http://dx.doi.org/10.5012/bkcs.2012.33.4.1371

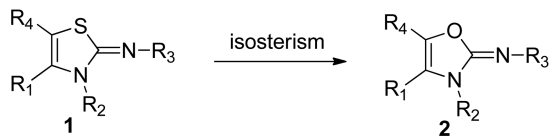
A Regioselective Synthesis of Multi-Substituted 2-Imino-1,3-oxazolines by One-Pot Reaction

Minsoo Han[†,‡] and Hoh-Gyu Hahn[†,*]

[†]*Organic Chemistry Laboratory, Korea Institute of Science and Technology, Seoul 136-791, Korea.* [*]*E-mail: hghahn@kist.re.kr*
[‡]*Department of Chemistry, Korea University, Seoul 136-701, Korea*
Received December 22, 2011, Accepted January 13, 2012

Key Words : Heterocycles, Carbodiimide, α-Hydroxyketones, 2-Imino-1,3-oxazoline

Heterocycles are significant chemical entities for research on small molecule drugs and their development in the pharmaceutical industry. Attention until now has focused on synthetic methods for forming heterocycles. However, new and efficient synthetic methods for the construction of heterocyclic molecules are now being researched continuously. In our previous papers, we reported the construction of two different combinatorial libraries, including novel 2-imino-1,3-thiazolines **1**, that show T-type calcium channel inhibitory activity[1] and fungicidal property.[2] Recently, a number of reports examined the significant biological activities of the 2-imino-1,3-thiazoline derivatives.[3] As an extension of our efforts to investigate the biological activities of their analogues, we synthesized 2-imino-1,3-oxazolines **2**, which are isosteres of 2-imino-1,3-thiazolines **1** (Figure 1). In the present study we investigate a method for synthesizing multi-substituted 2-imino-1,3-oxazolines **2** with the aim of increasing the diversity in chemical structures. A comparison of the biological activity of **1** and **2** promises to increase our understanding of the structure-activity relationship of this series.



1 **2**

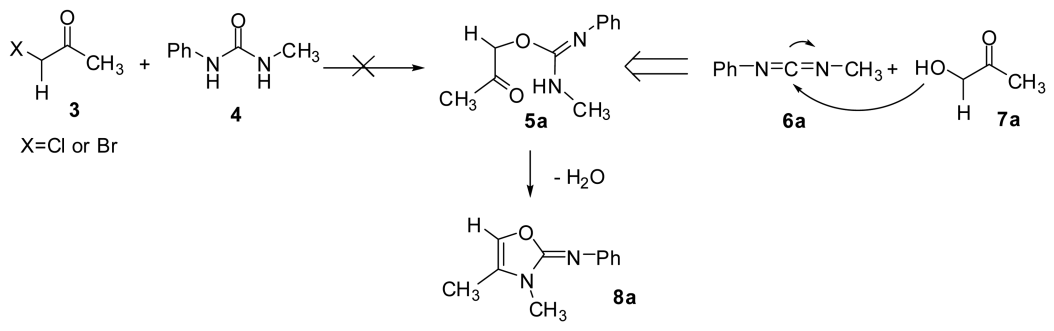
T-type Ca^{2+} channel inhibitiory
fungicidal, and
anti-*Helicobacter pylori*
activities

Figure 1. 2-Imino-1,3-thiazoline **1** and its isostere, 2-imino-1,3-oxazoline **2**.

A literature survey revealed few reports on the synthetic methods of 2-imino-1,3-oxazolines. The synthetic methodologies of 2-imino-1,3-oxazolines reported over the past three decades were classified into four categories. First, a condensation of α-haloketone and symmetrical diphenylurea in presence of bromine as the condensing agent gave 2-aryl-imino-3-aryl-1,3-oxazolines.[4] Second, electrochemical synthesis of substituted phenylmonoimine with *N*-acylcarbonimidoyl dichloride resulted in tetraaryliminooxazolines.[5] Third, the reaction of ketenimine with hydroxylamino derivatives gave 2-imino-1,3-oxazolines through 3-imino-isoxazolines.[6] Fourth, the reaction of alkyl diazoacetates with carbodiimides in presence of transition metal salts gave 2-imino-1,3-oxazoline derivatives.[7] Unfortunately, all these reported methods suffered the limitations of low yield, harsh reaction conditions, and lack of regioselectivity and chemical structural diversity of the products. Therefore, we herein report a very simple and convenient synthetic method for the preparation of multi-substituted 2-imino-1,3-oxazolines derivatives with the aim of increasing the product diversity and production yield, by reacting α-hydroxyketone and carbodiimide in the presence of copper salts as a catalyst.

