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Gallium(III) Chloride-Catalyzed Double Insertion of Isocyanides into Epoxides†

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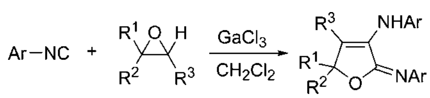
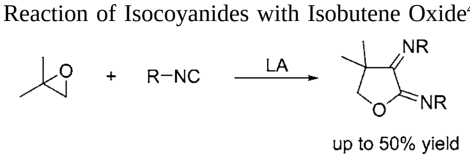
ABSTRACT



Gallium(III) chloride-catalyzed double insertion of aryl isocyanides into terminal and disubstituted epoxides leads to α,β-unsaturated α-amino iminolactones (3-amino-2-iminio-2,5-dihydrofurans).

Epoxides are very useful building blocks in organic synthesis due to the high reactivity of their three-membered ring.[1] Because of our ongoing research in epoxidation chemistry,[2] we became interested in the reaction of epoxide and isocyanide. Although isocyanides are very reactive toward cations, anions, and radicals,[3] they do not react with epoxides without a promoter. A careful literature search reveals that the reaction of isocyanides and epoxides has not been studied in detail. Only one paper briefly mentioned a Lewis acid (BF_3·Et_2O and $AlCl_3$)-catalyzed reaction of isocyanides with isobutene oxide. This reaction operates through an S_N1 mechanism, producing 2,3-diiminofurans in low yields (Scheme 1).[4] The authors also tried some other types of epoxides for this reaction but without success and concluded that only 2,2-dialkyl epoxides are suitable for such cycloaddition.[4]

Scheme 1. Lewis Acid (BF_3·Et_2O and $AlCl_3$)-Catalyzed Reaction of Isocoyanides with Isobutene Oxide[4]



$GaCl_3$ is a versatile catalyst for many organic reactions.[5] The use of $GaCl_3$ or its derivatives as catalysts for epoxide ring-opening reactions has been well documented in the literature. For example, Shibasaki et al. reported that gallium bis(binaphthoxide) complexes are good catalysts for highly enantioselective ring-opening of epoxides with *p*-methoxyphenol[6] and thiols[7] as nucleophiles. Similarly, Li et al. reported that $GaCl_3$ catalyzes ring-opening reaction of epoxides by alkynes.[8] Since $GaCl_3$ promotes carbocation formation from epoxides in the latter reaction[8] and it is also reported that $GaCl_3$ may be used together with isocyanides,[9] we envisaged that $GaCl_3$ should be a good catalyst for the

† Dedicated to Professor Waldemar Adam on the occasion of his 66th birthday.

(1) For reviews, see: (a) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis I−III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Germany, 1999; Vol. 3, pp 1309−1326. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F. *Trends Org. Chem.* **1997**, *6*, 181−195. (c) Chemla, F.; Ferreira, F. *Curr. Org. Chem.* **2002**, *6*, 539−570. (d) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421−433.

(2) (a) Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* **2003**, *44*, 7403−7406. (b) Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749−2755. (c) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995−3998.

(3) For reviews on isocyanides in organic synthesis, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3120. (b) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem.−Eur. J.* **1998**, *4*, 67−83. (c) Saegusa, T.; Ito, Y. *Synthesis* **1975**, 291−300.

(4) Saegusa, T.; Takaishi, N.; Takami, M.; Ito, Y. *Synth. Commun.* **1971**, *1*, 99−102.

(5) For reviews, see: (a) Kellogg, R. M. *Chemtracts* **2003**, *16*, 79−92. (b) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *Chemtracts* **2000**, *13*, 431−434.

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(8) Viswanathan, G. S.; Li, C.-J. *Synlett* **2002**, 1553−1555.

(9) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812−7813.

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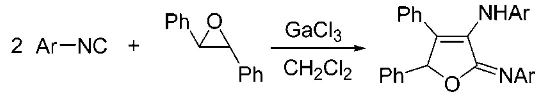
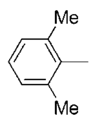
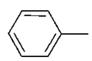
Table 1. Insertion of Isocyanides into *trans*-Stilbene Epoxide[a]



entry	epoxide (equiv)	Ar	$GaCl_3$ (equiv)	temp (°C)	yield[b] (%)
1	1.0		1.0	25	0
2	1.0		0.2	40	58
3	1.0		0.0	40	0
4	2.0		0.2	40	73
5	2.0		0.5	40	81
6	2.0		1.0	40	96
7	1.0		0.5	25	85

[a] To a solution of aryl isocyanide (0.1 mmol) and *trans*-stilbene epoxide (0.05 mmol to 0.1 mmol) in CH_2Cl_2 (5 mL) was added a 0.5 M solution of $GaCl_3$ in ether. The mixture was allowed to stir at the specified temperature for 2 h. [b] Yield of isolated product after column chromatography.

