An Approach to Synthesis of 3-Aryl-2-Oxazolidinones and *In Situ* 'Click' Assembly of 1,2,3-Triazole Oxazolidinones

Xingxian Zhang*, Cheng Li, Wei Chen and Xiang Wu

College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, Zhejiang 310032, P. R. China

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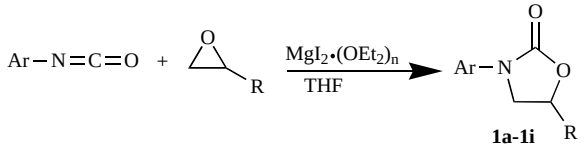
Abstract: A facile and efficient addition of isocyanates with epoxides in the presence of MgI_2 etherate was reported in good yields. The corresponding 2-oxazolidinone could be easily converted into 1,2,3-triazole-oxazolidinone by click reaction in excellent yield.

Keywords: Isocyanate, epoxide, oxazolidinone, MgI_2 etherate, click reaction.

INTRODUCTION

A number of 5-substituted oxazolidinones are shown to have high potency as biologically active molecules and are widely used in the pharmaceutical industry [1]. Consequently, much attention and extensive study have been focused on the synthesis of oxazolidinones. The addition of isocyanates with epoxides is one of the most useful and efficient method for preparation of 2-oxazolidinones. A variety of catalysts have been investigated, such as quaternary ammonium salts [2], LiBr/n-Bu_3PO or LiBr/HMPA [3], LiCl/DMF [4], Lewis bases [5], Lewis acids [6], *n*-Bu_3SnI-Ph_3PO [7], *n*-Bu_3SnI-Ph_4SbI [8] and lanthanide chlorides [9]. However, vigorous reaction temperatures, reactive polar solvents and a long reaction time are required, so they are accompanied by undesirable reactions such as the trimerization of isocyanates. In addition, many of these reagents are rather expensive and difficult to be handled especially on a large scale. From the viewpoints above, the development of less expensive, environmentally benign, and easily handled promoters for the addition of isocyanates with epoxides is still highly desirable. Due to its abundant, inexpensive and nontoxic character, Lewis acidic Mg(II) catalyst has been widely utilized in the various organic reactions [10]. In our previous paper [11], we have demonstrated that MgI_2 etherate could efficiently catalyze Mukaiyama-type aldol of aldehydes with trimethylsilyl enolates and allylation of aldehydes with allylstannane. Herein we will report an efficient and highly regioselective addition of aryl isocyanates with epoxides promoted by MgI_2 etherate under mild reaction condition (Scheme **1**).



Scheme 1. MgI_2•$(OEt_2)_n$-promoted addition of aryl isocyanates with epoxides.

*Address correspondence to this author at the College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, 310032, P. R. China; Fax: 86-(0)571-88320320; E-mail: zhangxx@zjut.edu.cn

RESULTS AND DISCUSSION

The initial reaction was carried out using phenyl isocyanate with epichlorohydrin promoted by 50 mol% of freshly prepared MgI_2 etherate in THF. After stirring at 65 °C for 2.0 h, the desired cycloadduct was afforded in 92% yield. Furthermore, addition of various aryl isocyanates with epoxides has been examined. The results are summarized in Table **1**. As shown in Table **1**, the reaction of various aryl isocyanates with epichlorohydrin proceeded smoothly and provided the desired products in good yields (Table **1**. entries 1-5). The addition of aryl isocyanates and propylene oxide also provided the desired products in high yield (Table **1**. entries 6 and 7). Moreover, the addition of 2-phenoxymethyl oxirane with phenyl isocyanate or 4-methylphenyl isocyanate underwent effectively in the presence of MgI_2 etherate (Table **1**. entries 8 and 9) to give the desired product in 91% and 94% yield, respectively. To examine the halide anion effect, halogen analogs of MgI_2 etherate, $MgBr_2$ etherate and $MgCl_2$ etherate were compared under parallel reaction conditions (50 mol % of catalyst) in the reaction of various aryl isocyanates with epichlorohydrin (Table **1**. entries 10-13). $MgCl_2$ etherate is almost inactive and $MgBr_2$ etherate provided the lower yield under the same condition. Apparently, the unique reactivity of MgI_2 etherate is attributed to the dissociative character of iodide counterion and a more Lewis acidic cationic $[MgI]^+$ species as a result of Lewis base activation of Lewis acid [12].