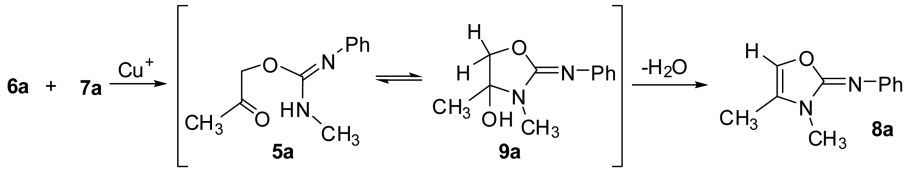
Results and Discussion

In initial synthetic attempts, α-haloketones **3** was condensed with urea **4**, in a similar manner to the synthesis of 2-imino-1,3-thiazoline derivatives (Scheme 1).[1,2,8] However, no 2-imino-1,3-oxazoline **8a** was produced, probably due to



3 **4** **5a** **6a** **7a** **8a**

Scheme 1. Retrosynthesis of **8a** *via* an intermediate **5a**.



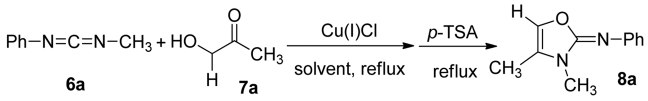
Scheme 2. Reaction pathway for the formation of **8a** *via* 2-iminooxazolidine **9a**.

the low nucleophilic character of the oxygen of urea **4**. The enhanced nucleophilicity of the oxygen due to the addition of sodium hydride failed the reaction. Therefore, we designed an alternative route for the preparation of pseudourea **5a**, which is a key intermediate in the preparation of 2-imino-1,3-thiazoline (see the retrosynthetic analysis in Scheme 1). The nucleophilic attack of the oxygen of alcohol **7a** on the imino carbon of **6a** formed the intermediate **5a**. A previous report[9] on the reaction of a carbodiimide with ethanol in the presence of CuI to give the corresponding pseudourea supported our proposed retrosynthetic analysis. In fact, the carbodiimides are widely used in preparation of various heterocycles.[10] Furthermore, this methodology is expected to facilitate the preparation of diverse derivatives of the products.

As a model reaction, we chose pre-prepared methylphenylcarbodiimide **6a** and commercially available α-hydroxyacetone **7a** as starting materials. No reaction proceeded when a mixture of **7a** and **6a** was refluxed at ambient temperature in various solvents. To enhance the low electrophilicity of the azomethine carbon atom in imine moiety, the reaction proceeded in the presence of 0.1 molar equivalent of Cu(I)Cl[11] in boiling tetrahydrofuran (THF) to give the desired 2-imino-1,3-oxazoline **8a** (48% yield by flash chromatography) accompanied by the intermediate **5a** as a by-product (see Scheme 2). Without the copper catalyst the reaction did not take place and the prolonged reaction time led to decomposition of the carbodiimide. Thin layer chromatography (TLC) monitoring of the reaction confirmed that it proceeded in two steps: coupling reaction and dehydration, as shown in Scheme 2. Under similar reaction conditions at low temperature (boiling methylene chloride or acetone) for a short reaction time (0.5 h), the dehydration did not occur and the production of the intermediate **5a** was confirmed quantitatively by TLC. The intermediate **5a** was in equilibrium with the closed form **9a**, which was determined by the structure of its phenyl analogue.[12]

Although an acid catalyst facilitated transformation of the intermediate **5a** to the desired **8a,** this reaction proceeded spontaneously at high temperature (boiling THF or benzene) under neutral conditions. In contrast, low temperature (boiling methylene chloride or acetone) dehydration required an acid catalyst. However, the reaction of **6a** with **7a** in the presence of acid catalyst produced a complex mixture of unknown compounds without the formation of any **5a**. Therefore, the acid catalyst should be treated with the reaction mixture after identification of the intermediate **5a** formed from the reaction mixture by TLC, in order to obtain

