JOC Article

Reactions of Monoaryl-Substituted Methylenecyclobutanes and Methylenecyclopropanes with 1-Hydroxybenzotriazole (HOBt), 1-Hydroxy-7-azabenzotriazole (HOAt), and 1-Hydroxysuccinimide (HOSu)

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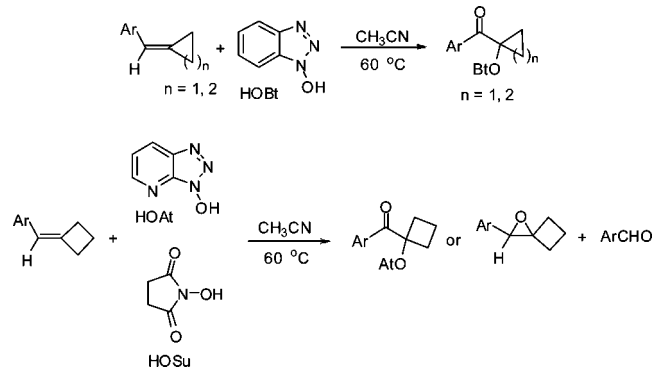

Monoaryl-substituted methylenecyclobutanes (MCBs) and methylenecyclopropanes (MCPs) react with 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), and 1-hydroxysuccinimide (HOSu) smoothly to produce the corresponding cyclobutylmethanone and cyclopropylmethanone derivatives **2**, **4**, and **5** via a cascade epoxidation and nucleophilic addition process or the corresponding epoxides **6** in moderate to good yields under mild conditions. A plausible mechanism has been proposed on the basis of the control experiments and the isolation of the reaction intermediates.

Introduction

The *N*-hydroxy-containing compounds, such as 1-hydroxybenzotriazole (HOBt·H_2O), 1-hydroxy-7-azabenzotriazole (HOAt), and 1-hydroxysuccinimide (HOSu), are widely used as activating reagents in combination with *N*,*N*′-dicyclohexylcarbodiimide (DCC) or *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC, WSC) for the construction of an amide bond during the synthesis of peptide[1] and β-lactam antibiotics.[2] Moreover, activated esters by these *N*-hydroxy-containing compounds have also been employed in the formation of a C(O)−C bond during the preparation of the antibiotic malonomicin.[3] It should be noted that, in the above cases, HOBt, HOAt, and HOSu acted as nucleophiles for the transformation. On the other hand, besides being the efficient coupling reagents in the peptide synthesis, acylated HOBt compound can also undergo an intramolecular rearrangement to produce the corresponding N-acylated benzotriazole oxide. For example, in 1985, Rinehart reported the rearrangement of the unsaturated acyl benzotriazole **A** to **B** in good yield in the presence of potassium carbonate in acetone (Scheme 1).[4,5] It is conceivable that species **B** could act as an oxidation reagent just like 4-methylmorpholine *N*-oxide (NMO) as co-oxidant in Sharpless asymmetric dihydroxylation for a

(1) (a) Konig, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788–798. (b) Castro, B.; Domoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, 1219–1222. (c) Meldal, M. *Acta Chem. Scand., Ser. B* **1986**, *B40*, 242–249.

(2) (a) Singh, J.; Przybyla, C.; Kissick, T. P.; Denzel, T.; Mueller, R. H.; Moniot, J. L.; Cimarusti, C. M. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, ORGN 243. (b) Blumbach, J.; Duerckheimer, W.; Reden, J.; Seliger, H. German Patent 2758000, 1977. (c) Wheeler, W. J.; Finley, D. R.; Ott, J. L. *J. Antibiot.* **1986**, *39*, 1611–1614.

(3) Van der Baan, J. L.; Barnick, J. W. F. K.; Bickelhaupt, F. *Tetrahedron* **1978**, *34*, 223–231.

(4) Nagarajan, S.; Wilson, S. R.; Rinehart, K. L. *J. Org. Chem.* **1985**, *50*, 2174–2178.

