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“*N*-Acyliminium Ion Pool” as a Heterodiene in [4 + 2] Cycloaddition Reaction

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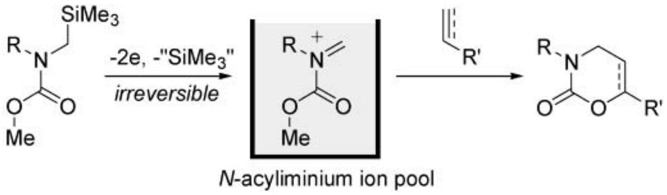
ABSTRACT



An *N*-acyliminium ion pool was found to undergo cycloaddition reaction with a variety of dienophiles such as alkenes and alkynes. A concerted mechanism seems to be most likely for alkyl-substituted alkenes as suggested by the DFT calculations, whereas a stepwise mechanism plays the major role for aryl-substituted alkenes. It is also noteworthy that the present study demonstrates the potential of the combination of the cation pool method and the micromixing in both mechanistic and synthetic aspects.

N-Acyliminium ions are versatile intermediates in organic synthesis; they not only react with various nucleophiles but also undergo cycloaddition reactions with unsaturated compounds.[1] It is especially noteworthy that *N*-acyliminium ions serve as electron-deficient 4π components in [4 + 2] cycloaddition with alkenes and alkynes.[2] This reaction serves as a useful method for the construction of heterocyclic rings and acyclic structures containing amino and hydroxyl groups. A concerted mechanism rather than a stepwise ionic mechanism is considered to be more plausible.[2,3] In some cases, however, a stepwise mechanism has been proposed because noncyclized products are also formed.[4]

N-Acyliminium ions are usually generated by acid-promoted reactions, which are reversible in most cases.[5] Another important point is that *N*-acyliminium ions are generated in the presence of counter-reaction components such as nucleophiles or dienophiles because they are highly unstable species. Thus, the reversibility of the generation and in situ follow-up reaction cause the difficulty in clarifying the detailed reaction mechanism. Recently, however, we have developed a “cation pool method” that involves *irreversible* generation and accumulation of cations by electrochemical oxidation in the absence of other reaction components.[6,7] This method has been successfully applied to *N*-acyliminium ions, which are identified as really ionic species by ^{1}H and ^{13}C

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(1) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.
(2) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525.
(3) Tomazela, D. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N.; D’Oca, M. G. M. *J. Org. Chem.* **2002**, *67*, 4652. See also: Schmidt, R. R.; Hoffmann, A. R. *Chem. Ber.* **1974**, *107*, 78.
(4) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 3445.

(5) (a) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52. (b) Zaugg, H. E. *Synthesis* **1984**, *85*, 181. Recent examples: (c) Vanier, C.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* **2001**, *7*, 2318. (d) Zhang, J.; Wei, C.; Li, C. J. *Tetrahedron Lett.* **2002**, *43*, 5731. (e) Schierle-Arndt, K.; Kolter, D.; Danielmeier, K.; Steckhan, E. *Eur. J. Org. Chem.* **2001**, 2425. (f) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809. (g) Metais, E.; Overman, L. E.; Rodrigues, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210. (h) Sun, P.; Sun, C.; Weinreb, S. M. *J. Org. Chem.* **2002**, *67*, 4337. (i) Veerman, J. N.; Klein, J.; Aben, R. W. M.; Scheeren, H. W.; Kruse, C. G.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2002**, 3133. Intramolecular [4 + 2] reaction using *N*-acyliminium ion: (j) Shimizu, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **2000**, *41*, 5715.
(6) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Suga, S.; Okajima, M.; Yoshida, J. *Tetrahedron Lett.* **2001**, *42*, 2173. (d) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30. (e) Yoshida, J.; Suga, S. *Chem. Eur. J.* **2002**, *8*, 2650.

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NMR and IR spectroscopies.[6,8] Thus, we initiated our study directed toward the elucidation of detailed insight into [4 + 2] cycloaddition of pooled *N*-acyliminium ions and its applications in organic synthesis. We report herein a preliminary result of this study.