Table 1. The yields depending on the reaction conditions

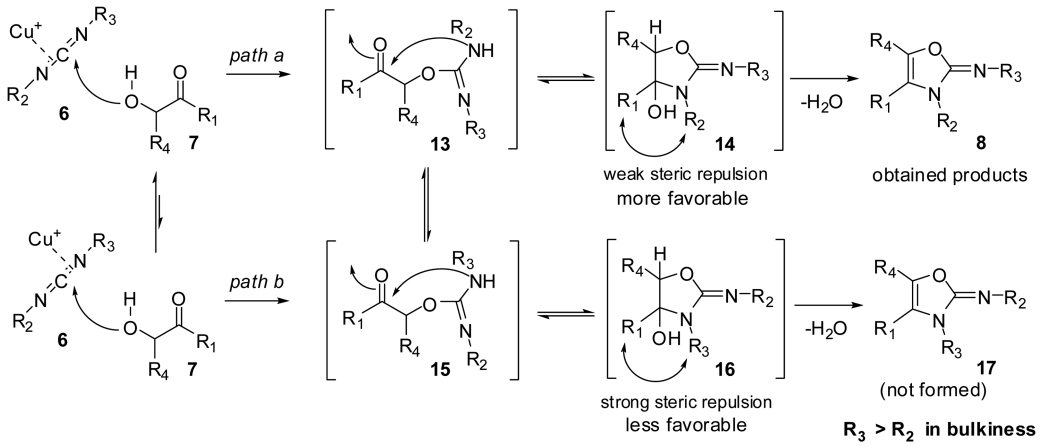


Entry	Solvent	Molar equivalent of *p*-TSA[a]	Reaction time[b]	Yield (%)[c]
1	THF	-	1.5 h	48[d]
2	THF	0.1	1.5 h	91
3	DCM	0.1	1.5 h	25
4	Acetone	0.1	1.5 h	33
5	Acetonitrile	0.1	1.5 h	83
6	Benzene	-	1.5 h	84
7	Toluene	-	1.5 h	83
8	DMF	-	1.5 h	67

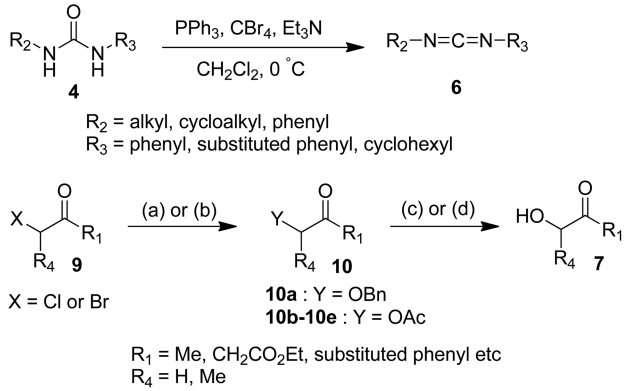
[a]*p*-Toluensulfonic acid: The catalyst was added after the completion of the coupling reaction of **6a** with **7a**. [b]Total reaction time. [c]Yield were determined by HPLC. [d]Isolated yield; a major by-product was the intermediate **5a** by TLC.

2-imino-1,3-oxazoline **8a** in high yield. For instance, the reaction of **6a** and **7a** in the presence of Cu(I)Cl (0.1 molar equivalent) in refluxing THF followed by sequential treatment of *p*-toluenesulfonic acid monohydrate (*p*-TSA) as an acid catalyst produced **8a** (entry 2 in Table 1) in high yield (91%). Without an acid catalyst, benzene or toluene was the best choice as a solvent for convenient preparation of **8a** in comparatively high yield. Under the refluxing temperature in the presence of copper catalyst (0.1 equiv.), the coupling reaction and the subsequent dehydration proceeded smoothly without the presence of acid catalyst to give a high yield of the product (entries 6, 7 in Table 1). For example, 2-imino-1,3-oxazoline **8a** was obtained in 84% yield under the refluxing benzene by one pot reaction.

The mechanism for the conversion can be explained as follows (Scheme 3). Coordination of the copper ion of diimide **6** followed by nucleophilic addition of oxygen of the hydroxy group of **7**[13] provides either 2-imino-1,3-oxazoline **8** or its structural isomer **17** through the respective intermediates **13**, **14** (*path a*) and **15**, **16** (*path b*). Two mechanisms are possible to explain the regiochemistry of the product (**8** or **17**). First, the copper ion can be coordinated in the less hindered site of diimide **6**. When R_3 is larger than R_2 in bulkiness the coordination of the copper ion takes place at the imino moiety in which nitrogen is attached at the smaller R_2, due to the steric repulsion between the copper ion and the bulky group R_3. In this case, *path a* is more favorable, thereby producing 2-imino-oxazoline **8**. Second, the inter-



Scheme 3. Regioselectivity for the formation of 2-imino-1,3-oxazoline **8**.