(5) For reviews on HOBt: (a) Chan, L. C.; Cox, B. G. *J. Org. Chem.* **2007**, *72*, 8863–8869. (b) Bright, R.; Dale, D. J.; Dunn, P. J.; Hussain, F.; Kang, Y.; Mason, C.; Mitchell, J. C.; Snowden, M. J. *Org. Process Res. Dev.* **2004**, *8*, 1054–1058.

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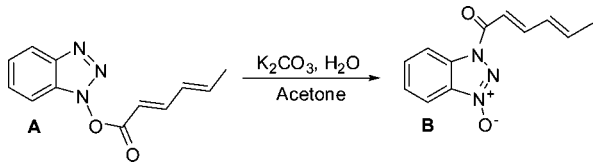
SCHEME 1. Rearrangement of A to B



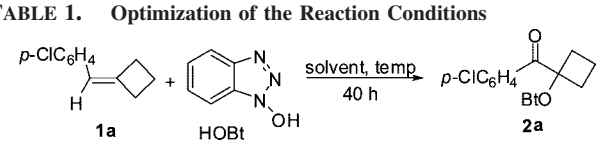
cascade transformation. Therefore, it is interesting to find a substrate which can react with HOBt, HOAt, and HOSu smoothly to give the corresponding cascade nucleophilic addition and oxidation product in good yield.

Methylenecyclobutanes (MCBs) and methylenecyclopropanes (MCPs) are both highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[6] MCBs and MCPs undergo a variety of ring-opening reactions in the presence of transition metal or Lewis acid because the relief of ring strain provides a potent thermodynamic driving force.[7,8] For example, recently, we have found that the ring-opening reactions of MCPs **1** with alcohols and other nucleophiles catalyzed by Lewis acids [Ln(OTf)$_3$] took place smoothly to give the corresponding homoallylic ring-opened products in good yields under mild conditions.[7j,k] These results stimulated us to investigate the reaction outcomes of MCBs and MCPs with HOBt, HOAt, and HOSu under similar conditions. In this paper, we wish to report the reaction of monoaryl-substituted methylenecyclobutanes (MCBs) and methylenecyclopropanes (MCPs) with *N*-hydroxy-containing compounds such as HOBt, HOAt, and HOSu to form the corresponding cyclobutylmethanone and cyclopropylmethanone derivatives via a cascade epoxidation and nucleophilic addition process as well as the corresponding epoxides in moderate to good yields at 60 °C in acetonitrile.

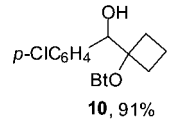
Results and Discussion

Initial examinations using *p*-chlorophenylmethylenecyclobutane **1a** as the substrate to react with HOBt in a variety of solvents were aimed at determining the resulting products as well as the optimal reaction conditions, and the results of these experiments are summarized in Table 1. It was found that using **1a** (1.0 equiv) with HOBt (1.0 equiv) in 1,2-dichloroethane (DCE) at 60 °C afforded cyclobutylmethanone derivative **2a** in 34% yield along with a trace of 4-chlorobenzaldehyde after 40 h under ambient atmosphere (Table 1, entry 1). When the ratio

TABLE 1. Optimization of the Reaction Conditions

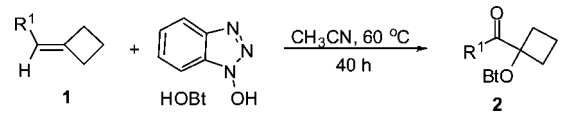


entry[a]	**1a**/HOBt	solvent	temp (°C)	yield (%)[b] **2a**
1	1/1	DCE	60	34
2	1/2	DCE	60	72
3	1/3	DCE	60	73
4	1/2	DCE	80	71
5	1/2	DCE	40	trace
6	1/2	CH_2Cl_2	60	trace
7	1/2	THF	60	trace
8	***1/2***	***CH_3CN***	***60***	***82***
9	1/2	Et_2O	30	NR
10	1/2	toluene	60	65



[a] Reaction conditions: **1a** (0.2 mmol), HOBt (*x* mmol), solvent (2 0.0 mL), and the reactions were carried out at various temperatures. [b] Isolated yields.

