

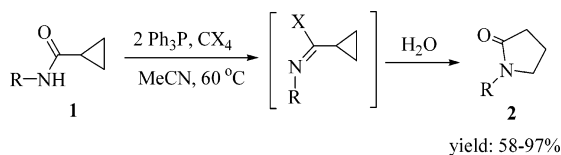
## Ring-Expanding Reaction of Cyclopropyl Amides with Triphenylphosphine and Carbon Tetrahalide

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R could be aryl groups and aliphatic groups, X = Cl, Br.

We succeeded in activating cyclopropyl amides (monoactivated cyclopropane) through the corresponding imidoyl halides prepared in situ in the presence of 2 equiv of  $\text{PPh}_3$  and 1 equiv of  $\text{CX}_4$ , and the ring-expanding products (*N*-substituted pyrrolidin-2-ones) were obtained in good yields. The reaction mechanism was investigated on the basis of oxygen-18 tracer experiment.

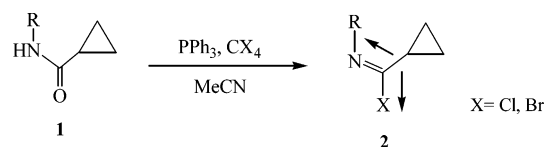
Cyclopropane derivatives as versatile building blocks have been more than laboratory curiosities for quite some time.<sup>1</sup> To activate strained three-membered ring, electron-donating or -accepting substituents are generally involved in their reactions to make polar processes more favorable. However, cyclopropane-involved synthetically useful reactions frequently contain two activating groups.<sup>2</sup> The ring-opening reactions of monoactivated cyclopropane derivatives are in general sluggish due to their low reactivities. So far, several examples have been reported under severe conditions either treated with stronger nucleophiles such as  $\text{I}^-$ <sup>3</sup> and stronger Lewis acids such as  $\text{TiCl}_4$ <sup>4</sup> or assisted by the  $\beta$ -effect of the silicon atom of trimethylsilyl group.<sup>5</sup> Therefore, it is necessary to develop a method for the ring-opening reaction of simple monoactivated cyclopropane derivatives under mild conditions.

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### SCHEME 1



Triphenylphosphine with carbon tetrachloride or carbon tetrabromide has been found widespread use as a reagent for the conversion of alcohols, acids, and amide derivatives into the corresponding halides, nitriles, and carbo imide derivatives.<sup>6</sup> Ziehn and co-workers also described the preparation of imidoyl halides (chlorides and bromides) through simultaneous treatment of the monosubstituted amides with triphenylphosphine and carbon tetrahalide ( $\text{CX}_4$ , X = Cl and Br) in acetonitrile.<sup>7</sup> On the basis of this result, we suppose that if cyclopropyl amides **1** can be converted into the corresponding imido-oxirane derivatives **2**, their reactivities would be increased because there exist two electron-withdrawing groups in their structures ( $\text{C}=\text{N}$  and  $\text{C}-\text{X}$ ) (Scheme 1).

To determine whether this speculation is possible, we attempted the reaction of cyclopropyl amides **1** with  $\text{PPh}_3/\text{CX}_4$  under similar conditions.

As an initial examination, we found that the reaction of *N*-phenylcyclopropylamide **1a** with 2 equiv of  $\text{Ph}_3\text{P}$  and 1 equiv of  $\text{CCl}_4$  produced the *N*-phenylpyrrolidin-2-one **3a** in 62% yield under reflux for 3 days in acetonitrile (Table SI-1, Supporting Information, entry 1). When we utilized  $\text{CBr}_4$  instead of  $\text{CCl}_4$ , this reaction proceeded smoothly at 60 °C under similar conditions to give **3a** in 97% yield after 3 h. After optimization of the reaction conditions (Table SI-1, Supporting Information), we found that 2 equiv of  $\text{Ph}_3\text{P}$  and 1 equiv of  $\text{CBr}_4$  are required in this reaction to give **3a** in good yield and acetonitrile is the best solvent, which is similar to those of other reaction systems using triphenylphosphine and carbon tetrahalide as reagents.<sup>6,8</sup> It should be emphasized here that we also attempted to activate cyclopropylamide **1a** with  $\text{PCl}_5$ <sup>9</sup> and  $\text{POCl}_3$ , respectively,<sup>10</sup> typical Vilsmeier-Haack reaction conditions, but the desired product **3a** was not formed. At the present stage, we only found that the reagent of  $\text{PPh}_3/\text{CBr}_4$  can effectively promote this ring-expanding reaction.

