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Efficient Conversion of O-Substituted 3-Hydroxy-4-imino-oxazolidin-2-ones into O-Substituted α-Hydroxyamidoximes

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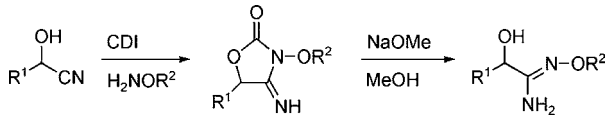
ABSTRACT



An efficient and convenient two-step synthesis of O-substituted α-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 α-hydroxyamidoximes.

α-Hydroxyamidoximes are α-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.[1] 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).[2] Amidoximes are versatile building blocks for the synthesis of various heterocycles.[1a,3] Furthermore, the ability of O-substituted amidoximes to act as prodrugs of amidines has recently attracted considerable attention in medicinal chemistry.[4]

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.[1a] *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 α-hydroxyamidoximes (**I**) are described in the literature. Compounds **I** are only accessible by treatment of cyanohydrins and α-hydroxyimidates with hydroxylamine.[5] However, due to the weaker nucleophilicity of O-substituted hydroxylamines, these methods cannot be applied for the synthesis of O-substituted α-hydroxyamidoximes (**II**).

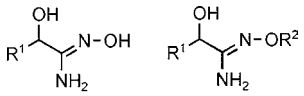


Figure 1. α-Hydroxyamidoximes.

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

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(4) (a) Anbazhagan M., Boykin D. W, Stephens, C. E. *Tetrahedron Lett.* **2002**, *43*, 9089. (b) Clement, B. *Drug Metab. Rev.* **2002**, *34*, 565.
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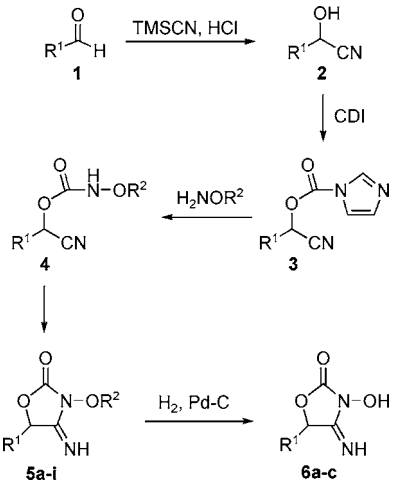
with trityl chloride in 40 and 60% yields, respectively, are reported in the literature.[6] In a previous publication we described the synthesis and decarbonylation of O-substituted 3-hydroxyoxazolidin-2,4-diones as a novel synthetic pathway for the preparation of O-protected α-hydroxy-hydroxamates.[7]

The lack of an efficient and general method for the preparation of O-substituted α-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.[7]

Compounds **5a**−**i** have now been synthesized in a convenient one-pot reaction by treatment of 1,1′-carbonyldiimidazole (CDI) with cyanohydrins (**2**),[7,8] 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

Scheme 1



of intermediates **3** and **4** was monitored by IR spectroscopy. The disappearance of the (CN) band in the IR spectra at 2231 cm^{-1} and the formation of two sharp absorption bands at 1695−1705 and 1795−1805 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 α-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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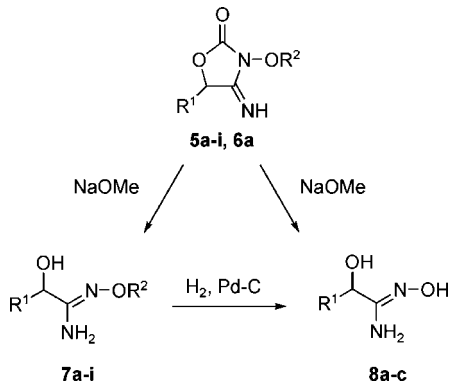
Table 1. Synthesis of O-Substituted and O-Unsubstituted 3-Hydroxy-4-imino-oxazolidin-2-ones (**5** and **6**)

entry	R^1	R^2	yield
5a	$PhCH_2$	$PhCH_2$	90%
5b	Ph_2CH	$PhCH_2$	86%
5c	*t*-Bu	$PhCH_2$	91%
5d	C_3H_5	$PhCH_2$	90%
5e	*t*-Bu	*t*-Bu	90%
5f	Ph_2CH	*t*-Bu	90%
5g	Ph_2CH	3,4-di-$(CH_3O)C_6H_3CH_2$	86%
5h	Ph_2CH	CH_3	87%
5i	Ph_2CH	Ph	86%
6a	$PhCH_2$	H	92%
6b	Ph_2CH	H	91%
6c	*t*-Bu	H	95%

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

Scheme 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 α-Hydroxyamidoximes (**7** and **8**)

entry	R^1	R^2	yield
7a	$PhCH_2$	$PhCH_2$	95%
7b	Ph_2CH	$PhCH_2$	92%
7c	*t*-Bu	$PhCH_2$	91%
7d	C_3H_5	$PhCH_2$	92%
7e	*t*-Bu	*t*-Bu	90%
7f	Ph_2CH	*t*-Bu	91%
7g	Ph_2CH	3,4-di-$(CH_3O)C_6H_3CH_2$	90%
7h	Ph_2CH	CH_3	95%
7i	Ph_2CH	Ph	90%
8a	$PhCH_2$	H	95%
8b	Ph_2CH	H	93%
8c	*t*-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 α-hydroxyamidoximes in high yields. Furthermore, deprotection of *O*-benzyl-substituted α-hydroxyamidoximes as well as decarbonylation of 3-hydroxy-4-imino-oxazolidin-2-one **6a** led to α-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.

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