Brønsted Acid TfOH-Mediated Reactions of Methylenecyclopropanes with Nitriles

Jin-Wen Huang, Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China Fax +86(21)64166128; E-mail: mshi@pub.sioc.ac.cn

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Abstract: In the presence of Brønsted acid TfOH, methylenecyclopropanes react with nitriles to give [3+2] cycloaddition products in good to high yields along with Ritter reaction products. In many cases, [3+2] cycloaddition products are obtained as the major products. The reaction conditions have been carefully examined and the plausible mechanism has been proposed.

Key words: methylenecyclopropanes, Brønsted acid, acetonitrile, benzonitrile, [3+2] cycloaddition, Ritter reaction

Recently, we found that the ring-opening reactions of methylenecyclopropanes (MCPs) **1** with alcohols and other nucleophiles catalyzed by Lewis acids $[Ln(OTf)_n]$ (Ln = Sn, Yb, Sc) or Brønsted acid such as TfOH (CF₃SO₃H) took place via an interesting pathway (homoallylic rearrangement) to give the corresponding ring-opened products under mild conditions.^{1–3} This interesting result stimulated us to further investigate the Lewis acid or Brønsted acid-mediated reactions of MCPs **1** with other reactants. Herein we wish to report an unprecedented Brønsted acid TfOH-mediated reaction of MCPs **1** with nitriles under mild conditions.

Using diphenylmethylenecyclopropane (1a) as the substrate, we found that **1a** (1.0 equiv) reacts with acetonitrile (2a, as a solvent) to give the corresponding [3+2] cycloaddition product 3a in 86% yield along with a ring-opened Ritter reaction product $4a^4$ (with ambient water) in 2% yield when the reaction was carried out in the presence of a Brønsted acid TfOH (1.0 equiv) at room temperature (25 °C) for 4 hours (Scheme 1). This reaction is sluggish in the presence of a variety of Lewis acids (1.0 equiv) such as Sn(OTf)₂, Sc(OTf)₃, Yb(OTf)₃, Cu(OTf)₂, Zn(OTf)₂, $BF_3 O Et_2$ and $Ti(Oi-Pr)_4$. Other Brønsted acids such as CF₃CO₂H and TsOH (*p*-MeC₆H₄SO₃H) did not catalyze this reaction. Sulfuric acid (99% H_2SO_4) also gave 3a in low yield under identical conditions. The strong Brønsted acid TfOH is the best promoter for this novel transformation of MCP 1a with acetonitrile to give the corresponding [3+2] cycloaddition product **3a** as the major product, and ring-opened Ritter reaction product 4a as the minor product under mild conditions.

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Scheme 1 The Brønsted acid (TfOH)-mediated reaction of MCP **1a** (1.0 equiv) with acetonitrile (**2a**) at room temperature ($25 \degree$ C).

During our further investigation on this reaction using other MCPs 1, we found that some MCPs 1 are not soluble in acetonitrile 2a very well and the co-solvent should be required. In order to extend the scope and limitations of this reaction, the solvent effects have been examined by use of 2a (5.0 equiv) as a reactant in 2.0 mL of dichloromethane, cyclohexane, MeNO₂, 1,4-dioxane, THF or diethyl ether (Et₂O) under the same conditions. The results are summarized in Table 1. The [3+2] cycloaddition product **3a** was obtained in moderate to good yields in dichloromethane, cyclohexane, MeNO₂, THF or 1,4-dioxane (Table 1, entries 1–6). In Et₂O, this reaction produced homoallylic ether in 72% as the major product^{2a} along with 4a in 12% without the formation of 3a (Scheme 2 and Table 1, entry 7). The ring-opened Ritter reaction product 4a was obtained as a by-product in trace to 12% yield in all cases (Table 1, entries 1-7).

Table 1 The Solvent Effects on the Brønsted Acid-Mediated Reac-
tion of MCP 1a with Acetonitrile at Room Temperature

C ₆ H ₅ C ₆ H	H_5 + MeCN $\frac{\text{TfOH}}{\text{solvent}}$ 2a	C_6H_5 C_6H_5 \rightarrow N + 3a	C_6H_5 C_6H_5 4a	O \\ NHCMe
			Yield (%) ^a	
Entry	Solvent	Time (h)	3a	4 a
1	-	0.5	86	2
2	CH ₂ Cl ₂	0.5	85	4
3	Cyclohexane	0.5	84	_
4	MeNO ₂	0.5	76	_
5	Dioxane	0.5	50	_
6	THF	0.5	40	_
7	Et ₂ O	0.5	-	12

^a Isolated yields.

