

An Efficient and Highly Regioselective Cycloaddition of Aryl Isocyanates with Oxiranes Promoted by MgI₂ Etherate

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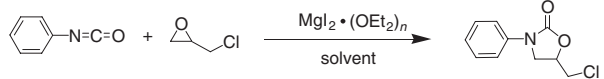
Cycloaddition of various aryl isocyanates with oxiranes was realized in the presence of 50 mol % MgI₂ etherate in a mild, efficient, and highly regioselective manner, which afforded 3-aryloxazolidin-2-one. Solvents (i.e., THF) and amounts of MgI₂ etherate catalyst played the critical roles for the unique reactivity of this catalytic system.

Oxiranes are useful intermediates in organic synthesis because of their easy accessibility and high reactivity being accompanied with their ring opening.¹ Cycloaddition reactions of oxiranes with heterocumulenes are efficient methods for the synthesis of heterocyclic compounds.² A number of catalysts have been investigated, such as quaternary ammonium salts,³ LiBr/*n*-Bu₃PO or LiBr/HMPA,⁴ LiCl/DMF,⁵ *n*-Bu₃SnI-Ph₃PO,⁶ *n*-Bu₃SnI-Ph₄SbI,⁷ and lanthanide chlorides⁸ have been reported to be efficient catalysts. However, many of these reagents are rather expensive and difficult to handle especially on a large scale. Therefore the development of inexpensive, environmentally benign, and easily handled promoters for cycloaddition of isocyanates with oxiranes is still highly desirable. Magnesium is an abundant, cheap, and benign element which exists in nature, and many reactions using magnesium salts have been developed recently in organic synthesis.⁹ In our previous papers,¹⁰ we have demonstrated that MgI₂ etherate could efficiently catalyze the Mukaiyama aldol reaction of aldehydes with trimethylsilyl enolates and allylation of aldehydes with allylstannane. Herein we wish to report the preliminary results of the catalytic reactivity of MgI₂ etherate for the mild, efficient, and regioselective cycloaddition of isocyanates with oxiranes.

At the onset of this work, we investigated a variety of conditions with a model reaction of phenyl isocyanate with epichlorohydrin using MgI₂ etherate¹¹ as promoter. The results are summarized in Table 1. By screening various solvents we have found that THF and CH₂ClCH₂Cl are the best solvents for this reaction (Table 1, Entries 7 and 9). Moderate yield was given in benzene, toluene, Et₂O, CH₃CN, and CH₂ClCH₂Cl (Table 1, Entry 1–5). Low yield was provided in 2-MeTHF (Table 1, Entry 6). Diphenyl urea was obtained other than the desired product when polar solvent DMF was used as solvent (Table 1, Entry 8). We also studied the influence of amounts of MgI₂ etherate on the reaction yields. The yield of cycloaddition was significantly affected by the amounts of MgI₂ etherate. It has been found that only diphenyl urea was given when using less than 5 mol % of MgI₂ etherate (Table 1, Entry 10).¹² By increasing the amount of MgI₂ etherate, the yield was obviously improved (Table 1, Entries 11–15). However, no increased yield was found in the presence of 100 mol % of MgI₂ etherate (Table 1, Entry 16).

Furthermore, the yield of cycloaddition product was affected by the reaction temperature. It showed that higher

Table 1. Cycloaddition of phenyl isocyanate with epichlorohydrin under different reaction conditions^a



Entry	Solvent	Temp /°C	Loading ^b /%	Time /h	Yield ^c /%
1	CH ₂ ClCH ₂ Cl	25	50	4	65
2	Et ₂ O	25	50	2	65
3	CH ₃ CN	25	50	3	71
4	Benzene	25	50	2	74
5	Toluene	25	50	4	70
6	2-MeTHF	25	50	6	22
7	CH ₂ Cl ₂	25	50	2	80
8	DMF	25	50	2	— ^d
9	THF	25	50	2	82
10	THF	25	<5	8	— ^d
11	THF	25	10	10	18
12	THF	25	15	10	32
13	THF	25	20	10	42
14	THF	25	25	3	51
15	THF	25	30	3	71
16	THF	25	100	2	82
17	THF	50	50	2	87
18	THF	65	50	2	92

^aThe reaction was carried out by the addition of phenyl isocyanate (5 mmol) to the mixture of epichlorohydrin (6 mmol) and MgI₂·(OEt₂)_n in above solvent at indicated temperature. ^bRelative to phenyl isocyanate. ^cIsolated yield by silica gel flash column chromatography. ^dOnly diphenyl urea was obtained.¹²

temperature would be favorable to improve the reaction yield. The reaction was efficiently carried out in refluxing THF (65 °C) to give the desired product in 92% yield (Table 1, Entry 18).

