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DMAP-catalyzed synthesis of 2-oxazolidinones from corresponding halohydrins using KOCN/DMF

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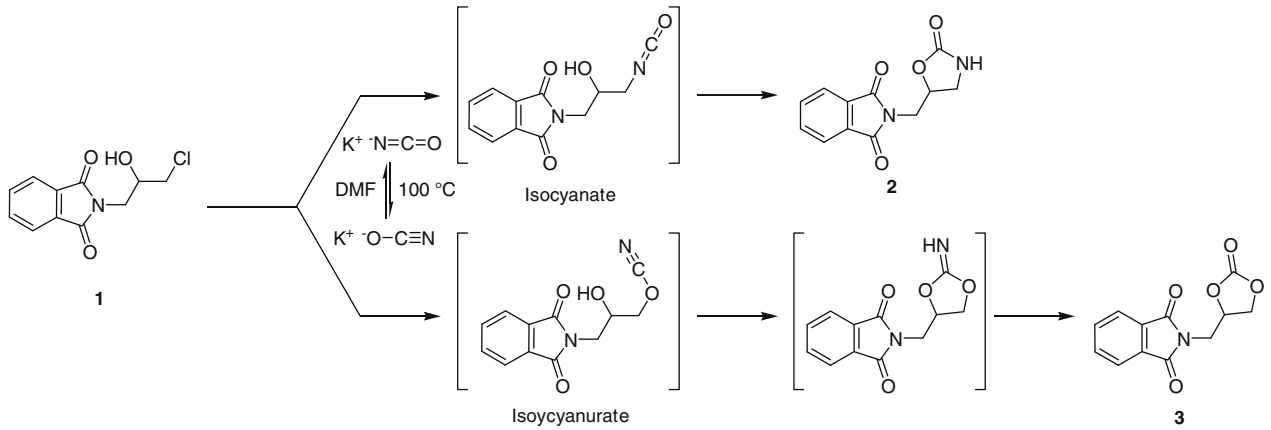
ABSTRACT

We report facile and simple synthesis of a variety of 2-oxazolidinones from the corresponding halohydrins by reaction with KOCN in DMF catalyzed by DMAP. DMAP and temperature play key roles in enriching the yield of 2-oxazolidinones. A few examples in this Letter are applicable to pharmaceutically important processes.

2-Oxazolidinones are a very important class of heterocyclic compounds and their derivatives have attracted attention in various areas of drug development for antibacterial activity, fine chemicals, pesticides, herbicides[1] and many other applications.[2] The chiral 2-oxazolidinones have been used as chiral auxiliaries in a wide range of asymmetric reactions.[3–11]

A few of the molecules containing 2-oxazolidinone moiety such as Linezolid[12b,12d–f] (Zyvox), DUP-105[12] and DUP-721[12] have attracted much interest as monodrug- or multidrug-resistant antibacterial agents.[12g] New molecules in this class, Radezolid, Torezolid and RWK-416457 are already in various stages of clinical trials. In addition to their importance in antibacterial molecules, chiral 2-oxazolidinones have been widely utilized as excellent chiral auxiliaries in Evans asymmetric chemistry, allowing for high levels of diastereo selection in a variety of chirality transfer reactions[13] and are highly successful in the asymmetric synthesis of natural products.[13]



Scheme 1.

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A wide choice of synthetic methods are available in the literature to prepare 2-oxazolidinones such as base-meditated cyclization of *N*-boc-β-amino alcohols,[14a–c] reduction followed by carbonyl insertion of β-azido alcohols,[14a,15e] carbonyl insertion in β-amino alcohols using either phosgene derivatives,[14d–g] carbon dioxide pressure[15a–c] or 1,1′-carbonyldiimidazole.[15d] A few of the reports describe the preparation of 2-oxazolidinones by treating epoxides with metal cyanates or carbonates.[16] However, most of these methods suffer from either lower yields or use of hazardous reagents.

We required a general and efficient method for the synthesis of analogues containing 2-oxazolidinone moiety without using pyrophoric (*n*-BuLi, NaH) or non-eco friendly reagents as part of our research work on2-oxazolidinones.[14a] In this pursuit, Elenkov et al. have used potassium cyanate (KOCN) as a versatile reagent for the preparation of 2-oxazolidinones from epoxides catalyzed by an enzyme, halohydrin dehaloginase.[17] KOCN has been well utilized to prepare alkylisocyanates and their derivatives from alkyl halides.[18] Nevertheless, the possible formation of cyanurates and lower yields are major drawbacks of this strategy.