Prior to experimental studies, we carried out theoretical studies using DFT calculations of a model system (*N*-methoxycarbonyl-*N*-methyliminium ion) in the gas phase.[9] The geometry optimization gave two structures, and the cisoid structure was found to be more stable (ca. 0.8 kcal) than the transoid structure.[10] The calculations also indicate that the reaction with ethylene proceeds in a concerted fashion in the gas phase and two new bonds seem to form asynchronously as shown in Figure 1.

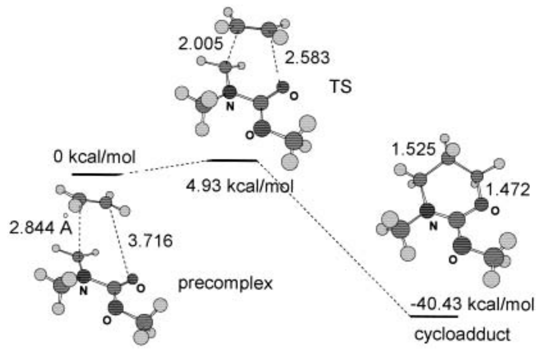


Figure 1. Energy diagram of the reaction of *N*-methoxycarbonyl-*N*-methyliminium ion with ethylene.

Having the results of MO calculations in hand, we investigated the reaction of *N*-acyliminium ion **2** with dienophiles (Scheme 1 and Table 1). Compound **2** was generated from *N*-methoxycarbonyl-*N*-(trimethylsilylmethyl)-butylamine **1** by low-temperature electrochemical oxidation and accumulated as a solution (cation pool).[11] In ^{1}H and ^{13}C NMR spectroscopies **2** exhibited signals at 8.56 and 8.83 ppm due to the two methylene protons and a signal at 174.7 ppm due to the methylene carbon in CD_2Cl_2. These values indicate the formation of **2** as an ionic species.[6]

Scheme 1

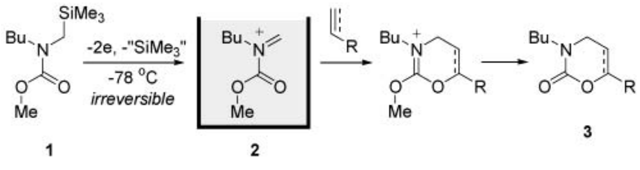
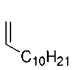
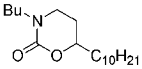
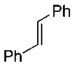
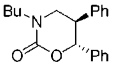
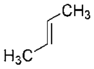
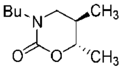
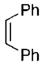
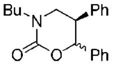
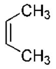
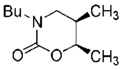
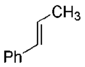
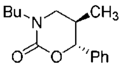
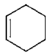
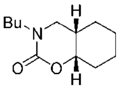
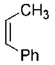
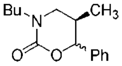
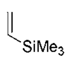
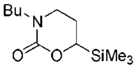
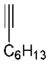
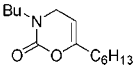
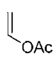
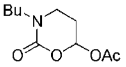
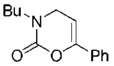
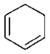
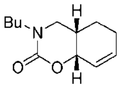
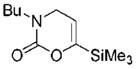


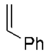
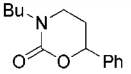
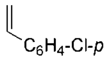
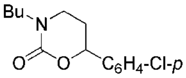
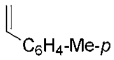
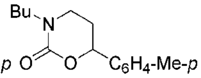
Table 1. [4 + 2] Cycloaddition of *N*-Acyliminium Ion **2** and Dienophiles[a]

dienophile	cycloadduct	% yield[b]	dienophile	cycloadduct	% yield[b]
		72			87
		68[d]			80 (cis/trans 55: 45)
		65[d]			88
		84			83 (cis/trans 56: 44)
		86			64
		81[c]			46
		70			90

[a] Mixing of **2** (generated from 1.2 equiv of **1**) and dienophiles was carried out using method A (see Table 2) at −78 °C. Mixture was stirred at 0 °C for 10 min and then treated with Et_3N. Yields were determined on the basis of dienophiles. [b] Isolated yield. [c] GC yield. [d] Mixture was stirred at −27 °C for 10 min before treatment of Et_3N.