The further application of these readily prepared 2-oxazolidinones, the structural modification of 2-oxazolidinones was investigated. The oxazolidinones **1a** reacted with 1, 2, 4-triazole and benzotriazole with the treatment of KOH in DMF to give the product in 73% and 65% yield based on the recovery of substrate **1a**, respectively [13] (Scheme **2**).

Among the known isosteres for an amide group, 1,2,3-triazoles have recently gained increasing attention in drug discovery since the introduction of the concept of "click" chemistry by Sharpless [14, 15]. 1,2,3-triazoles serve as rigid linking units that can mimic the topological and electronic features of an amide bond. However, unlike amides, triazoles are extremely stable to hydrolysis and oxidative/reductive

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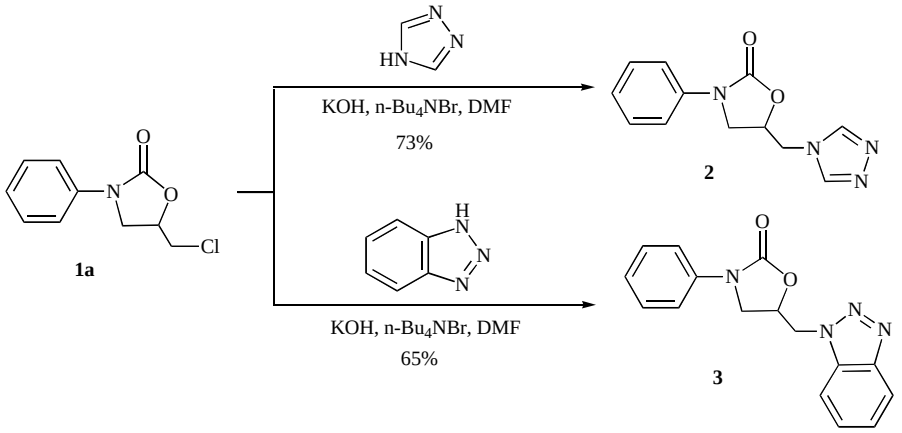
Table 1. The Addition of Isocyanates with Epoxides Promoted by MgX_2 Etherate

Entry	Ar	R	MgX_2[a]	Time (h)	Product[b]	Yield(%)[c]	Refs.
1	C_6H_5	CH_2Cl	MgI_2	2	**1a**	92	[7]
2	2,3-$Me_2C_6H_3$	CH_2Cl	MgI_2	4	**1b**	90	[13]
3	3,4,5-$F_3C_6H_2$	CH_2Cl	MgI_2	2	**1c**	83	[13]
4	4-ClC_6H_4	CH_2Cl	MgI_2	3	**1d**	79	[16]
5	4-BrC_6H_4	CH_2Cl	MgI_2	4	**1e**	78	[13]
6	4-ClC_6H_4	CH_3	MgI_2	1	**1f**	82	[16]
7	2-Me-5-ClC_6H_3	CH_3	MgI_2	2	**1g**	78	[13]
8	C_6H_5	CH_2OPh	MgI_2	4	**1h**	91	[7]
9	4-MeC_6H_4	CH_2OPh	MgI_2	1	**1i**	94	[13]
10	C_6H_5	CH_2Cl	$MgBr_2$	5	**1a**	78	[7]
11	2,3-$Me_2C_6H_3$	CH_2Cl	$MgBr_2$	6	**1b**	67	[13]
12	4-ClC_6H_4	CH_2Cl	$MgBr_2$	8	**1d**	66	[16]
13	4-BrC_6H_4	CH_2Cl	$MgBr_2$	5	**1e**	68	[13]

