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A facile synthesis of 2-oxazolines using a PPh_3–DDQ system

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ABSTRACT

A facile and efficient synthesis of 2-oxazolines from *N*-(2-hydroxyethyl)amides using a triphenylphosphine–2,3-dichloro-5,6-dicyanobenzoquinone (PPh_3–DQQ) system is described. The reaction proceeds under neutral and mild conditions, and excellent yields are obtained.

Embedded in natural products of a wide range of biological activities[1] and also employed as synthetic intermediates,[2] 2-oxazolines are important functional compounds in organic chemistry. They can act as masked amino alcohols and carboxylic acids in organic reactions, and are easily unmasked to the acid or 2-amino alcohols upon hydrolysis.[3,4] The hydrolyzable property also makes 2-oxazolines desirable precursors of carboxylic acids in pharmacology. Furthermore, chiral oxazolines have found extensive applications as auxiliaries and ligands in asymmetric synthesis in recent years.[5]

Due to the importance of 2-oxazolines, considerable efforts have been devoted to their synthesis. One synthetic method involves the reaction between amino alcohols and carboxylic acid derivatives like esters[6–9] and nitriles.[10] Another conceptually simple and synthetically versatile method is the dehydrative cyclization of *N*-(2-hydroxyethyl)amides. In the latter process, it is necessary to first convert the hydroxyl group into a good leaving group, such as a chloride (using $SOCl_2$[11] or PPh_3/CCl_4,[12]) or a sulfonate (using $TsCl/Et_3N$). Subsequently, an intramolecular S_N2 reaction under basic conditions[13] or in the presence of Lewis acids provides the 2-oxazolines.[14]

Even though many syntheses of 2-oxazolines have been reported, the exploration of new methods has been very active in recent years. Linclau reported that *N*,*N*′-diisopropyl carbodiimide (DIC) was an efficient dehydrating reagent in the transformation of *N*-(2-hydroxyethyl)amides into 2-oxazolines via an isourea.[15] Alternative dehydrative reagents reported for this transformation are DAST,[16] Deoxo-Fluor reagent,[17] or 2-chloro-4,6-dimethoxy-1,3,5-triazine,[6] and PPh_3/DEAD.[18] The synthesis of 2-oxazolines starting from aldehydes or even benzyl alcohols in the presence of an oxidizing reagent has also been reported.[19]

On the other hand, the combination of PPh_3 and DDQ instead of PPh_3 and DEAD as an efficient dehydration system has been investigated by Iranpoor's group.[20–22] The advantages of using DDQ include its high reactivity and thermal stability, and good selectivity toward desired products. The combination of PPh_3–DDQ has been successfully applied in the conversion of 2-hydroxy-benzaldehyde oximes to 1,2-benzisoxazoles in high yield (90–95%) after a dehydration process,[20] the transformation of alcohols to cyanides,[21] alkyl halides, or alkyl azides, and the conversion of diethyl α-hydroxyphosphonates to diethyl α-halo (or α-azido) phosphonates.[22]

We have been interested in studying the reactivities of isoureas formed from alcohols and diimides and have reported that they provide an efficient functional group interconversion of alcohols into halides.[23] The similarity of diimide and DDQ–PPh_3 as dehydrating reagents, and the success of converting *O*-2-hydroxyalkyl isourea into 2-oxazolines[15] led us to explore the reaction using DDQ–PPh_3. In this Letter, we report that DDQ–PPh_3 can efficiently convert *N*-(2-hydroxyethyl)amides into 2-oxazolines.

When *N*-(2-hydroxyethyl)benzamide (**1a**) was treated with PPh_3–DDQ in dichloromethane, a change in the color of the reaction was observed, while new spots were also found using TLC.[24] One spot has the same R_f as that of 2-phenyloxazoline, which was prepared separately according to a well-established method.[13,19] Complete characterizations by spectral methods confirmed the product as 2-phenyloxazoline (Eq. 1):

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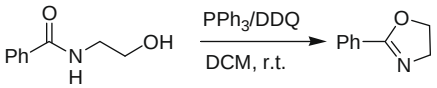
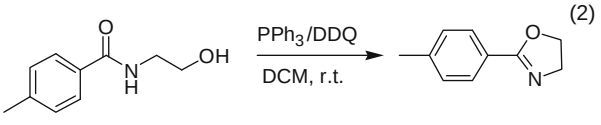