With these optimal conditions in hand, cycloaddition of a variety of aryl isocyanates with epichlorohydrin was investigated (Table 2, Entries 1–8).¹³ As shown in Table 2, the reaction proceeded smoothly in refluxing THF and provided the desired products in good to excellent yields. The electronic effect of substituted groups on the aromatic ring of isocyanates has no obvious effect on the conversion and yield of the cycloaddition product. The cycloaddition of propylene oxide with aryl isocyanates also provided the desired products in high yield (Table 2, Entries 9–11). In addition, the cycloaddition of 2-(phenoxy)methyl oxirane with aryl isocyanates also proceeded effectively in the presence of MgI₂ etherate to give the desired product in good yield (Table 2, Entries 12–14). It is noted that MgI₂ etherate could efficiently promote the reaction of 2-

Table 2. Cycloaddition of aryl isocyanates with oxiranes promoted by MgX₂ etherate^a

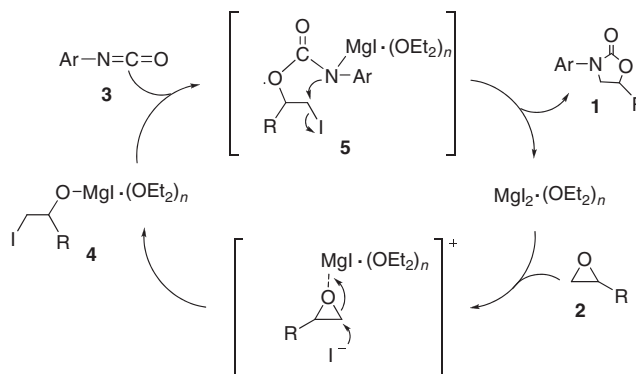
Entry	Ar	R	MgX ₂	Time/h	Product ^b	Yield/% ^c
1	C ₆ H ₅	CH ₂ Cl	MgI ₂	2	1a	92
2	4-NO ₂ C ₆ H ₄	CH ₂ Cl	MgI ₂	3	1b	82
3	4-BrC ₆ H ₄	CH ₂ Cl	MgI ₂	3	1c	78
4	2-Me-5-ClC ₆ H ₃	CH ₂ Cl	MgI ₂	3	1d	88
5	3,4,5-F ₃ C ₆ H ₂	CH ₂ Cl	MgI ₂	1	1e	84
6	2,4-F ₂ C ₆ H ₃	CH ₂ Cl	MgI ₂	2	1f	88
7	2,6-(<i>i</i> -Pr) ₂ C ₆ H ₃	CH ₂ Cl	MgI ₂	4	1g	89
8	4-ClC ₆ H ₄	CH ₂ Cl	MgI ₂	1	1h	79
9	3,4,5-F ₃ C ₆ H ₂	CH ₃	MgI ₂	1	1i	87
10	2-Me-5-ClC ₆ H ₃	CH ₃	MgI ₂	1	1j	78
11	4-NO ₂ C ₆ H ₄	CH ₃	MgI ₂	1	1k	70
12	C ₆ H ₅	C ₆ H ₅ OCH ₂	MgI ₂	2	1l	88
13	2-Me-5-ClC ₆ H ₃	C ₆ H ₅ OCH ₂	MgI ₂	2	1m	81
14	2,6-(<i>i</i> -Pr) ₂ C ₆ H ₃	C ₆ H ₅ OCH ₂	MgI ₂	4	1n	85
15	4-MeC ₆ H ₄	(4-MeOCH ₂ CH ₂)C ₆ H ₄ OCH ₂	MgI ₂	12	1o	70
16	C ₆ H ₅	CH ₂ Cl	MgBr ₂	5	1a	78
17	4-NO ₂ C ₆ H ₄	CH ₂ Cl	MgBr ₂	6	1b	73
18	4-BrC ₆ H ₄	CH ₂ Cl	MgBr ₂	5	1c	68

^aReactions were run with a mixture of 5 mmol of aryl isocyanate, 6 mmol of oxirane, and 50 mol % of MgX₂ etherate in refluxing THF.

^bAll products were identified by their ¹H NMR and IR spectra. ^cIsolated yield by silica flash column chromatography.

(phenoxymethyl)oxirane with more sterically hindered 2,6-diisopropylphenyl isocyanate and gave the product in 85% yield (Table 2, Entry 14). In terms of more bulky oxirane (Table 2, Entry 15), the reaction could also afford the desired cycloadduct in good yield. To examine the halide anion effect, halogen analogs of MgI₂ etherate, MgBr₂ etherate, and MgCl₂ etherate were compared under parallel reaction conditions (50 mol % of catalyst) in the reaction of phenyl isocyanate with epichlorohydrin, respectively. MgCl₂ etherate is almost inactive and MgBr₂ etherate is less effective in terms of substrate conversion and yield (Table 2, Entry 16). Moreover, the cycloaddition of other aryl isocyanates with epichlorohydrin was further studied in the presence of MgBr₂ etherate (Table 2, Entries 17 and 18). The relatively lower yield of the parent cycloaddition promoted by MgBr₂ etherate was afforded under the same condition. We propose the mechanism of this reaction as shown in Scheme 1. MgI₂ would act as a Lewis acid and as an iodide source. The ring opening of oxirane **2** occurs via formation of an oxonium salt with MgI₂ etherate from its high oxophilic character, which is followed by the nucleophilic attack of the iodide from the less hindered position.¹⁴ The cationic character¹⁵ of this more Lewis acidic Mg(II) coordinated with peripheral ethereal ligands results from the dissociation of iodide ion in accordance with the coordination of the Lewis basic oxygen atom. A magnesium alkoxide **4** would be a strong nucleophile and would attack the isocyanate **3** to give the intermediate **5**, which would proceed smoothly to provide the desired oxazolidin-2-one **1**.

In conclusion, we have demonstrated the unique reactivity of MgI₂ etherate in the cycloaddition of aryl isocyanates with oxiranes. This catalytic system has some advantages, such as



Scheme 1. A plausible mechanism of MgI₂ etherate-promoted cycloaddition of isocyanate with oxirane.

mild reaction conditions, simplicity in operation, high regioselectivity, and good yield. The details of this reaction and its extension to the cycloaddition of oxiranes with other heterocumulenes are now under investigation.

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