It is well-known that lactam rings are important structures in a number of biologically and pharmaceuti-

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**TABLE 1.** Reaction of Various *N*-Substituted Cyclopropyl Amides with PPh<sub>3</sub> and CBr<sub>4</sub> in Acetonitrile

entry	R <sup>1</sup>	R <sup>2</sup>	temp. (°C)	time	yield/[%] <sup>a</sup> 3
1	<b>1a</b> , C <sub>6</sub> H <sub>5</sub>	H	60	3 h	<b>3a</b> , 97
2	<b>1b</b> , <i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	H	60	3 h	<b>3b</b> , 83
3	<b>1c</b> , <i>m</i> , <i>m</i> -(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	60	3 h	<b>3c</b> , 75 <sup>b</sup>
4	<b>1d</b> , <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	60	3 h	<b>3d</b> , 68
5	<b>1e</b> , <i>m</i> -FC <sub>6</sub> H <sub>4</sub>	H	reflux	5 h	<b>3e</b> , 93
6	<b>1f</b> , <i>o</i> -Me- <i>p</i> -ClC <sub>6</sub> H <sub>3</sub>	H	60	10 h	<b>3f</b> , 86
7	<b>1g</b> ,	H	60	10 h	<b>3g</b> , 75
8	<b>1h</b> , naphthalen-1-yl	H	60	10 h	<b>3h</b> , 71 <sup>c</sup>
9	<b>1i</b> , cyclohexyl	H	60	10 h	<b>3i</b> , 58
10	<b>1j</b> , benzyl	H	60	10 h	<b>3j</b> , 91
11	<b>1k</b> , <i>m</i> , <i>m</i> -(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Ph	60	24 h	<b>3k</b> , 26

<sup>a</sup> Isolated yields. <sup>b</sup> The structure was determined by X-ray diffraction (see the Supporting Information). <sup>c</sup> The yield was determined by <sup>1</sup>H NMR spectroscopic data.

cally active compounds as well as some alkaloids such as cotinine or manno lactam.<sup>11</sup> Among these lactam compounds, pyrrolidinones are often found in a variety of pharmacologically active compounds, for example, convulstamides,<sup>12</sup> enzyme inhibitors,<sup>13</sup> and various drugs.<sup>14</sup> Therefore, to extend the scope of this interesting ring-expanding reaction, we next carried out the reactions of a variety of *N*-substituted cyclopropylamides **1** in the presence of PPh<sub>3</sub>/CBr<sub>4</sub> under the optimized reaction conditions. In all of the cases we examined, the corresponding ring-expanding products (*N*-substituted pyrrolidin-2-ones) **3** were exclusively formed in 58–97% yields. The results are summarized in Table 1. For both aromatic cyclopropylamides and aliphatic cyclopropylamides, the reactions proceeded smoothly to give the desired products **3** in good to high yields. More importantly, for sterically hindered ortho-substituted cyclopropyl amide **1f**, this reaction also proceeded smoothly to give the corresponding pyrrolidin-2-one product **3f** in 86% yield (Table 1, entry 6). For cyclopropyl amide **1k** (R<sup>2</sup> = phenyl group), the reaction became sluggish and the corresponding ring-expanding product **3k** was only obtained in 26% yield even if the reaction time was prolonged to 1 day, and in the meantime, decomposition of starting material was also observed (Table 1, entry 11). It should be noted that the ester group is tolerable under the reaction conditions

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(Table 1, entry 7). Moreover, these reactions can be carried out under ambient atmosphere.

Interestingly, when *N,N'*-bis(cyclopropylcarbonyl)benzidine **4** was utilized as a substrate, the corresponding ring-expanding product **5** can also be obtained in 86% yield (Scheme 2). However, when *N,N'*-bis(cyclopropylcarbonyl)[1,1']binaphthalenyl-2,2'-diamine **6** (racemate) was employed as a substrate, the ring-opened product **7** was exclusively obtained. We believe that the significant steric hindrance in this substrate hampered the ring-expanding reaction. Moreover, this result mechanistically suggests that the ring-opened product, 4-bromobutyramide, may be a key intermediate in this reaction.

Therefore, to clarify the mechanism of this reaction, we treated 4-bromo-*N*-phenylbutyramide **8** under the same conditions with PPh<sub>3</sub> and CBr<sub>4</sub> at 60 °C in acetonitrile and found that the corresponding pyrrolidin-2-one **3a**, as expected, was formed in 94% yield after 10 h (Scheme 3). On the other hand, the control experiments showed that treatment of **1a** with base such as NaOEt, Brønsted acid such as hydrobromic acid (HBr), or Lewis acid TiX<sub>4</sub> containing halogen ions (X = Cl or Br) did not promote this reaction under similar conditions. These results again indicated that the combination of PPh<sub>3</sub> and CBr<sub>4</sub> is the only useful reagents for this reaction.