(1)

1a **2a**

Optimization of the conditions for the reaction of *N*-(2-hydroxyethyl)-4-methylbenzamide (**1b**) at room temperature with different solvents as shown in Table 1 resulted in product **2b** in nearly quantitative yield in 20 min when the reactions were performed in dichloromethane, 1,2-dichloroethane, toluene, THF, or 1,4-dioxane (entries 4–7). The reaction of **1a** also afforded a 96% yield of **2a** in 20 min. Compared to the fact that 24–48 h under refluxing THF conditions was needed to afford reasonable yields of 2-oxazolines via Linclau's isourea protocol, the present dehydrative cyclization is much more efficient.

Table 1
Cyclization of **1b** with PPh_3–DDQ in different solvents[a]



(2)

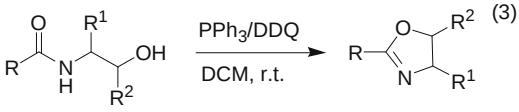
1b **2b**

Entry	Solvent	Time	Yield (%)
1	Acetonitrile	24 h	0
2	Ethyl acetate	24 h	35
3	Dichloromethane	20 min	99
4	1,2-Dichloroethane	6 h	98
5	Toluene	20 min	96
6	1,4-Dioxane	20 min	99
7	THF	20 min	96

Reaction conditions: **1b** 1 mmol, 1.5 equiv PPh_3, 1.5 equiv DDQ.

The success of the cyclizations of *N*-2-hydroxylethylbenzamide and *N*-2-hydroxylethyl-4-methylbenzamide encouraged us to explore more substrates (Fig. 1), and the results are summarized in Table 2. With aroylated amino alcohols (R = Ar), >80% yields of 2-oxazolines were obtained in 20 min (entries 2–5). The use of

Table 2
Cyclization of *N*-2-hydroxyethylamides with PPh_3–DDQ[a]



(3)

1a - 1o **2a - 2o**

Entry	Substrate	Reaction time	Yield (%)
1	**1a**	20 min	96
2	**1b**	20 min	99
3	**1c**	20 min	97
4	**1d**	60 min	92
5	**1e**	60 min	82
6	**1f**	20 min	98
7	**1g**	24 h	97
8	**1h**	60 min	93
9	**1i**	60 min	97
10	**1j**	20 min	90
11	**1k**	24 h	70
12	**1l**	24 h	93
13	**1m**	24 h	91
14	**1n**	24 h	73[b]
15	**1o**	12 h	80

[a] Reaction conditions were the same as those in Table 1 except that dichloromethane was employed as the solvent.
[b] Contains 3.2% of trans isomer in the products.