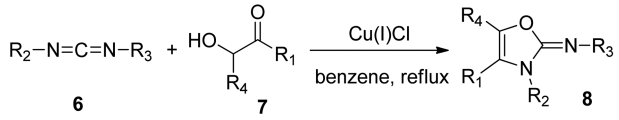
Scheme 4. Preparation of carbodiimides **6** and α-hydroxyketones **7** used in this study. Reagent and conditions: (a) NaH, benzyl alcohol, THF, 40 °C, (b) KOAc, acetone, reflux, (c) H_2, 10% Pd/C, EtOH, rt, (d) Novozyme 435^{TM}, EtOH, rt.

mediate **15** or its closed form **16** has a less favorable spatial arrangement, due to the steric repulsion between the R_1 group at C-4 and R_3 of the 1,3-oxazoline scaffold (*path b*). Thus, the reaction probably resulted in 2-imino-oxazoline **8** through the more favorable intermediate **14** (*path a*).

The structures of the prepared 2-imino-1,3-oxazolines were confirmed based on ^{1}H NMR, ^{13}C NMR, and HRMS spectral data. The regiochemistry of the product was established by X-ray crystallographic analysis (see Supplementary Material).[14]

In order to extend the scope of the reaction substrates, a group of various starting carbodiimide and α-hydroxyketone derivatives was prepared. Carbodiimides **6** were prepared in 41-98% yields through the treatment of urea **4** with carbon tetrabromide in the presence of triphenylphosphine.[15] The

Table 2. The isolated yields of the 2-imino-1,3-oxazolines derivatives **8a-8r**



Entry	Products	R_1	R_2	R_3	R_4	Yield (%)[a]
1	**8a**	CH_3	CH_3	C_6H_5	H	91
2	**8b**	CH_3	C_6H_5	C_6H_5	H	48
3	**8c**	C_6H_4(4-Cl)	CH_3	C_6H_4(4-CH_3)	H	95
4	**8d**	CH_2CO_2Et	CH_3	C_6H_4(4-CH_3)	H	63
5	**8e**	$CH_2CONHC_6H_5$	CH_3	C_6H_3(3,4-diCl)	H	69
6	**8f**	CH_3	CH_3	C_6H_4(4-CH_3)	CH_3	67
7	**8g**	CH_3	cyclopropyl	C_6H_4(4-OCH_3)	H	54
8	**8h**	C_6H_4(4-Cl)	cyclopropyl	C_6H_4(4-OCH_3)	H	51
9	**8i**	CH_3	*n*-propyl	C_6H_3(2-F,4-Cl)	H	83
10	**8j**	CH_3	*n*-propyl	C_6H_3(2-F,4-Cl)	CH_3	89
11	**8k**	C_6H_4(4-C_6H_5)	cyclopropyl	C_6H_4(2-CH_3)	H	93
12	**8l**	CH_2Pt[b]	cyclopropyl	C_6H_4(2-CH_3)	H	78
13	**8m**	C_6H_4(4-C_6H_5)	CH_3	C_6H_3(2-F,4-F)	H	63
14	**8n**	CH_2Pt[b]	CH_3	C_6H_3(2-F,4-F)	H	84
15	**8o**	CH_3	Ethyl	C_6H_4(4-NO_2)	CH_3	82
16	**8p**	$CH_2CONHC_6H_5$	Ethyl	C_6H_4(4-NO_2)	H	87
17	**8q**	C_6H_4(4-Cl)	CH_3	C_6H_5	H	72
18	**8r**	CH_2CO_2Et	Ethyl	Cyclohexyl	H	40

[a]The yields (%) were calculated based on the weight of the product obtained. [b]Pt = Phthalimide group.

other starting material, α-hydroxyketones **7**, was prepared by the previously reported methods.[16]

The pre-prepared carbodiimides **6** were treated with various α-hydroxyketones **7** in the presence of Cu(I)Cl (0.1 molar equivalent) in refluxing benzene. This procedure gave the corresponding 2-imino-1,3-oxazolines in moderate to high yield (40-95% isolated yields), and the results are summarized in Table 2.

Experimental

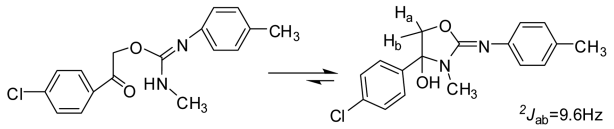
General Procedure.