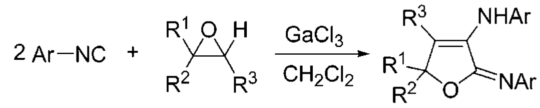
reaction of epoxides and isocyanides. We report here our preliminary results of $GaCl_3$-catalyzed double insertion of aryl isocyanides into terminal and disubstituted epoxides, which yields α,*β*-unsaturated α-amino iminolactones in a single step.

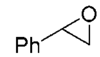
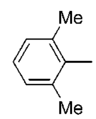
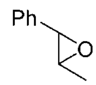
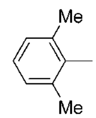
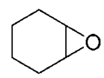
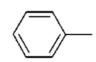
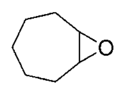
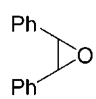
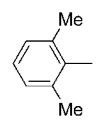
The reaction was initially studied with *trans*-stilbene epoxide (Table 1). When a mixture of *trans*-stilbene epoxide and 2,6-dimethylphenyl isocyanide in CH_2Cl_2 [10] was treated with 1.0 equiv (with respect to the isocyanide used, the same throughout the rest of this paper) of $GaCl_3$ at room temperature, there was no reaction (entry 1). However, when the temperature was elevated to the boiling point of CH_2Cl_2 (40 °C), the reaction took place immediately and finished within 2 h (entry 2). Even at this elevated temperature, no reaction took place without $GaCl_3$ (entry 3). The product of this reaction was found to be an α,*β*-unsaturated α-amino iminolactone.[11] With a catalytic amount of $GaCl_3$ (0.2 equiv), the yield was 58% (entry 2). The yield of this product could be further improved by employing more epoxide and catalyst. For example, with 2.0 equiv of epoxide and 0.2 equiv of $GaCl_3$, the yield was improved to 73% (entry 4). By using 0.5 equiv of $GaCl_3$, an 81% yield was obtained (entry 5). An optimum yield of 96% was obtained by employing 2.0 equiv of epoxide and 1.0 equiv of $GaCl_3$ (entry 6). With phenyl isocyanide, an 85% yield of the corresponding product was obtained by using a stoichiometric amount of epoxide and a catalytic amount of $GaCl_3$ at room temperature (entry 7).

(10) $CHCl_3$, CH_3CN, Et_2O, THF, benzene, and toluene are poorer solvents.

(11) Formation of *saturated* iminolactones has been achieved by a BF_3·Et_2O-catalyzed reaction of isocyanides and oxetanes; see: Saegusa, T.; Takaishi, N.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2473−2479.

Table 2. Insertion of Isocyanides into Epoxides



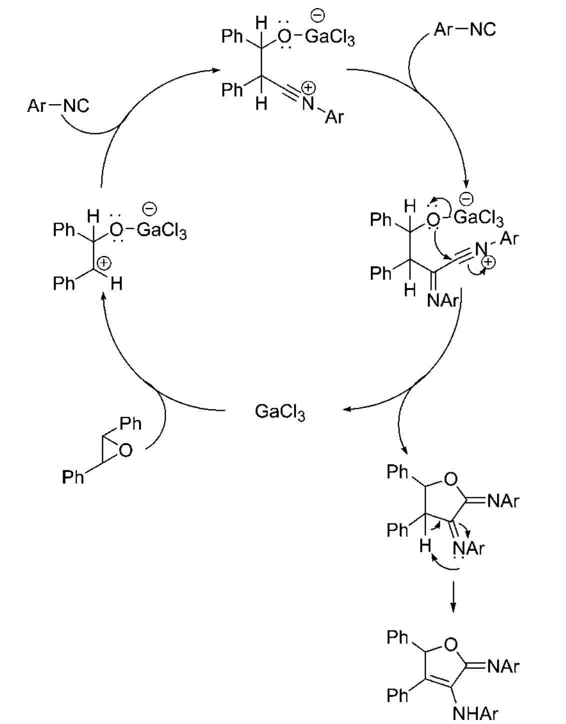
entry	epoxide	Ar	$GaCl_3$ (equiv)	time (h)	yield (%)[b]
1			1.0	2	31
2			0.5	4	28
3			0.2	7	25[c]
4[d]			1.0	2	61
5[d]			2.0	2	53
6			1.0	2	73
7[e]			1.0	4	15
8			1.0	2	14
9[f]			1.0	2	11
10			1.0	2	51
11[d]			0.5	1	68
12			0.5	1	90

[a] For reaction conditions, see Table 1. All reactions were carried out at room temperature (ca. 25 °C), unless otherwise indicated. The molar ratio of isocyanide to epoxide was 1:1, unless otherwise specified. [b] Yields of purified products after column chromatography. [c] An unidentified product also formed in this case (cf. ref 12). [d] Molar ratio of isocyanide to epoxide was 2:1. [e] Carried out at 40 °C. [f] Carried out at 0 °C.