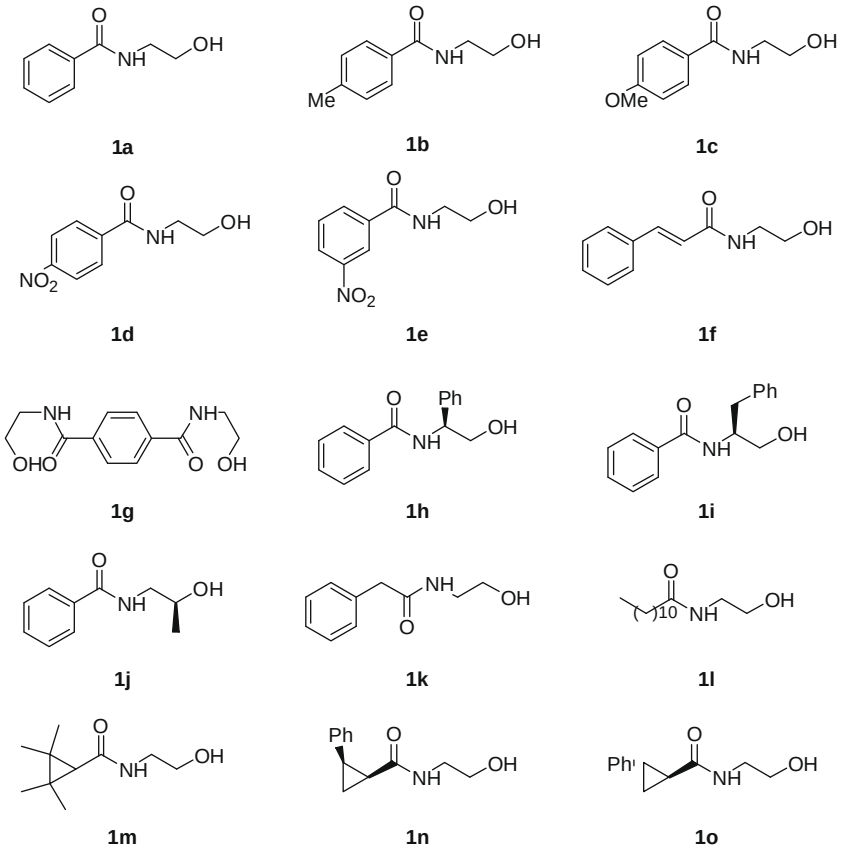


Figure 1. Structures of substrates **1a**–**o**.

N-(2-hydroxyethyl)*trans*-cinnamamide also resulted in a high yield of the oxazoline (entry 6). The reaction of bis-*N*,*N*-(2-hydroxyethyl)amide with PPh_3–DDQ also occurred, even though it proceeded slowly, requiring 24 h for a complete conversion (entry 7), whereupon a bisoxazoline was obtained.

Amides derived from chiral amino alcohols may form enantiopure oxazolines if no racemization occurs in the conversion. Thus, (*S*)-*N*-(2-hydroxy-1-phenyl-ethyl)-benzamide and (*S*)-*N*-(1-benzyl-2-hydroxyethyl)benzamide of >98% ee were used as the starting materials. Under the same reaction conditions, enantiopure oxazolines of >98% ee were obtained[25] (entries 8 and 9). The use of substrate **1j**, which bears an α-chiral center, also yielded optically active product in high yield in a short time. However, the reaction was slow when the substrate was a secondary alcohol. For example, the amide derived from (1*S*,2*R*)-2-amino-1,2-diphenylethanol did not react completely even after 24 h at room temperature.

According to the literature, 2-alkyloxazolines are more difficult to synthesize than their aryl analogues.[26] Therefore, the cyclizations of *N*-(2-hydroxyethyl)alkylamides were also explored. In these cases, longer reaction times of about 24 h are necessary to produce the oxazolines in high yields (entries 11 and 12). The presence of a cyclopropyl ring is tolerated in the process (entries 13–15). When *trans*-, *cis*-cyclopropyl carboxylic amides were used, the expected corresponding products were obtained. The stereochemistry of the cyclopropyl ring was largely unchanged in the cyclization of the trans isomer (entry 15), while a slight isomerization of the *cis* amide to the *trans* oxazoline was observed (entry 14).

In summary, the cyclization of *N*-2-hydroxylamides with PPh_3–DDQ is an efficient method to synthesize 2-oxazolines. It is applicable to aliphatic and aromatic carboxylic acid derivatives, and the synthesis procedure is simple and high yielding.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.127.

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24. *Typical procedure for the conversion of N-2-hydroxyethylamide into 2-oxazoline*: PPh_3 (0.393 g, 1.5 mmol), DDQ (0.341 g, 1.5 mmol), and 5 mL of DCM were added to a dried Schlenk tube under an argon atmosphere, and the mixture was stirred at room temperature for 3 min. *N*-(2-Hydroxyethyl)benzamide (**1a**, 0.165 g, 1 mmol) was then added. The color of the mixture changed to yellow and a precipitate was formed. After 20 min, TLC showed the absence of the substrate, and the presence of a spot corresponding to a new compound. The mixture was then washed with aqueous NaOH solution (5%, 40 mL), and the separated water layer was back-extracted with DCM (15 mL × 4). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Filtration and evaporation of the solvent followed by column chromatographic separation (silica gel) using petroleum ether/ethyl acetate (4:1, v/v) gave the corresponding 2-phenyloxazoline (**1a,** 0.156 g, 96%). oil, ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ 7.95 (d, J = 7.2 Hz, 2H), 7.48–7.40 (m, 3H), 4.44 (t, J = 9.6 Hz, 2H), 4.07 (t, J = 9.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 164.5, 131.2, 128.2, 128.0, 127.6, 67.5, 54.8 ppm. MS: m/z = 147. 148 (7) $[M+1]^+$, 147 (67) $[M]^+$, 117 (100). IR (Nujol): 2931, 1651, 1529, 1493, 1456, 1346, 1269, 1201, 1038, 967, 899, 712, 607 cm^{-1}.
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