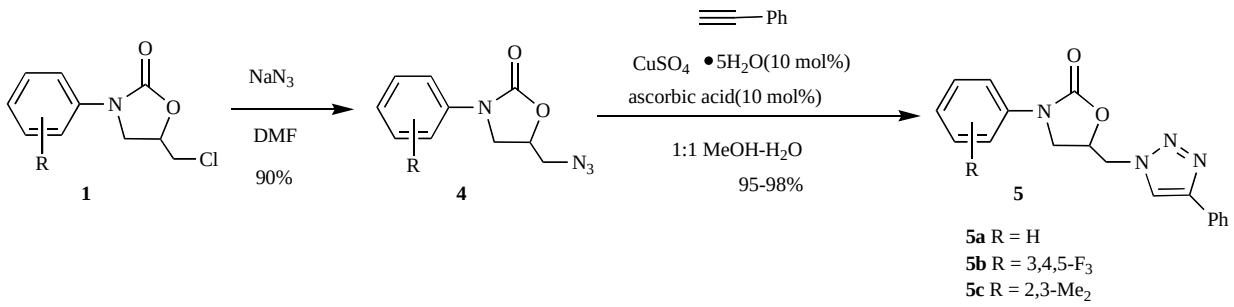
[a]50 mol% of MgX_2 etherate was used respectively.
[b]All products were identified by their ^1H NMR and IR spectra.
[c]Yields of products isolated by flash column chromatography.



Scheme 2. Preparation of 5-triazole-oxazolidinone.

conditions. In our preliminary experiments, we succeded to fulfill the conversion of oxazolidinone **1** to the triazole-oxazolidinone **5** by click reaction in 85-88% yield over the two steps (Scheme **3**), which provided a facile and effective route to acquire the novel triazole-oxazolidinone derivatives.

In conclusion, we have firstly demonstrated that the unique reactivity of MgI_2 etherate in the addition of isocyanates with epoxides. This catalytic system is advantagenous in that they are mild, give high yield of products, and are operationally convenient. A click reaction



Scheme 3. Synthesis of 1,2,3-triazole-oxazolidinone by click reaction.

protocol demonstrated a convenient approach toward a library of active 1,2,3-triazole-oxazolidinone derivatives in the search for future therapeutic antibiotics.

GENERAL EXPERIMENTAL PROCEDURE

General

For product purification by flash column chromatography, silica gel (200~300 mesh) and light petroleum ether (PE, b.p. 60~90 °C) were used. ^{1}H NMR spectra were taken on a Bruker Avance-500 spectrometer with TMS as an internal standard and $CDCl_3$ as solvent. FT-IR was recorded on a Bruker Tensor 27 spectrometer. Melting points were measured on BUCHI B-540 and uncorrected.

The Representative Procedure for the Synthesis of 2-oxazolidinones

To a stirred solution of freshly prepared MgI_2 etherate (2.5 mmol) in THF (10 mL) was added dropwise epichlorohydrin (552 mg, 6 mmol) followed by addition of phenyl isocyanate (595 mg, 5 mmol) at room temperature. After addition, the reaction mixture was allowed to warm to 65 °C and continued to be stirred for 2 hours. The resulting homogeneous reaction mixture was quenched with saturated Na_2SO_3 aqueous solution. Extractive workup with CH_2Cl_2 and flash chromatographic purification of the crude product on silica gel gave the 2-oxazolidinone **1a** (970 mg) in 92% yield.

