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Graphical Abstract

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ABSTRACT

2-Carbomethoxycyclobutanone reacted with *N*-phenyl-*C*-arylnitrones to afford methyl 5-oxo-2-[aryl(phenylamino)methyl]tetrahydrofuran-2-carboxylates by the catalysis of indium(III) triflate in the presence of magnesium sulfate.

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Nitrones are useful synthetic intermediates in organic synthesis and have been used mainly in the 1,3-dipolar cycloaddition with olefins to give isoxazolidines.¹ In addition to olefins, nitrones reacted with donor-acceptor cyclopropanes and cyclobutanes for [3+3]^{2,3} and [4+3]⁴ cycloadditions, respectively. Moreover, nucleophilic additions to nitrones have been studied for carbon nucleophiles such as Grignard reagents,⁵ cyanide ion,⁶ and sodium salts of diethyl malonate.⁷ We were interested in a reaction of 2-carbomethoxycyclobutanone (**1**)⁸ with nitrones because four-membered ketoester **1** can work as a carbon nucleophile and it has a characteristic feature of facile ring cleavage.⁹ Thus, we tried to synthesize a seven-membered ring compound **3a'** by nucleophilic addition of **1** to nitrone **2a** followed by ring cleavage of four-membered ring of **4** (Scheme 1). However, we found unexpected formation of a γ -butyrolactone derivative **3a** by Lewis acid-catalyzed reaction of nitrone **2a** with **1**, and we report here the results.

Scheme 1

Formation of γ -butyrolactone **3a** by Lewis acid-catalyzed reaction between **1** and **2a**

First, various Lewis acids were screened in a model reaction between **1** and nitrone **2a** to afford γ -butyrolactone **3a** (Table 1). In the absence of a Lewis acid, cyclobutanone **1** was not react with **2a** at refluxing temperature of toluene, and even ring cleavage of **1** did not observed by TLC analysis (Entry 1). The use of catalytic amounts (10 mol%) of the typical Lewis acids TiCl_4 , $\text{BF}_3\cdot\text{Et}_2\text{O}$ and Me_3SiOTf gave the desired product **3a** in 16%, 34% and 27% yields, respectively (Entries 2–4), while the use of more than stoichiometric amounts (1.3 equiv) of these Lewis acids did not afford **3a** at all. Catalytic amounts (10 mol%) of several metal triflates were then tested in this reaction, and it was found that $\text{In}(\text{OTf})_3$ promoted the reaction most efficiently (Entries 5–11). The Brønsted acid TsOH also

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catalyzed the reaction, but the reaction proceeded sluggishly (Entry 12). It should be noted that high diastereoselectivity was observed in the Lewis acid-catalyzed reaction of **1** and **2a** as shown in Table 1. We employed In(OTf)₃ in the following experiments since the reaction time was shorter than that for BF₃-OEt₂ (Entries 3 and 11).¹⁰

Table 1

Effects of Lewis acids in a reaction of **1** and **2a** to give γ -butyrolactone **3a** (eq 1)^a

Entry	Lewis acid	Time (h)	Isolated yield (%)	dr ^b
1 ^c	none	48	0	
2	TiCl ₄	48	16	99:1
3	BF ₃ -Et ₂ O	48	34	96:4
4	Me ₃ SiOTf	18	27	98:2
5	AgOTf	24	29	96:4
6	Zn(OTf) ₂	23	18	97:3
7	Cu(OTf) ₂	53	1	98:2
8	Yb(OTf) ₃	19	12	96:4
9	La(OTf) ₃	29	17	98:2
10	Sc(OTf) ₃	19	19	96:4
11	In(OTf) ₃	20	32	96:4
12	TsOH-H ₂ O	48	20	96:4

^a Unless otherwise mentioned, the following reaction conditions were used: cyclobutanone **1** (1.0 equiv), nitrone **2a** (1.3 equiv), and Lewis acid (10 mol%) were reacted in toluene at 45 °C.

^b Determined by ¹H NMR.

^c Reaction conditions: 45 °C (24 h) and reflux (24 h).

Next, effects of additives in the In(OTf)₃-catalyzed reaction of **1** and **2a** were investigated (Table 2). Some drying agents were employed as additives because benzaldehyde was detected by TLC analysis in the above-mentioned Lewis acid screening. The use of molecular sieves 4A and 5A was not effective and led to considerably lower yields of the desired product **3a** (Entries 2 and 3). The addition of Na₂SO₄ did not cause any change compared with the case of no additives, whereas the use of MgSO₄ greatly improved the yield of **3a** to 56% (Entries 4 and 5). TLC analysis of the reaction mixture showed smooth consumption of cyclobutanone **1** in the presence of MgSO₄, but benzaldehyde was still detected even in the presence of MgSO₄. MgSO₄ did not work as a Lewis acid in this reaction because the product **3a** was detected only in a trace amount by using MgSO₄ in the absence of In(OTf)₃ (Entry 6). Therefore, at present, the role of MgSO₄ is not clear. The use of Mg(ClO₄)₂ gave the desired product **3a** in 6% yield (Entry 7), and it was found that MgSO₄ was an appropriate additive in the present In(OTf)₃-catalyzed reaction.¹¹

Table 2

Effects of additives in an In(OTf)₃-catalyzed reaction of **1** and **2a** to afford **3a** (eq 1)^a

Entry	Additive	Time (h)	Isolated yield (%)	dr ^b
1	none	24	36	96:4
2	MS4A	48	0	
3	MS5A	72	5	99:1
4	Na ₂ SO ₄	14	39	97:3
5	MgSO ₄	24	56	98:2
6 ^c	MgSO ₄	48	trace	
7	Mg(ClO ₄) ₂	24	6	87:13

^a Reaction conditions: cyclobutanone **1** (1.0 equiv), nitrone **2a** (2.0 equiv), In(OTf)₃ (10 mol%), and additive (300 mg/mmol of **2**) were reacted in toluene at 45 °C.