TABLE 2. Scope and Limitations of the Reaction of MCBs 1 with HOBt



entry[a]	MCBs (R^1)	yield (%)[b] of **2**
1	**1b** (*p*-BrC_6H_4)	**2b**, 81
2	**1c** (*m*-BrC_6H_4)	**2c**, 79
3	**1d** (*m*-ClC_6H_4)	**2d**, 76
4	**1e** (*p*-FC_6H_4)	**2e**, 78
5	**1f** (C_6H_5)	**2f**, 7 9
6	**1g** (*p*-MeC_6 H_4)	**2g**, 76
7	**1h** (*m*-MeC_6 H_4)	**2h**, 73
8	**1i** (*p*-EtC_6H_4)	**2i**, 7 8
9	**1j** (*o*-ClC_6H_4)	**2j**, 62
10	**1k** (*o*,*m*-$Cl_2C_6H_3$)	**2k**, 60
11	**1l** (C_4H_9)	**2l**, −

[a] Reaction conditions: **1a** (0.2 mmol), HOBt (0.4 mmol), CH_3 CN (2 0.0 mL), and the reactions were carried out at 60 °C for 40 h. [b] Isolated yields.

of **1a**/HOBt changed to 1/2, **2a** was obtained in 72% yield under identical conditions (Table 1, entry 2). Increasing the employed amounts of HOBt to 3 equiv or raising the reaction temperature to 80 °C did not significantly change the reaction outcomes (Table 1, entries 3 and 4). When the reaction was carried out at 40 °C, a trace of **2a** was obtained and the compound **10** was produced as the major product in 91% yield (Table 1, entry 5). Further examination of the solvent effects revealed that acetonitrile (CH_3CN) is the best one for this transformation, affording **2a** in 82% yield within 40 h (Table 1, entries 6−10). It should be also noted that HOBt is completely soluble in acetonitrile. Therefore, the best conditions are to carry out the reaction in CH_3CN at 60 °C for 40 h using 1.0 equiv of **1a** and 2.0 equiv of HOBt as the substrates.

With these optimal conditions in hand, we next carried out this reaction using a variety of MCBs **1** with HOBt, and the reaction outcomes are outlined in Table 2. We found that the corresponding products **2** were obtained in moderate to good yields within 40 h for a variety of MCBs **1** with electron-

(6) (a) Binger, P.; Wedemann, P.; Kozhushkov, S. I.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 113–119. (b) de Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, 3809–3822. (c) Molchanov, A. P.; Diev, V. V.; Magull, J.; Vidovic, D.; Kozhushkov, S. I.; de Meijere, A.; Kostikov, R. R. *Eur. J. Org. Chem.* **2005**, 593–599. (d) de Meijere, A.; Becker, H.; Stolle, A.; Kozhushkov, S. I.; Bes, M. T.; Salaün, J.; Noltemeyer, M. *Chem.—Eur. J.* **2005**, *11*, 2471–2482.

(7) For recent reviews on MCPs, see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1270. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867–877. (d) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019–8024. (e) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Green Chem.* **2003**, *5*, 85–88. (f) Shi, M.; Chen, Y. *J. Fluorine Chem.* **2003**, *122*, 219–227. (g) Chen, Y.; Shi, M. *J. Org. Chem.* **2004**, *69*, 426–431. (h) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298–1300. (i) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203–6205. (j) Shi, M.; Xu, B. *Org. Lett.* **2002**, *4*, 2145–2148. (k) Shi, M.; Chen, Y.; Xu, B.; Tang, J. *Tetrahedron Lett.* **2002**, *43*, 8019–8024. (l) Shi, M.; Jiang, M.; Liu, L.-P. *Org. Biomol. Chem.* **2007**, *5*, 438–440.

(8) For references on MCBs, see: (a) Graham, S. H.; William, A. J. S. *J. Chem. Soc.* **1959**, 4066–4072. (b) Farcasiu, D.; Schleyer, P. V. R.; Ledlie, D. *J. Org. Chem.* **1973**, *38*, 3455–3459. (c) Shen, Y. M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2002**, *45*, 1429–1432. (d) Jiang, M.; Liu, L.-P.; Shi, M. *Tetrahedron* **2007**, *63*, 9599–9604. (e) Jiang, M.; Shi, M. *Org. Lett.* **2008**, *10*, 2239–2242. (f) Jiang, M.; Shi, M. *Tetrahedron* **2009**, *65*, 798–801.