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Scheme 2 The reaction of MCP 1a with diethyl ether in the presence of TfOH

We next examined the reactions of various MCPs 1 with **2a** using an acetonitrile–dichloromethane (2.0:1) mixture⁵ in the presence of 1.0 equivalent of TfOH at room temperature for four hours. The results are summarized in Table 2. The substituents on the benzene ring of MCPs 1 did not significantly affect the reaction. For MCPs 1 having an electron-withdrawing group such as a chlorine or fluorine atom on the benzene ring or an electron-donating group such as a methyl or methoxy group on the benzene ring, these reactions proceeded smoothly to give the corresponding [3+2] cycloaddition products **3b**-g in good yields (Table 2, entries 1-6). For unsymmetric MCPs 1f having two different aromatic groups and 1g having a methyl group and an aromatic group, the [3+2] cycloaddition products 3f and 3g were obtained as mixtures of Z- and Eisomers (see supporting information; Table 2, entries 5 and 6). For MCP 1f having a substituent at the o-position of benzene ring, the [3+2] cycloaddition product **3f** was obtained in 60% yield along with the Ritter reaction product 4f in 21% (Table 2, entry 5). This is presumably due to the steric hindrance in MCP 1f impairs the intermolecular [3+2] cycloaddition. Therefore, the reaction with ambient water proceeded to give the Ritter reaction product in higher yield. In other cases, the ring-opened products 4 were obtained as minor products (Table 2, entries 1-4 and 6).

For aliphatic MCP **1h**, we found that this reaction is sluggish and gives many unidentified products under the same conditions (Table 2, entry 7). Thus, one aromatic group for MCPs **1** is required for this novel reaction with nitriles to give a [3+2] cycloaddition product under mild conditions. Their structures were assigned on the basis of their ¹H NMR and ¹³C NMR spectroscopic data and HRMS or microanalyses and X-ray diffraction (Figure 1).⁶

Using benzonitrile (2b) as a substrate, we found that the reactions proceeded smoothly to give the corresponding [3+2] cycloaddition products 5 in higher yields under similar conditions.⁷ The results are summarized in Table 3. In most cases, products 5 were obtained in 85–96% yields and the ring-opened Ritter reaction products 6 were formed in traces (Table 3, entries 1-5). For MCP 1f having a substituent at the o-position of benzene ring, the [3+2] cycloaddition product was obtained in 42% yield as mixture of Z- and E-isomers along with the Ritter reaction product 6f in 56% yield (Table 3, entry 6). This is also presumably due to the steric hindrance in MCP 1f impairs the intermolecular [3+2] cycloaddition with 2b [2b is sterically more demanding (bulkier) than 2a]. Therefore, the reaction with ambient water proceeded to give the Ritter reaction product in higher yield (56%). For aliphatic MCP **1h**, we found that this reaction produced the [3+2] cycloaddition product 7 in 10% yield derived from the Ritter reaction of the [3+2] cycloaddition product **5h** (in trace) with **2b** along with many unidentified products (Scheme 3). Its structure was assigned on the basis of its ¹H NMR, ¹³C NMR, 2D NMR spectroscopic data and HRMS (see supporting information). For monosubstituted MCP 1i, this reaction gave complicated products under the same conditions (Scheme 3).

A plausible mechanism for this novel [3+2] cycloaddition reaction of MCPs **1** and Ritter reaction with nitriles is shown in Scheme 4. The MCP **1** is first positively charged (protonated by TfOH) to give intermediate **A** which reacts with nitrile to give intermediate **B** (electrophilically assisted nucleophilic ring opening).⁸ The subsequent

$\overset{R^1}{\searrow}\overset{R^2}{\bigvee}$	+ MeCN 2a	TfOH CH ₂ Cl ₂	R^1 + R^2 +	$R^1 \xrightarrow{O}_{u} NHCMe$ $R^2 4$
1			3	