Halohydrins are found to be one of the better starting materials to prepare 2-oxazolidinones. Piper et al, have reported the preparation of 5-pthalimidomethyloxazolidin-2-one **2** using **1** on reaction with potassium cyanate (KOCN) in *N*,*N*-dimethylformamide (DMF) in 27% yield.[19] We intend to improve the yield of this reaction by studying various parameters such as temperature, solvent, molar equivalents of KOCN and role of phase transfer catalysts (PTCs).

While preparing the compound **2** by a reported method[19] we observed the formation of various impurities along with the product by TLC. Among those impurities, one was noticed as a major component and was isolated, characterized and identified as 2-dioxolanone **3**. The formation of dioxolanone **3** along with the compound **2** can be explained through the reactivity of two isomeric forms of cyanate anion (OCN^-).

One of them has nitrogen as the nucleophile, where as the other has oxygen nucleophile (Scheme 1). Substrate **1** reacts with the nitrogen nucleophile of OCN^- to form corresponding 2-oxazolidinone **2** via a β-hydroxy isocyanate intermediate. The formation of impurity **3** can be explained by the reactivity of halohydrin **1** with the oxygen nucleophile of cyanate (Scheme 1). A lower yield of the compound **2** was observed because of the formation of competitive dioxolanone impurity **3** in the reaction.

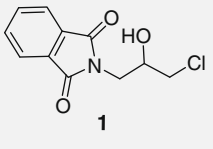
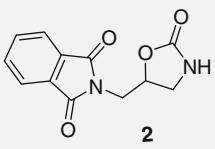
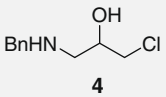
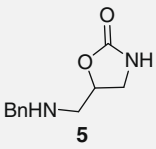
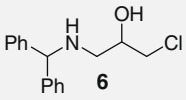
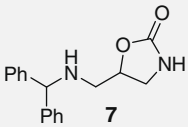
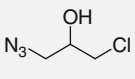
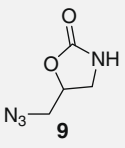
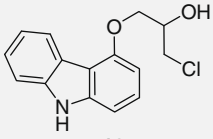
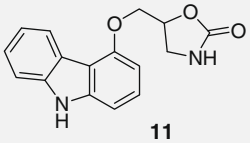
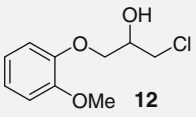
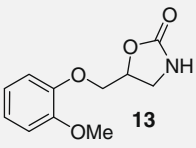
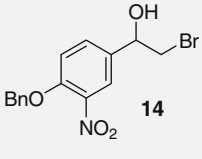
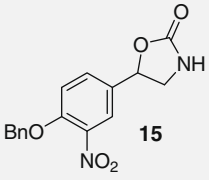
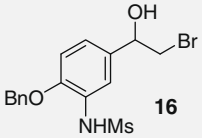
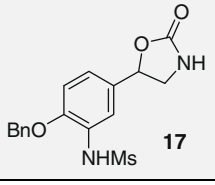
To improve the efficiency of this reaction, obstacles such as longer reaction time (>48 h), formation of various impurities and poor yields needed to be addressed. Since, this reaction is interfacing between organic and inorganic materials, we thought PTC would be beneficial. Various PTCs and catalysts such as TBAC, TBAB, TBAI, 18-crown-6, 4-(*N*,*N*-dimethylamino)pyridine (DMAP) were attempted in the reaction in various molar equivalents (from 0.1 to 1.0 equiv). However the uses of TBAC, TBAB and TBAI have not shown any impact on the reaction with respect to the rate of reaction and yield. Whereas in the case of 18-crown-6, the rate of reaction did increase but not the yield. Whenever DMAP is used in the reaction with halohydrin **1**, the rate of reaction was enhanced. The reaction was completed within 24 h at 80 °C and a relatively lower level of impurity **3** was observed.

Since this reaction requires polar aprotic solvent such as DMF, a few attempts were made in DMSO without any success. The impact of reaction temperature on conversion and impurity formation was also studied. A series of reactions were carried out at different temperatures (from 60 °C to 140 °C) and the amount of 2-oxazolidinone **2** and 2-dioxolanone **3** formation was compared in each case. The reaction did not progress at temperatures lower than 80 °C and ~30% of compound **3** was observed at 100 °C. A minimal amount of dioxolanone impurity **3** was observed at 120 °C which was found to be optimum for the reaction.