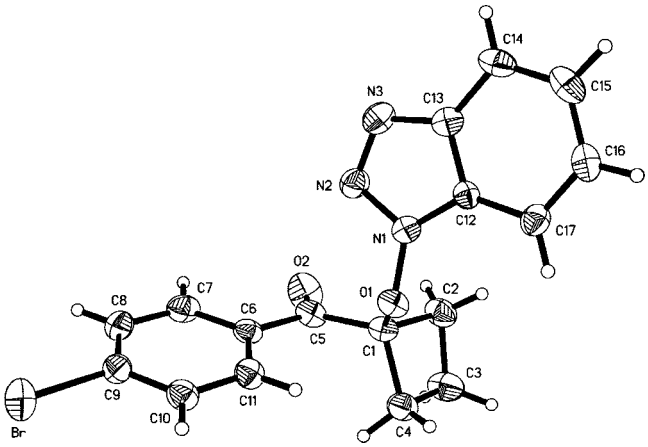


FIGURE 1. ORTEP drawing of **2b**.

donating, electron-neutral, and electron-withdrawing substituents on the benzene ring under ambient atmosphere. The substituents on the aromatic ring of MCBs **1** did not have significant influence on the reaction outcomes. As can be seen from Table 2, in the presence of an electron-poor or electron-rich substituent at the *para* or *meta* position of benzene ring, the corresponding products **2b**−**2i** were afforded in 73−81% yields (Table 2, entries 1−8). However, as for MCBs **1j** and **1k** with the substituents at the *ortho* position of benzene ring, the corresponding products **2j** and **2k** were obtained in lower yields (62 and 60%), presumably due to the steric effect (Table 2, entries 9 and 10). Using aliphatic MCB **1l** as the substrate, the reaction became disordered to give the complex product mixtures, suggesting that an aromatic group is required in this transformation (Table 2, entry 11).

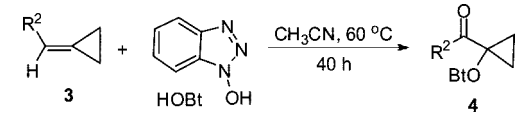
Their structures were determined by ^{1}H and ^{13}C NMR spectroscopic data, HRMS, and microanalyses (see the Supporting Information). Furthermore, the X-ray crystal structure of **2b** was determined, and its CIF data are presented in the Supporting Information (Figure 1).[9]

Using MCPs **3** instead of MCBs **1** as the substrates, we found that these reactions also proceeded smoothly to give the corresponding cyclopropylmethanone derivatives **4a**−**4f** in 76−81% yields whether they have electron-poor or electron-rich aromatic rings (Table 3, entries 1−6). Their structures were also determined by ^{1}H and ^{13}C NMR spectroscopic data, HRMS, and microanalyses (see the Supporting Information).

Furthermore, under these optimal conditions, we investigated the reaction of a variety of MCBs **1** with the other *N*-hydroxy-containing compounds such as HOAt and HOSu and found that, as for MCBs **1** bearing electron-poor substituents on the benzene ring, the epoxides **6** were obtained along with the corresponding arylaldehydes **7** in overall 75−81% yields rather than the expected cyclobutylmethanone products under the standard conditions (Table 4, entries 1−4 and 8−11). The epoxides **6** and arylaldehydes **7** might be derived from the oxidation of **1** with HOAt or HOSu upon heating at 60 °C.[10] As for the reaction of MCBs **1f**, **1g**, and **1i** bearing neutral or electron-rich aromatic ring with HOAt, the expected cyclobutylmethanone products **5** were isolated in 51−62% yields exclusively (Table 4, entries 5−7). However, in the reaction of MCBs **1f**, **1g**, and **1i** with HOSu, complicated product mixtures were produced under identical conditions, and the results were not shown in Table 4.