Synthesis of 2-Imino-1,3-oxazolines 8 (General Procedure): To a solution of carbodiimide **6** (1.0 mmol) in benzene (6 mL) was added α-hydroxyketones **7** (1.0 mmol) and Cu(I)Cl (0.1 mmol), and the reaction mixture was heated to reflux for 2-6 h. The solvent was removed under reduced pressure. The residue was diluted with methylene chloride, washed with water, and then dried with $MgSO_4$. The solvent was removed by evaporation, and the residue was purified either by crystallization from ethyl acetate/*n*-hexane or by flash chromatography on silica gel to obtain the corresponding 2-imino-1,3-oxazolines **8a-8r** (40-95% isolated yields).

Acknowledgments. This work was financially supported by Korea Institute of Science and Technology.

References and Notes

1. Han, M.; Nam, K. D.; Shin, D.; Jeong, N.; Hahn, H.-G. *J. Comb. Chem.* **2010**, *12*, 518.
2. Bae, S.; Hahn, H. G.; Nam, K. D. *J. Comb. Chem.* **2005**, *7*, 826.
3. (a) Katsura, Y.; Nishino, S.; Inoue, Y.; Sakane, K.; Matsumoto, Y.; Morinaga, C.; Ishikawa, H.; Takasugi, H. *J. Med. Chem.* **2002**, *45*, 143. (b) Fritch, P. C.; McNaughton-Smith, G.; Amato, G. S.; Burns, J. F.; Eargle, C. W.; Roeloffs, R.; Harrison, W.; Jones, L.; Wickenden, A. D. *J. Med. Chem.* **2010**, *53*, 887. (c) Ohta, H.; Ishizaka, T.; Yoshinaga, M.; Morita, A.; Tomishima, Y.; Yoda, Y.; Saito, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5133. (d) Tegley, C. M.; Viswanandhan, V. N.; Biswas, K.; Frohn., M. J.; Peterkin, T. A. N.; Chang, C.; Bürli, R. W.; Dao, J. H.; Veith, H.; Rogers, N.; Yoder, S. C.; Biddlecome, G.; Tagari, P.; Allen, J. R.; Hungate, R. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3925.
4. Patnaik, B. K.; Rout, D. N.; Mahapatra, G. N. *J. Indian Chem. Soc.* **1978**, *55*, 925.
5. Guirado, A.; Zapata, A.; Jones, P. G. *Tetrahedron* **1995**, *51*, 10375.
6. Sarlo, F. D.; Guarna, A.; Mascagni, P.; Carrié, R.; Guenot, P. *J. Chem. Soc., Perkin Trans. I* **1981**, 1367.
7. Drapier, J.; Feron, A.; Warin, R.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1979**, *20*, 559.
8. Xiang, J.; Ipek, M.; Suri, V.; Massefski, W.; Pan, N.; Ge, Y.; Tam, M.; Xing, Y.; Tobin, J. F.; Xu, X.; Tam, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2865.
9. Tsuge, O.; Hatta, T.; Shrnomka, M.; Tashiro, H.; Maeda, H.; Kakehi, A. *Org. Prep. Proced. Int.* **2000**, *32*, 469.
10. Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589.
11. We investigated several kinds of metal salts: Cu(I)Cl, $Cu(II)Cl_2$, Cu(I)Br, Cu(I)I, $Cu(II)(NO_3)_2{\cdot}H_2O$, $Ni(II)Cl_2{\cdot}6H_2O$, and $Zn(II)Cl_2$ for the reaction. Using Cu(I)Cl (0.1 molar equivalent) gave the highest product yield.
12. We isolated phenyl analogue **18** as a solid, and its structure was elucidated as its closed form **19** by ^{1}H NMR spectroscopy. Thus, methylene proton of **19** showed the characteristic AB quartet (J_{ab} = 9.6 Hz) at 4.12 ppm and 4.23 ppm, which was consistent with the structure.



18 **19**

13. Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338.
14. We obtained X-ray crystallographic data for 2-imino-1,3-oxazoline **8q**: See the ORTEP plots and the data in Supplementary Material. The data (excluding structure factors) for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-850176. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
15. Boguszewski, P. A.; Rahman, S. S.; Ganesan, A. *J. Comb. Chem.* **2004**, *6*, 32.
16. (a) Yasohara, Y.; Kizaki, N.; Hasegawa, J.; Wada, M.; Michihiko Kataokac, M.; Shimizuc, S. *Tetrahedron: Asymmetry* **2001**, *12*, 1713. (b) Paizs, C.; Tosa, M.; Majdik, C.; Bódai, V.; Novák, L.; Irimie, F.-D.; Poppe, L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2400.