

# Efficient Conversion of O-Substituted 3-Hydroxy-4-imino-oxazolidin-2-ones into O-Substituted $\alpha$ -Hydroxyamidoximes

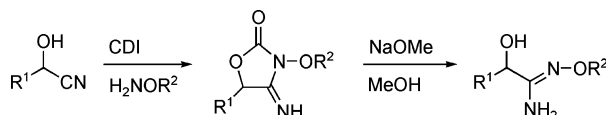
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## ABSTRACT



An efficient and convenient two-step synthesis of O-substituted  $\alpha$ -hydroxyamidoximes has been developed. The first step involves a high-yielding one-pot synthesis of the so far unknown O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones by reacting cyanohydrins stepwise with 1,1'-carbonyldiimidazole and O-substituted hydroxylamines. The second step represents a novel, sodium methoxide-mediated conversion of O-substituted 3-hydroxy-4-imino-oxazolidin-2-ones into the corresponding O-substituted  $\alpha$ -hydroxyamidoximes.

$\alpha$ -Hydroxyamidoximes are  $\alpha$ -functionalized derivatives of amidoximes, a class of compounds that has found applications in organic, analytical, and medicinal chemistry.

As a metal ion chelating functional group, the amidoxime moiety represents a promising pharmacophore for the development of metalloenzyme inhibitors.<sup>1</sup> In analytical chemistry, amidoximes are used as selective extracting reagents for the quantitative spectrophotometric determination of toxic metal cations such as cadmium (II), vanadium (V), and osmium (VIII).<sup>2</sup> Amidoximes are versatile building blocks for the synthesis of various heterocycles.<sup>1a,3</sup> Furthermore, the ability of O-substituted amidoximes to act as prodrugs of amidines has recently attracted considerable attention in medicinal chemistry.<sup>4</sup>

O-Alkyl(aralkyl)-substituted amidoximes are commonly prepared by alkylation of hydroxyamidines with alkyl(aralkyl) halides and alkyl sulfates in the presence of a suitable base.<sup>1a</sup> O-Aryl- and O-*t*-Bu-substituted amidoximes

have not been reported so far. Although the chemistry of amidoximes has been studied intensively, relatively few O-unsubstituted  $\alpha$ -hydroxyamidoximes (**I**) are described in the literature. Compounds **I** are only accessible by treatment of cyanohydrins and  $\alpha$ -hydroxyimides with hydroxylamine.<sup>5</sup> However, due to the weaker nucleophilicity of O-substituted hydroxylamines, these methods cannot be applied for the synthesis of O-substituted  $\alpha$ -hydroxyamidoximes (**II**).

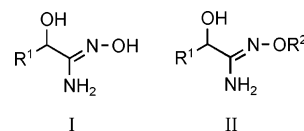


Figure 1.  $\alpha$ -Hydroxyamidoximes.

Only two O-substituted  $\alpha$ -hydroxyamidoximes (**II**), which have been prepared by treatment of  $\alpha$ -hydroxyamidoximes

(1) (a) Eloy, F.; Lenaers, R. *Chem. Rev.* **1962**, 62, 155. (b) Briggs, L. K.; Cambie, R. C.; Dean, C.; Rutledge, P. S. *Aust. J. Chem.* **1976**, 29, 327.

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(3) (a) Zinner, G. Perner, M., Grünefeld, J., Schecker, H.-G. *Arch. Pharm.* **1986**, 319, 1073. (b) Hussein, A. C. *Heterocycles* **1987**, 26, 163.

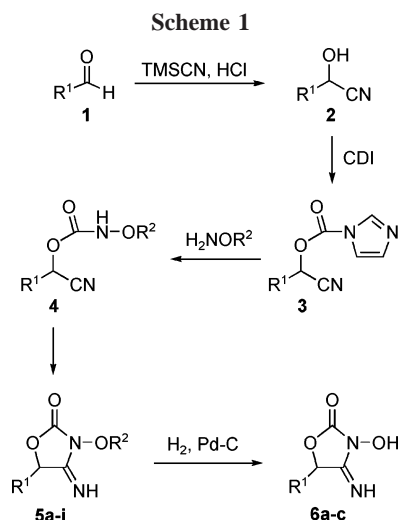
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with trityl chloride in 40 and 60% yields, respectively, are reported in the literature.<sup>6</sup> In a previous publication we described the synthesis and decarbonylation of *O*-substituted 3-hydroxyoxazolidin-2,4-diones as a novel synthetic pathway for the preparation of *O*-protected  $\alpha$ -hydroxy-hydroxamates.<sup>7</sup>

The lack of an efficient and general method for the preparation of *O*-substituted  $\alpha$ -hydroxyamidoximes prompted us to investigate the synthesis and applicability of *O*-substituted 3-hydroxy-4-imino-oxazolidin-2-ones as precursors for the synthesis of the title compounds. So far, *O*-substituted 3-hydroxy-4-imino-oxazolidin-2-ones (**5**) have only been reported as intermediates but not isolated and characterized.<sup>7</sup>

Compounds **5a–i** have now been synthesized in a convenient one-pot reaction by treatment of 1,1'-carbonyldiimidazole (CDI) with cyanohydrins (**2**),<sup>7,8</sup> followed by addition of *O*-substituted hydroxylamines to the CDI-activated cyanohydrins (**3**) at room temperature in 86–91% yield (Scheme 1, Table 1). During the reaction, the formation



of intermediates **3** and **4** was monitored by IR spectroscopy. The disappearance of the (CN) band in the IR spectra at 2231  $\text{cm}^{-1}$  and the formation of two sharp absorption bands at 1695–1705 and 1795–1805  $\text{cm}^{-1}$  clearly indicated the ring closure of **4** to **5**.