The MCBs **1** having a hydrogen atom are essential in this transformation because no reactions occurred if using MCBs **8a** (R^3 = C_6H_5) and **8b** (R^3 = Me) as the substrates to react with HOBt, HOAt, and HOSu under the standard conditions (Table 5, entries 1−3). Moreover, as for the reactions of MCPs **8c** and **8d** with HOBt, the ring-opening product **9a** and the alcohol **9b** were obtained in 82 and 74% yield, respectively (Table 5, entries 4 and 7), although no reactions occurred with HOAt and HOSu under the standard conditions (Table 5, entries 5−6 and 8−9). Using aliphatic MCPs **8e** and **8f** as the substrates to react with HOBt, complex product mixtures were formed, indicating again that one aromatic group is required in this transformation (Table 5, entries 10 and 11). Furthermore, the reactions of monoaryl-substituted methylenecyclopentane **8g** with HOBt, HOAt, and HOSu produced the complex product mixtures under the standard conditions (Table 5, entries 12−14). Using 2,2-dimethyl-1-phenylethene **8h** as the substrate to react with HOBt produced the compound **9c** in 24% yield. However,

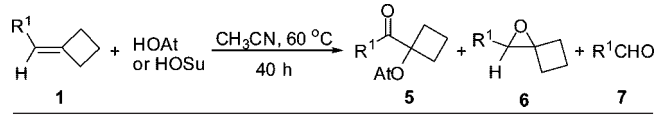
TABLE 3. Scope and Limitations of the Reaction of MCPs 3 with HOBt



entry[a]	MCBs (R^2)	yield (%)[b] of **4**
1	**3a** (p-ClC_6H_4)	**4a**, 81
2	**3b** (p-BrC_6H_4)	**4b**, 79
3	**3c** (o-ClC_6H_4)	**4c**, 76
4	**3d** (m-FC_6H_4)	**4d**, 78
5	**3e** (C_6H_5)	**4e**, 79
6	**3f** (p-EtC_6H_4)	**4f**, 76

[a] Reaction conditions: **3** (0.2 mmol), HOBt (0.4 mmol), CH_3 CN (2.0 mL), and the reactions were carried out at 60 °C for 40 h. [b] Isolated yields.

TABLE 4. Scope and Limitations of the Reaction of MCBs 1 with HOAt and HOSu



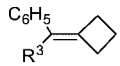
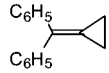
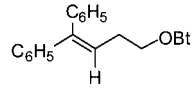
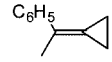
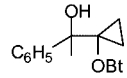
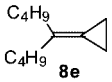
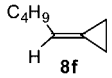
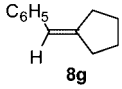
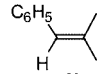
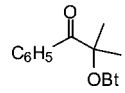
entry[a]	MCBs (R^1)	*N*-hydroxy-containing compound	yield (%)[b] of **5**	yield (%)[b] of **6** + **7** (**6**:**7**)[c]
1	**1a** (p-ClC_6H_4)	HOAt	−	80 (1.00:1.20)
2	**1b** (p-BrC_6H_4)		−	76 (1.00:1.21)
3	**1c** (m-BrC_6H_4)		−	77 (1.00:1.24)
4	**1d** (m-ClC_6H_4)		−	75 (1.00:1.12)
5	**1f** (C_6H_5)		**5a**, 52	−
6	**1g** (p-MeC_6H_4)		**5b**, 62	−
7	**1i** (p-EtC_6H_4)		**5c**, 51	−
8	**1a** (p-ClC_6H_4)	HOSu	−	75 (1.00:1.18)
9	**1b** (p-BrC_6H_4)		−	76 (1.00:1.25)
10	**1c** (m-BrC_6H_4)		−	81 (1.00:1.16)
11	**1d** (m-ClC_6H_4)		−	76 (1.00:1.21)

[a] Reaction conditions: **1** (0.2 mmol), *N*-hydroxy compound (0.4 mmol), CH_3CN (2 0.0 mL), and the reactions were carried out at 60 °C. [b] Isolated yields. [c] The mixtures of **6** and **7** cannot be separated by silica gel column chromatography, and the ratios of **6** and **7** were determined by ^{1}H NMR spectroscopic data.