To further clarify the mechanism of this reaction, we carried out the reaction of **1a** with PPh<sub>3</sub>/CBr<sub>4</sub> in the presence of <sup>18</sup>O<sub>2</sub>.<sup>15</sup> As a result, we found that **3a**-<sup>18</sup>O was formed in 88% yield with 59.2% <sup>18</sup>O content in the oxygen atom of carbonyl group, which was determined by magnetic mass spectroscopic analysis (see Scheme SI-4, Supporting Information). This result clearly indicates that the oxygen atom of the carbonyl group in lactam product **3** comes from H<sub>2</sub>O in the reaction system and the original oxygen atom in **1a** is taken away by Ph<sub>3</sub>P as Ph<sub>3</sub>PO. After examination of the resulted byproducts, we confirmed that Ph<sub>3</sub>PO was indeed formed in this reaction system.

In view of the above results, a plausible reaction mechanism is proposed in Scheme 4. At first, triphenylphosphine reacts with carbon tetrahalide to give the corresponding dihalogen triphenylphosphorane **9** and dihalogenmethylene ylide **10**. Next, the intermediate **A** is formed by the reaction of *N*-substituted cyclopropylamide **1** with dihalogen triphenylphosphorane **9** to release a dihalogenmethyl triphenylphosphonium salt **11** as white precipitates, which was dissolved in MeCN after the solution was heated to 60 °C.<sup>8</sup> Thus, the corresponding *N*-substituted cyclopropylformimidoyl halogen **B**, as an anticipated active iminocyclopropane intermediate having two electron-withdrawing groups, is formed along with the generation of triphenylphosphine oxide. From intermediate **B**, two reaction pathways can be considered for the formation of pyrrolidin-2-one product **3**. Formally, the intermediate **C** can be first formed via a Cloke-type rearrangement from intermediate **B**. The corresponding pyrrolidin-2-one product **3** is formed through water substituting X by OH (Scheme 4, path a). However, it has been reported that typical Cloke rearrangement normally proceeds from an imine by acid catalysis at

(15) H<sub>2</sub>O (1.0 equiv) must be added slowly to the reaction mixture of **1a** with PPh<sub>3</sub>/CBr<sub>4</sub> in MeCN at 60 °C; otherwise, the yield of **3a** would be decreased.



mL). A short time later, a white precipitate was formed from the reaction solution. Then, the reaction system was heated to 60 °C, and the precipitate was dissolved again in the reaction solution. The solvent was evaporated after all starting amides were consumed. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and washed with H<sub>2</sub>O (50 mL × 2). After the residue was dried over anhydrous MgSO<sub>4</sub>, the solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography to give pyrrolidin-2-one product.

**1-Phenylpyrrolidin-2-one 3a.** This compound was obtained as a white solid. Yield: 47 mg, 97%. Mp: 64–65 °C. IR (CH<sub>2</sub>-Cl<sub>2</sub>):  $\nu$  1120, 1226, 1301, 1396, 1459, 1500, 1597, 1684, 2930, 2986 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  2.12 (tt, *J* = 8.1 Hz, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 2.58 (t, *J* = 8.1 Hz, 2H, CH<sub>2</sub>), 3.82 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.10–7.15 (m, 1H, Ar), 7.32–7.38 (m,

2H, Ar), 7.57–7.61 (m, 2H, Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, TMS):  $\delta$  18.0, 32.7, 48.8, 119.9, 124.5, 128.8, 139.4, 174.2. MS (EI) *m/z*: 161 (M<sup>+</sup>, 42), 132 (3), 119 (3), 106 (100), 104 (11), 91 (5), 79 (6), 77 (28), 51 (15). HRMS (MALDI) calcd for (C<sub>10</sub>H<sub>12</sub>NO + H)<sup>+</sup> 162.0913, found 162.0913.

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**Supporting Information Available:** The spectroscopic data, the detailed description of experimental procedures, the mass spectroscopy of <sup>18</sup>O-labeled *N*-phenylpyrrolidin-2-one **3a**, and the X-ray crystal data of **3c**.<sup>19</sup> This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) The crystal data of **3c** have been deposited at the CCDC, no. 264862: empirical formula, C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>; formula weight, 221.25; crystal size, 0.508 × 0.249 × 0.214; crystal color, habit, colorless, prismatic; crystal system, triclinic; lattice type, primitive; lattice parameters, *a* = 8.4864(11) Å, *b* = 8.5841(11) Å, *c* = 8.6437(12) Å,  $\alpha$  = 98.452(2)°,  $\beta$  = 101.450(2)°,  $\gamma$  = 114.134(2)°, *V* = 544.40(12) Å<sup>3</sup>; space group, *P*-1; *Z* = 8; *D*<sub>calc</sub> = 1.350 g/cm<sup>3</sup>; *F*<sub>000</sub> = 236; R1 = 0.0579, wR2 = 0.1479. Diffractometer: Rigaku AFC7R.