Other epoxides were also found to undergo this reaction, and the results are summarized in Table 2. With styrene oxide, which did not yield any useful product under the catalysis of BF_3·Et_2O or $AlCl_3$,[4] 31% yield of the expected product was obtained (entry 1). Similarly, *trans*-*β*-methylstyrene epoxide gave a 28% yield (entry 2). When a stoichiometric amount of cyclohexene oxide was treated with a catalytic amount of $GaCl_3$ at room temperature, the expected product was obtained in 25% yield (entry 3). The yield was lower since another unidentified product[12] was also generated in this case. However, the yield of the desired product can be improved by using an appropriate (1.0 equiv) amount of $GaCl_3$ (entries 4 and 5). Finally a 73% yield was obtained when 2.0 equiv of cyclohexene oxide and 1.0 equiv

(12) This product is formed by 2 molecules of the epoxide and 4 molecules of the isocyanide according to NMR studies.

Scheme 2. Proposed Mechanism for the Formation of α,*β*-Unsaturated α-Amino Iminolactones



of $GaCl_3$ were used (entry 6). Phenyl isocyanide proved to be inferior to 2,6-dimethylphenyl isocyanide for this reaction. The yields of the desired product were no better than 15% (entries 7−9). Among other cyclic alkene epoxides studied, cycloheptene oxide gave a 51% yield of the product (entry 10), while *cis*-cyclooctene oxide was not reactive. Cyclopentene oxide, instead, yielded only the other type of product (41%, data not shown).[12]

cis-Stilbene epoxide, like its trans isomer, also produced the expected product in high yields (entries 11 and 12). In contrast to the $BF_3{\cdot}Et_2O$- and $AlCl_3$-catalyzed reactions,[4] no diiminofurans could be obtained from the epoxides of α-methylstyrene or triphenylethylene. Instead, a complex mixture was obtained for these epoxides.

The formation of the α,*β*-unsaturated α-amino iminolactone products can be rationalized by $GaCl_3$-catalyzed double insertion of isocyanide into the epoxide followed by a 1,3-hydrogen shift (Scheme 2). The epoxide is ring-opened to give the corresponding carbocation under the action of $GaCl_3$, which reacts with two molecules of the isocyanide. This is then cyclized to give the diiminofuran intermediate. In this procedure, $GaCl_3$ is released and enters into another catalytic cycle. The fact that both *cis*- and *trans*-stilbene epoxides yield the same product in high yields is indicative of an S_N1-type mechanism. The diiminofuran intermediate then undergoes a 1,3-hydrogen shift (or enamine-type tautomerism) to give the final product. The driving forces for this rearrangement are probably less ring strain and better conjugation in the final product. The 1,3-hydrogen shift is essential for the success of this reaction since the reaction does not work when such a hydrogen is lacking (epoxides of α-methylstyrene and triphenylethylene do not yield any identifiable products). However, it is still not certain whether $GaCl_3$ also plays a role in this process.

1 2

Figure 1. Sotolone (**2**) and its amino precursor **1**.

Since the imino group can be converted to a carbonyl group, for example, through acid-catalyzed hydrolysis,[13] the products of this reaction should be useful synthetic precursors for α,*β*-unsaturated α-amino lactones (such as **1**) and α,*β*-unsaturated α-hydroxy lactones (such as **2**), which are structural units of many biologically active materials and natural products (Figure 1). For example, sotolone (**2**) is an important aroma used in tobacco industries and as a food additive.[14] Compound **1** is believed to be its biological precursor. Therefore, this novel $GaCl_3$-catalyzed reaction of isocyanide and epoxide will provide easy access to these types of compounds.

In summary, gallium(III) chloride-catalyzed double insertion of isocyanides into epoxides yields 3-amino-2-imino-2,5-dihydrofurans in a single step, which are potential substrates for the synthesis of sotolone-type natural products.

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Supporting Information Available: Detailed experimental procedures and ^{1}H and ^{13}C NMR data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Raffauf, R. F.; Zennie, T. M.; Onan, K. D.; Le Quesne, P. W. *J. Org. Chem.* **1984**, *49*, 2714−2718. (b) Ottinger, H.; Soldo, T.; Hofmann, T. *J. Agric. Food Chem.* **2001**, *49*, 5383−5390. (c) Peraza-Luna, F.; Rodriguez-Mendiola, M.; Arias-Castro, C.; Bessiere, J.-M.; Calva-Calva, G. *J. Agric. Food Chem.* **2001**, *49*, 6012−6019.