Finally, catalytic hydrogenation of **5a–c** afforded 3-hydroxy-4-imino-oxazolidin-2-ones (**6a–c**) in 92–95% yield.

Conversion of compounds **5a–i** into *O*-alkyl-, *O*-aralkyl-, and *O*-phenyl-substituted  $\alpha$ -hydroxyamidoximes (**7a–i**) was accomplished in high yields of 90–95% by refluxing **5a–i** in the presence of sodium methoxide (0.2 equiv) in methanol for 1 h. When **6a** was reacted with sodium methoxide (0.2 equiv), no decarbonylation occurred due to neutralization of sodium methoxide by **6a**. However, treatment of **6a** with an excess of sodium methoxide in methanol afforded **8a** in 70%

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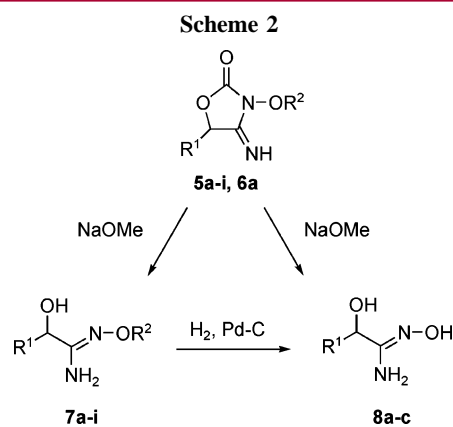
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**Table 1.** Synthesis of *O*-Substituted and *O*-Unsubstituted 3-Hydroxy-4-imino-oxazolidin-2-ones (**5** and **6**)

entry	R <sup>1</sup>	R <sup>2</sup>	yield
<b>5a</b>	PhCH <sub>2</sub>	PhCH <sub>2</sub>	90%
<b>5b</b>	Ph <sub>2</sub> CH	PhCH <sub>2</sub>	86%
<b>5c</b>	<i>t</i> -Bu	PhCH <sub>2</sub>	91%
<b>5d</b>	C <sub>3</sub> H <sub>5</sub>	PhCH <sub>2</sub>	90%
<b>5e</b>	<i>t</i> -Bu	<i>t</i> -Bu	90%
<b>5f</b>	Ph <sub>2</sub> CH	<i>t</i> -Bu	90%
<b>5g</b>	Ph <sub>2</sub> CH	3,4-di-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>	86%
<b>5h</b>	Ph <sub>2</sub> CH	CH <sub>3</sub>	87%
<b>5i</b>	Ph <sub>2</sub> CH	Ph	86%
<b>6a</b>	PhCH <sub>2</sub>	H	92%
<b>6b</b>	Ph <sub>2</sub> CH	H	91%
<b>6c</b>	<i>t</i> -Bu	H	95%

(Scheme 2). Catalytic hydrogenation of **7a–c** led to *O*-unsubstituted  $\alpha$ -hydroxyamidoximes **8a–c** in 93–97% yield (Scheme 2, Table 2).



In conclusion, we have developed an operationally simple one-pot protocol for the preparation of previously unpub-

**Table 2.** Synthesis of *O*-Substituted and *O*-Unsubstituted  $\alpha$ -Hydroxyamidoximes (**7** and **8**)

entry	R <sup>1</sup>	R <sup>2</sup>	yield
<b>7a</b>	PhCH <sub>2</sub>	PhCH <sub>2</sub>	95%
<b>7b</b>	Ph <sub>2</sub> CH	PhCH <sub>2</sub>	92%
<b>7c</b>	<i>t</i> -Bu	PhCH <sub>2</sub>	91%
<b>7d</b>	C <sub>3</sub> H <sub>5</sub>	PhCH <sub>2</sub>	92%
<b>7e</b>	<i>t</i> -Bu	<i>t</i> -Bu	90%
<b>7f</b>	Ph <sub>2</sub> CH	<i>t</i> -Bu	91%
<b>7g</b>	Ph <sub>2</sub> CH	3,4-di-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>	90%
<b>7h</b>	Ph <sub>2</sub> CH	CH <sub>3</sub>	95%
<b>7i</b>	Ph <sub>2</sub> CH	Ph	90%
<b>8a</b>	PhCH <sub>2</sub>	H	95%
<b>8b</b>	Ph <sub>2</sub> CH	H	93%
<b>8c</b>	<i>t</i> -Bu	H	97%

lished *O*-substituted 3-hydroxy-4-imino-oxazolidin-2-ones. Their treatment with sodium methoxide (0.2 equiv) in methanol furnished *O*-alkyl-, *O*-aralkyl-, and *O*-phenyl-substituted  $\alpha$ -hydroxyamidoximes in high yields. Furthermore, deprotection of *O*-benzyl-substituted  $\alpha$ -hydroxyamidoximes as well as decarbonylation of 3-hydroxy-4-imino-oxazolidin-2-one **6a** led to  $\alpha$ -hydroxyamidoximes **8**.

**Acknowledgment.** We thank Prof. Dr. D. Geffken for his valuable help in the preparation of this manuscript.

**Supporting Information Available:** Experimental procedures, spectroscopic data, elemental analysis, and melting points for compounds **5–8**. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL040045V