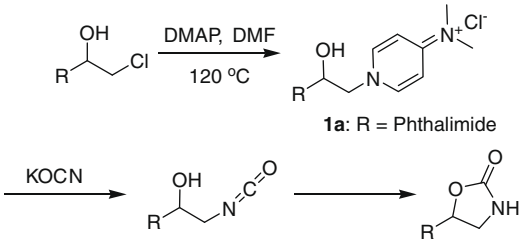
Usually, the title reaction without DMAP takes more than 24 h to complete even at 120 °C, but the same reaction was completed within 5 h in presence of DMAP. The presence of DMAP and higher temperature (120 °C), improves the yield from 27% to 65%. Finally the optimized reaction condition for the conversion of chlorohydrin to 2-oxazoldinone was found to be KOCN (2.0 equiv), DMAP (0.1 equiv) in DMF at 120 °C (Table 1, entry 1).[20b]

The versatility of these conditions was demonstrated by choosing various kinds of halohydrins.[20a] A few of these experiments were conducted with/without DMAP to study its influence on concerned reaction and achieved both minimized reaction time and improved yield whenever DMAP is used. All the results have been tabulated in Table 1.

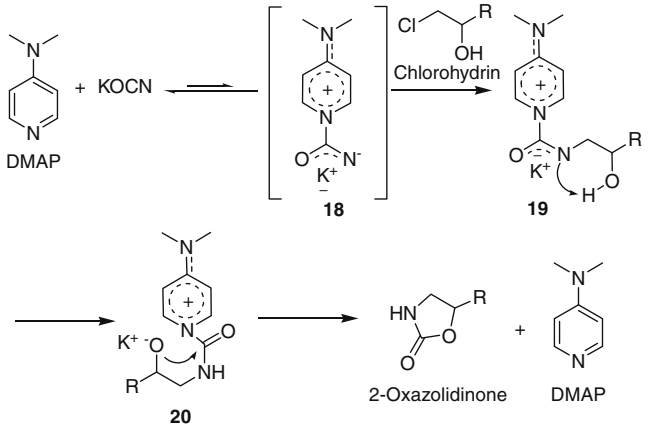
Table 1
Examples of DMAP-catalyzed synthesis of 2-oxazolidinones from corresponding halohydrins using KOCN/DMF

Entry no.	Halohydrin	2-Oxazolidinone	Yield (%)
1	 **1**	 **2**	27.0[a] 65.0[b]
2	 **4**	 **5**	64.0[b]
3	 **6**	 **7**	66.0[b]
4	 **8**	 **9**	70.0[b]
5	 **10**	 **11**	37.0[a] 55.0[b]
6	 **12**	 **13**	65.0[b]
7	 **14**	 **15**	65.0 [b]
8	 **16**	 **17**	61.0[b]

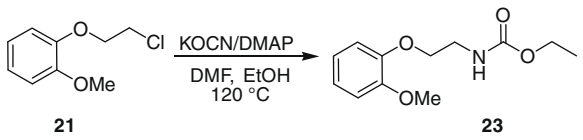
[a] Yield without DMAP.
[b] Yield with DMAP (0.1 equiv).



Scheme 2. Schematic presentation of anticipated mechanism for the formation of 2-oxazolidinones.



Scheme 3. Schematic presentation of reaction mechanism for the formation of 2-oxazolidinones.



Scheme 4.

From the above results it is very clear that DMAP plays a vital role in reducing the reaction time and improving the yield of 2-oxazolidinone from corresponding halohydrin on the reaction with KOCN. It was interesting to identify the DMAP role in this reaction. DMAP usually enhances reactivity of acyl halides or benzyl halides, but unusual with alkyl halides. The initial hypothesis was, probably DMAP reacts with halohydrin and makes facile leaving group β-hydroxy(4-*N*,*N*-dimethylamino)pyridonium moiety which further reacts with KOCN to form required 2-oxazolidinone.