(9) The crystal data of **2b** have been deposited in CCDC with number 668263. Empirical formula: $C_{17}H_{14}BrN_3O_2$; formula weight: 372.22; crystal color, habit: colorless, prismatic; crystal dimensions: 0.256 × 0.113 × 0.079 mm; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 5.8939(10) Å, b = 10.3365(18) Å, c = 26.251(5) Å, α = 90°, β = 90.417(4)°, γ = 90°, V = 1599.2(5) Å^3; space group: $P2(1)/c$; Z = 4; D_{calcd} = 1.546 g/cm^3; F_{000} = 752; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0527, 0.1172.

TABLE 5. Scope and Limitations of this Reaction

8 + N-hydroxy compound $\xrightarrow[40\ h]{CH_3CN,\ 60\ ^oC}$ **9**

entry[a]	8	N-hydroxy containing compound	product, 9
1		HOBt	NR
2		HOAt	NR
3	**8a**, $R^3 = C_6H_5$; **8b**, R^3 = Me	HOSu	NR
4		HOBt	**9a**, 82% 
5		HOAt	NR
6	**8c**	HOSu	NR
7		HOBt	**9b**, 74% 
8		HOAt	NR
9	**8d**	HOSu	NR
10	 **8e**	HOBt	complex
11	 **8f**	HOBt	complex
12		HOBt	complex
13		HOAt	complex
14	**8g**	HOSu	complex
15		HOBt	**9c**, 24% 
16		HOAt	complex
17	**8h**	HOSu	complex

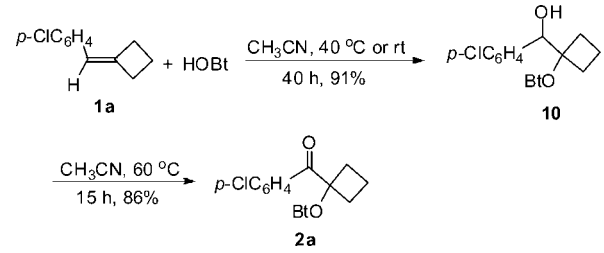
[a] Reaction conditions: **8** (0.2 mmol), HOBt (0.4 mmol), solvent (2.0 mL), and the reactions were carried out at 60 °C for 40 h. [b] Isolated yields.

using HOAt and HOSu instead of HOBt, the reactions became disordered to produce the complex product mixtures (Table 5, entries 15−17). These results suggest that monoaryl-substituted MCBs and MCPs are the suitable substrates in this transformation to produce the corresponding cyclobutylmethanone and cyclopropylmethanone derivatives in moderate to good yields.

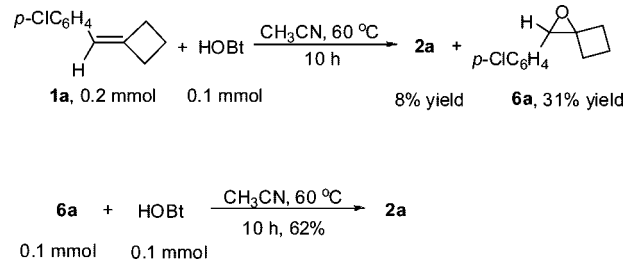
To confirm the reaction pathway, we attempted to determine the intermediates in this reaction. During the examination of the optimal conditions, we found that when the reaction was carried out at 40 °C the alcohol **10** was obtained in 91% yield along with the trace of product **2a** (Table 1, entry 5). Interestingly, if alcohol **10** was heated to 60 °C in CH_3CN without any reagent, **2a** was produced in 86% yield, suggesting that alcohol **10** is the reaction intermediate (Scheme 2).