			Yield (%) ^a	
Entry	R^{1}/R^{2}	Time (h)	3	4
1	p-ClC ₆ H ₄ / p -ClC ₆ H ₄ 1b	4	3b , 85	4b , 10
2	p-FC ₆ H ₄ / p -FC ₆ H ₄ 1c	4	3c , 75	4c , Trace
3	$p-\text{MeC}_6\text{H}_4/p-\text{MeC}_6\text{H}_4$ 1d	4	3d , 73	4d , Trace
4	p-MeOC ₆ H ₄ / p -MeOC ₆ H ₄ 1e	4	3e , 88	4e , Trace
5	<i>o</i> -ClC ₆ H ₄ /C ₆ H ₄ 1f	4	3f , 60 (14:1) ^b	4f , 21 (14:1) ^b
6	p-EtOC ₆ H ₄ /Me 1g	4	3g , 56 (3:1) ^b	_
7	Bu/Bu 1h	4	Complex mixture of products	

Table 2 The Reaction of MCPs 1 (1.0 equiv) with Acetonitrile 2a (2.0 mL) in Dichloromethane (1.0 mL) in the Presence of TfOH (1.0 equiv)

^a Isolated yields.

^b Mixtures of Z- and E-isomers (ratio = E/Z).

Table 3 The Reaction of MCPs 1 (1.0 equiv) with Benzonitrile (2b) in the Presence of TfOH (1.0 equiv)



			Yield (%) ^a	
Entry	R^1/R^2	Time (h)	5	6
1	C ₆ H ₅ 1a	4	5a , 87	6a , 5
2	p-ClC ₆ H ₄ / p -ClC ₆ H ₄ 1b	4	5b , 93	6b , Trace
3	<i>p</i> -FC ₆ H ₄ / <i>p</i> -FC ₆ H ₄ 1c	4	5c , 96	6c , Trace
4	p-MeC ₆ H ₄ / p -MeC ₆ H ₄ 1d	4	5d , 91	6d , Trace
5	p-MeOC ₆ H ₄ / p -MeOC ₆ H ₄ 1e	4	5e , 85	6e , Trace
6	<i>o</i> -ClC ₆ H ₄ /C ₆ H ₄ 1f	4	5f , 42 (2:1) ^b	6f , 56 (2:1) ^b
7	p-EtOC ₆ H ₄ /Me 1g	4	5g , 30 (4:1) ^b	-

^a Isolated yields.

^b Mixtures of Z- and E-isomers (ratio = E/Z)



Figure 1 The ORTEP plot of 3a



Scheme 3 The reaction of MCP 1h with 2b in the presence of TfOH

intramolecular electrophilic attack produces intermediate C which gives [3+2] cycloaddition product via deprotonation after workup. The intermediate **B** reacts with ambient water to give the ring-opened Ritter reaction product (Scheme 4). It appears that an stabilized cyclopropyl-



Scheme 4 Proposed mechanism of the reaction of MCPs 1 with nitriles mediated by TfOH

methyl carbocation is required here. Therefore, two substituents with one aromatic group is at least required to stabilize intermediate **A** for this type of reaction.

In conclusion, we disclosed an unknown transformation of MCPs **1** with nitriles in the presence of the Brønsted acid TfOH in this paper. In this type of transformation of MCPs **1**, the novel [3+2] cycloaddition products **3** and **5** can be obtained in good to excellent yields depending on the substituents in MCPs **1**.⁹ Efforts are underway to elucidate the mechanistic details and subsequent transformation thereof.

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- (5) This is because some MCPs 1 such as MCPs 1b and 1c are not very soluble in MeCN and the co-solvent CH_2Cl_2 is therefore required.
- (6) The crystal data of **3a** has been deposited in CCDC with number 219397. Empirical Formula: $C_{18}H_{17}N$; formula weight: 247.33; crystal color, habit: colorless, prismatic; crystal dimensions: $0.433 \times 0.357 \times 0.258$ mm; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 23.589 (3)Å, b = 7.8691 (11)Å, c = 18.498 (3)Å, $a = 90^{\circ}$, $\beta = 127.366$ (2)°, $\gamma = 90^{\circ}$, V = 2729.0(6)Å³; space group: C2/c; Z = 8; $D_{calc} = 1.204$ g/cm³; $F_{000} = 1056$; diffractometer: Rigaku AFC7R; residuals: *R*, *Rw*: 0.0432, 0.0784.
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