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[13] **Spectroscopic Data for Selected Products (Table 1):** compound **1b:** Mp. 97.5-98.5 °C; IR (KBr) 1735 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.30 (s, 3H), 3.75-3.82 (m, 1H), 3.83 (dd, *J* = 2.0, 6.0 Hz , 2H), 4.03 (t, *J* = 9.0 Hz, 1H), 4.89-4.94 (m, 1H), 7.09 (dd, *J* = 2.5, 6.5 Hz , 1H), 7.12-7.16 (m, 2H) ppm. compound **1c:** Mp 73.0-73.8 °C; IR (KBr) 1736 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 3.77-3.85 (m, 2H), 3.94 (dd, *J* = 5.0, 9.5 Hz , 1H), 4.17-4.21 (m, 1H), 4.93-4.98 (m, 1H), 7.00-7.06 (m, 1H), 7.27-7.31 (m,1H) ppm; EI-MS: 265 ([M]$^+$, 22), 267 ([M+2]$^+$, 8),186 (100), 166(31), 158 (63). compound **1e:** Mp 125.0-127.2 °C; IR (KBr) 1738 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 3.74-3.80 (m, 2H), 3.91 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.13 (t, *J* = 9.0 Hz, 1H), 4.85-4.90 (m, 1H), 7.41-7.44 (m, 2H), 7.46-7.49 (m, 2H) ppm. compound **1g:** Mp 43.4-44.0 °C; IR (KBr) 1748 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.54 (d, *J* = 6.5Hz, 3H), 2.26 (s, 3H), 3.50 (dd, *J* = 6.5, 8.5 Hz, 1H), 3.98 (t, *J* = 8.0 Hz, 1H), 4.80-4.86 (m, 1H), 7.20-7.22 (m, 3H)ppm. compound **1i:** Mp 126.5-127.5 °C; IR (KBr) 1745 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 4.03 (dd, *J* = 6.0, 9.0 Hz , 1H), 4.14-4.23 (m, 3H), 4.95 (dd, *J* = 4.5, 9.0 Hz , 1H), 6.90 (d, *J* = 8.0 Hz , 2H), 6.99 (t, *J* = 7.5 Hz , 1H), 7.18 (d, *J* = 8.5 Hz , 2H), 7.29 (dd, *J* = 7.5, 8.0 Hz , 2H), 7.44 (d, *J* = 8.5 Hz , 2H) ppm. compound **2:** Mp 115.4-115.7 °C; IR (KBr) 1740 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 4.01 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.17 (t, *J* = 9.0 Hz, 1H), 4.56 (d, *J* = 5.0 Hz, 2H), 5.00-5.05 (m, 1H), 7.14-7.17 (m, 1H), 7.35-7.39 (m, 2H), 7.43-7.46 (m, 2H), 7.95 (s, 1H), 8.24 (s, 1H) ppm. compound **3:** Mp 150.5-151.4 °C; IR (KBr) 1741 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$) δ 4.07 (dd, *J* = 6.0, 9.0Hz, 1H), 4.21 (t, *J* = 9.0 Hz, 1H), 4.98-5.06 (m, 2H), 5.17-5.22 (m, 1H), 7.13 (t, *J* = 7.0 Hz, 1H), 7.31-7.37 (m, 4H), 7.42 (t, *J* = 7.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H) ppm. compound **5a**: Mp 175.0-175.5 °C; IR (KBr) 1761 cm^{-1} (C=O); H NMR ($CDCl_3$) δ 3.95 (dd, *J* = 6.5, 9.5 Hz, 1H), 4.19 (t, *J* = 9.0 Hz, 1H), 4.74 (dd, *J* = 5.0, 14.5 Hz, 1H), 4.81 (dd, *J* = 4.0, 14.5 Hz, 1H), 5.05-5.08 (m, 1H), 7.14 (t, *J* = 7.0 Hz, 1H), 7.32-7.36 (m, 3H), 7.40-7.44 (m, 4H), 7.81-7.82 (m, 2H), 8.00 (s, 1H) ppm.

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