To prove this, halohydrin **1** was reacted with DMAP in similar conditions without KOCN and compound **1a** was identified by ^{1}H NMR. However, further reaction of compound **1a** with KOCN under optimized conditions has not produced the requisite results. It has been considered that the reaction is not proceeding as per the described mechanism. (Scheme 2)

In order to identify DMAP's role, investigations were extended to study its effect on reactivity of KOCN. Generally, organic isocyanates on reaction with DMAP produce the more reactive *N*-carbaonylpyridinium ion which reacts readily with carboxylates, phenolates and alkoxides to yield amides or urethanes.[21] In a similar way, it is assumed that DMAP and potassium isocyanate are in equilibrium with **18**, which reacts with halohydrin followed by protonation (from hydrodxyl) producing more reactive *N*-carbonylpyrodinium ion **20**. Compound **20** evolves by in situ cyclization producing the required 2-oxazolidinones. (Scheme 3)

To prove this mechanism, we need to establish the impact of DMAP on KOCN and its further reactivity with halohydrin, wherever hydroxyl group of halohydrin acts as nucleophilic agent. Instead of halohydrin, alkyl halide **21** is chosen for this exercise. Compound **21** is treated with KOCN, DMF with/without DMAP in two independent experiments. Both the cases had shown similar reactivity on the formation of isocyanate. Whereas upon reaction of compound **21** with KOCN, DMF, alcohol (methanol/ethanol) with/without DMAP in two independent experiments, nature of the reactions were extremely different in both the cases and the formation of anticipated compound **23** was observed in 78% yield in the case of KOCN, DMF, EtOH with DMAP and ~30% yield without DMAP. (Scheme 4).[20c] The structure of compound **23** was confirmed by its preparation from the corresponding amine with ethyl chloroformate in DCM. In the present experiment an external alcohol interacts with an intermediate similar to **19** and forms the carbamate **23**.

This is a simpler method to prepare protected amines from corresponding alkyl halides. Evaluation of this concept is under progress in our research group.

A few illustrations of how this methodology can be extendable to important pharmaceutical ingredients such as side chain of Linezolid (Table 1, entries 1–4), Carvedilol, (Table 1, entry 5) and Farmeterol (Table 1, entries 7 and 8) have been shown. Previously, (*R*)-5-azidomethyl-2-oxazolidinone **8** (Table 1, entry 4) was utilized by us in the synthesis of Linezolid.[14a]

In conclusion, DMAP plays a vital role in improving the reaction kinetics and yield of the oxazolidin-2-one. Along with DMAP, temperature also plays a key role to avoid dioxolan-2-one impurity. Thus a versatile DMAP catalyzed simple, convenient, generalized, single-step method was developed to prepare a 2-oxazolidinone from the corresponding halohydrin intermediate.

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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.2009.12.115.

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20. (a) The halohydrins (**1**, **4**, **6**, **8**, **10**, **12**) were prepared by treating epichlorohydrin with corresponding amine in isopropanol, without usage of any base. The halohydrins (**14** and **16**) were prepared by α-bromination of corresponding acetophenone with NBS followed by reduction of ketogroup yielded appropriate halohydrin.; (b) *N*,*N*-Dimethylformamide (3 vol) was added to a mixture of halohydrine (1.0 mmol), potassium cyanate (2.0 mmol) and DMAP (0.05 mmol). The reaction mixture was heated to 120 °C for 8–14 h and filtered to remove excess potassium cyanate. The solvent was removed from the filtrate under vacuum at 65–70 °C to get residue. The resulting residue was partitioned between ethyl acetate and water. The reaction mixture was stirred for 10 min. and both the layers were separated. The aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over sodium sulfate, filtered and washed with ethyl acetate. The solvent was removed from the organic layer by distilling at 40–45 °C under vacuum to obtain 2-oxazolidinone.; (c) *N*,*N*-Dimethylformamide (3 vol) was added to a mixture of halohydrin (1.0 mmol), potassium cyanate (2.0 mmol), ethanol or methanol (1.5 mmol), and DMAP (0.05 mmol). The reaction mixture was heated to 120 °C for 8–14 h and filtered to remove excess potassium cyanate. The solvent was removed from the filtrate under vacuum at 65–70 °C to get residue. The resulting residue was partitioned between ethyl acetate and water. The reaction mixture was stirred for 10 min. and both the layers were separated. The aqueous layer was extracted with ethyl acetate. Combined organic layers were dried over sodium sulfate, filtered and washed with ethyl acetate. The solvent was removed from the organic layer by distilling at 40–45 °C under vacuum to obtain corresponding carbamate.
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