NaOCl.

(14) For selected examples on the syntheses of benzoxazoles from *ortho*-hydroxylaryl oximes *via* Beckmann rearrangement at elevated temperature, see: (a) Gadakh, A. V.; Pandit, C.; Rindhe, S. S.; Karale, B.; K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5572. (b) Sardarian, A. R.; Shahsavari-Fard, Z. *Synlett* **2008**, *9*, 1391.