To clarify the mechanism of this reaction, two control experiments were carried out as shown in Scheme 3. First, using 0.5 equiv of HOBt to react with MCB **1a** (1.0 equiv) and quenching the reaction after 10 h, we found that the product **2a** was formed in 8% yield along with the epoxide **6a** in 31% yield and the trace of arylaldehyde (Scheme 3). Second, the isolated epoxide **6a** was further used to react with 1.0 equiv of HOBt at 60 °C in CH_3CN. It was found that **2a** was obtained in 62% yield after 40 h, indicating that **2a** is derived from the reaction of epoxide **6a** with HOBt (Scheme 3). It is noteworthy that benzotriazole (**11**) was isolated from the reaction mixture in

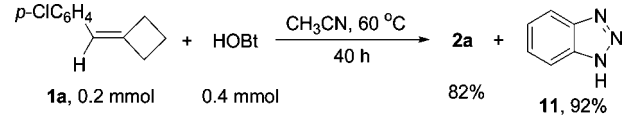
SCHEME 2. Reation Pathway



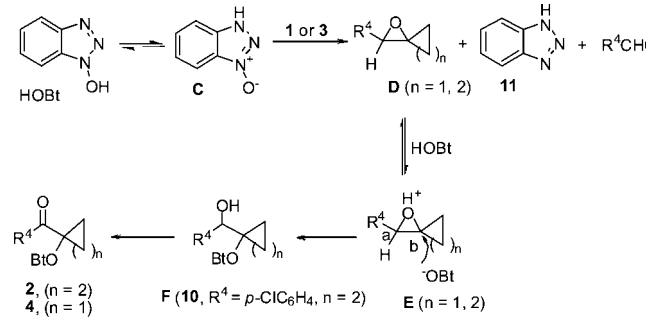
SCHEME 3. Control Experiments



SCHEME 4. Determination of the Other Product



SCHEME 5. Proposed Mechanism for the Reaction of MCBs 1 and MCPs 3 with HOBt



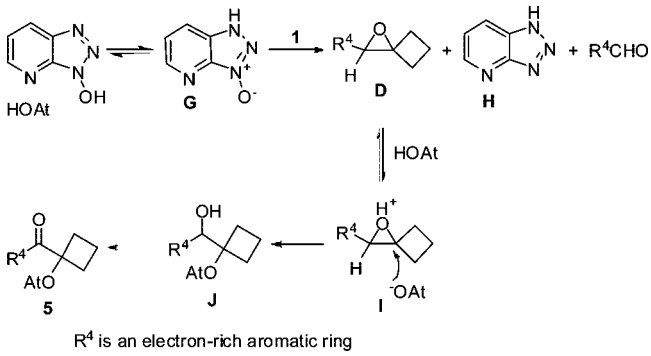
92% yield along with **2a** in 82% yield under the standard conditions, and its ^{1}H NMR spectroscopic data are identical with the authentic sample (Scheme 4 and see the Supporting Information).

On the basis of above control experiments and the isolation of the reaction intermediates, a plausible mechanism for the formation of products **2**, **4**, **5** and **6** is outlined in Schemes 5 and 6, respectively. In Scheme 5, HOBt generates intermediate **C** as mentioned in the Introduction,[4] which acts as an oxidant like as *N*-methylmorpholine oxide (NMO)[11] to oxidize substrate **1** or **3** to give the epoxide **D** along with the compound **11**. The arylaldehyde is derived from the decomposition of epoxide **D** during the reaction. Then, the epoxide is activated by the protonation of another molecule of HOBt[12] to give intermediate

(10) (a) Sawaki, Y.; Ogata, Y. *J. Am. Chem. Soc.* **1981**, *103*, 2049–2053. (b) Rigaudy, J.; Scribe, P.; Breliere, C. *Tetrahedron* **1981**, *37*, 2585–2593. (c) Zieger, H. E.; Tsang, C. H.; Malik, M.; Todaro, L. J. *Tetrahedron Lett.* **2002**, *43*, 4845–4848. (d) Hayashi, Y.; Takeda, M.; Miyamoto, Y.; Shoji, M. *Chem. Lett.* **2002**, 414–415.

(11) (a) Katarina, B.; Joeri, J. N.; Backvall, J. E. *J. Org. Chem.* **1999**, *64*, 2545–2548. (b) Hou, Y. X.; Tulevski, G. S.; Valint, P. L. *Macromolecules* **2002**, *35*, 5953–5962.