^b Determined by ¹H NMR.

^c In the absence of In(OTf)₃.

The scope and limitations of the reaction of cyclobutanone **1** and nitrones were investigated by employing various nitrones **2b–g** (Table 3). *N*-Phenyl-*C*-arylnitrones **2b–d** with electron-withdrawing groups such as fluoro, chloro, and bromo groups at the *p*-position of the phenyl ring gave results comparable to those with the parent unsubstituted nitrone **2a** (Entries 1–3). Substitution with a methyl group resulted in a slightly decreased yield of **3e** (Entry 4). The use of a nitrone **2f** bearing a *C*-2-naphthyl group instead of the *C*-phenyl group lowered the yield of the corresponding γ -butyrolactone **3f** (entry 5). *C*-Alkyl nitrone **2g**, which was prepared in situ from 3-phenylpropanal and *N*-phenylhydroxylamine, reacted with **1** to afford **3g** in 24% yield (Entry 6) whereas *N*-methyl nitrone **2h** did not react with **1** (Entry 7). Stereochemistry of **3** was determined by X-ray crystallography of **3d**.

Table 3

Scope and limitations of In(OTf)₃-catalyzed reaction of cyclobutanone **1** and nitrone **2b–g** to give γ -butyrolactone **3b–g**^a

Entry	2	R ¹	R ²	3	Yield (%)	dr ^b
1	2b	Ph	X = F	3b	51	96:4
2	2c	Ph	X = Cl	3c	46	97:3
3	2d	Ph	X = Br	3d	51	97:3
4	2e	Ph	X = Me	3e	41	98:2
5	2f	Ph	2-Naphthyl	3f	40	95:5
6	2g	Ph	(CH ₂) ₂ Ph	3g	24	93:7
7	2h	Me	Ph	3h	0	

^a Reaction conditions: cyclobutanone **1** (1.0 equiv), nitrone **2** (2.0 equiv), In(OTf)₃ (10 mol%), and MgSO₄ (300 mg/mmol of **2**) were reacted in toluene at 45 °C.

^b Determined by ¹H NMR.

A proposed mechanism for the In(OTf)₃-catalyzed reaction between cyclobutanone **1** and nitrone **2a** is shown in Scheme 2. Nucleophilic attack of cyclobutanone **1** to nitrone **2a** which is activated with In(OTf)₃ gives hydroxylamine **5**, in which intramolecular attack of the hydroxyl group to the carbonyl group of cyclobutanone gives isoxazolidine derivative **4**.¹² Valence rearrangement¹³ of the isoxazolidine ring of **4** gives aziridin-2-yl carboxylic acid **6**. Intramolecular attack of the carboxylic acid

group to the aziridine ring gives γ -butyrolactone **3a**. Each step shown in Scheme 1 can be catalyzed with $\text{In}(\text{OTf})_3$.

Scheme 2

A proposed mechanism for $\text{In}(\text{OTf})_3$ -catalyzed reaction of **1** and nitrone **2a** to γ -butyrolactone **3a**

In conclusion, we found a new method for synthesis of functionalized γ -butyrolactone by a reaction of 2-carbomethoxycyclobutanone¹⁴ with *N*-phenyl-*C*-arylnitrones. This reaction was effectively promoted by using a catalytic amount of $\text{In}(\text{OTf})_3$ in the presence of MgSO_4 . Valence rearrangement of an isoxazolidine intermediate followed by intramolecular attack of a carboxylate group to an aziridine ring was proposed for the formation of γ -butyrolactone.

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- Use of other solvents such as dichloromethane, THF, and acetonitrile gave **3a** in low yields.
- Under the reaction conditions of entry 5 (Table 1), the starting material **1** was completely consumed, and some very polar co-products were detected by TLC analysis.
- A concerted mechanism for [3+2] cycloaddition between an enol form of **1** and nitrone **2a** is also possible for generation of **4**. [3+2] Cycloaddition of nitrones and silyl enol ethers: (a) Hosomi, A.; Shoji, H.; Sakurai, H. *Chem. Lett.* **1985**, 1049; (b) Dhavale, D. D.; Trombini, C. *J. Chem. Soc., Chem. Commun.* **1992**, 1268; (c) Camiletti, C.; Dhavale, D. D.; Gentilucci, L.; Trombini, C. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3157.
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- Indium(III) triflate-catalyzed reaction of nitrone **2a** with ethyl 2-oxocyclopentanecarboxylate or ethyl 2-oxocyclohexanecarboxylate did not afford the corresponding lactones

Supplementary Material

Supplementary data associated with this article can be found in the online version.