SCHEME 6. Proposed Mechanism for the Reaction of MCBs 1 with HOAt



E,[8d] which undergoes counteranion ($^-$OBt) attack at the position b to provide the alcohol **F** (compound **10** in Scheme 2). The alcohol can be transformed to the product **2** or **4** upon heating at 60 °C.

Moreover, HOAt can also produce intermediate **G**,[4] which can oxidize MCB **1** to give the corresponding epoxide **D** along with compound **H** similarly. Since the counteranion AtO^- do not have the strong nucleophilicity as that of BtO^- due to the electron-withdrawing 2-pyridyl group and the protonation can also take place at the pyridine ring, the counteranion AtO^- can only attack at the epoxide **I** having an electron-rich or a neutral aromatic ring to form the product **5**[8d,12] through intermediate **J**. However, as for the epoxide **D** having an electron-poor aromatic ring, the protonated epoxide **I** is not stable enough to undergo the nucleophilic attack by $^-$OAt. Therefore, in this case, epoxide **D** can be isolated as the product.

In summary, we have developed a novel reaction of monoaryl-substituted methylenecyclobutanes and methylenecyclopropanes with *N*-hydroxy-containing compounds such as HOBt, HOAt, and HOSu to produce cyclobutylmethanone and cyclopropylmethanone derivatives **2**, **4**, and **5** via a cascade epoxidation and nucleophilic addition process as well as the corresponding epoxides **6** in moderate to good yields under mild conditions. A plausible mechanism has been proposed on the basis of control experiments and the isolation of the reaction intermediates. Clarification of the reaction mechanism and further application of this transformation are in progress.

(12) (a) Stevens, C. L.; Coffield, T. H. *J. Am. Chem. Soc.* **1958**, *80*, 1919–1922. (b) Calvin, L.; Stevens, J. T. *J. Am. Chem. Soc.* **1954**, *76*, 715–717. (c) Wuts, P. G. M.; Ashford, S. W.; Anderson, A. M.; Atkins, J. R. *Org. Lett.* **2003**, *5*, 1483–1485.

Experimental Section

General Procedure for the Reactions. Under an argon atmosphere, methylenecyclobutanes (MCBs **1** or MCPs **3**) (0.2 mmol) and HOBt·H_2O (HOAt or HOSu) (0.4 mmol) were added into a Schlenk tube. After 2.0 mL of dry CH_3CN was added rapidly into the tube via a syringe, the reaction mixture was stirred at 60 °C for 40 h. Then, the solvent was removed under reduced pressure, and the residue was purified by a flash column chromatography (SiO_2) to give the corresponding product **2**, **4**, **5**, or **6** in moderate yields.

Compound 2a: A colorless oil; IR (CH_2Cl_2) ν 2986, 2957, 1686, 1588, 1488, 1402, 1217, 1090, 966, 843, 781, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 1.75−1.88 (1H, m, CH_2), 1.98−2.10 (1H, m, CH_2), 2.62−2.73 (2H, m, CH_2), 2.76−2.85 (2H, m, CH_2), 7.33−7.38 (2H, m, ArH), 7.45 (1H, d, J = 8.1 Hz, ArH), 7.51 (2H, d, J = 8.4 Hz, ArH), 7.98 (1H, d, J = 8.1 Hz, ArH), 8.18 (2H, d, J = 8.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 12.8, 29.7, 94.0, 108.6, 120.3, 124.7, 128.4, 128.6, 129.0, 131.5, 131.6, 140.0, 142.9, 193.3; MS (EI) *m*/*z* (%) 327 (7.93) [M$^+$], 201 (13.96), 193 (27.47), 166 (7.43), 139 (100.00), 111 (30.54), 91 (6.7), 75 (9.08); HRMS (EI) calcd for $C_{17}H_{14}N_3O_2Cl$ (M$^+$) requires 327.0775, found 327.0775.

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Supporting Information Available: Spectroscopic data (^{1}H, ^{13}C spectroscopic data), HRMS of the compounds shown in Tables 1−4, the X-ray crystal structure of compound **2b** along with the detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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