The additions of alkyl-substituted alkenes to a solution of **2** took place smoothly (method A, see Table 2), and the corresponding cycloadducts were formed. (*E*)-2-Butene gave *trans*-cycloadduct exclusively, while (*Z*)-2-butene gave the *cis*-cycloadduct exclusively. The complete stereospecificity of the reaction is consistent with the concerted mechanism

Table 2. Mixing Effect of Reaction of **2** with Styrenes[a,b]

olefin	cycloadduct	% yield[c]			
		method A	method B	method C	micro-mixing[d]
		57	20	55	79
		43	12	54	70
		45	16	58	66

[a] Method A: Addition of a solution of an alkene to a solution of **2** at −78 °C. Method B: Addition of a solution of **2** to a solution of an alkene at −78 °C. Method C: Addition of a solution of an alkene and a solution of **2** into a reaction flask simultaneously at −78 °C. [b] Reactions were immediately quenched by triethylamine. [c] Isolated yield. Yields were determined on the basis of dienophiles. [d] IMM (Institut für Mikrotechnik Mainz GmbH) standard micromixier was used.

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[7] Although electrochemical and chemical oxidations are widely utilized, *N*-acyliminium ions thus generated are usually trapped in situ with nucleophiles. For example: (a) Shono, T. *Tetrahedron* **1984**, *40*, 811. (b) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527. (c) Naota, T.; Nakato, T.; Murahasi, S. *Tetrahedron Lett.* **1990**, *31*, 7475.

[8] Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941.

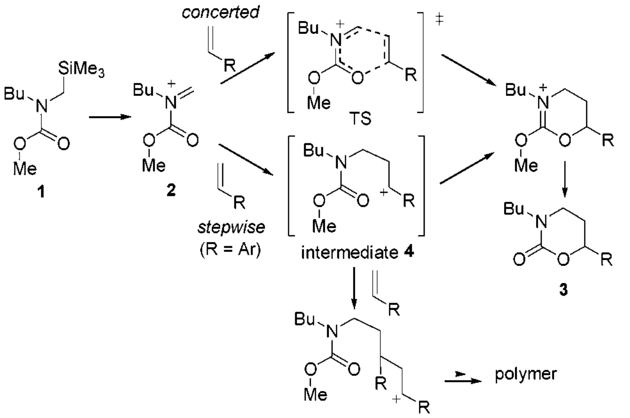
[9] Calculations were carried out at the B3LYP/6-31G(d) level using G98W.

[10] (a) Kupfer, R.; Würthwein, E.-U.; Nagle, M.; Allmann, R. *Chem. Ber.* **1985**, *118*, 643. (b) Lamatsch, B.; Seebach, D.; Ha, T.-K. *Helv. Chim. Acta* **1992**, *75*, 1095.

suggested by the calculations. The regioselectivity of the reaction with vinyltrimethylsilane also implies the concerted mechanism, because the stepwise mechanism involving the less stable carbocation alpha to silicon seems to be unlikely.

In contrast to the reaction with alkyl-substituted alkenes, the additions of aryl-substituted alkenes such as 1,2-diphenylethenes seem to involve a cationic intermediate like **4** in Scheme 2. The reaction with (*Z*)-1,2-diphenylethene led to the formation of a 55:45 mixture of *trans*- and *cis*-cycloadducts, while (*E*)-1,2-diphenylethene gave exclusively *trans*-cycloadduct, the stereochemistry of which was confirmed by X-ray analysis. Partial loss of stereospecificity in the reaction with (*Z*)-1,2-diphenylethene implies that the bond rotation competes with the cyclization in the intermediate **4**. The cycloadditions of (*E*)- and (*Z*)-1-methyl-2-phenylethenes proceeded in a similar fashion.

Scheme 2



It is also noteworthy that the reaction with styrene gave rise to the formation of a significant amount of polymer.[12] This observation also indicates the presence of cationic intermediate **4**, which reacts with another molecule of styrene and eventually gives the polymer. More outstanding is the observation that the yield of the cycloadduct strongly depends on the method of mixing as shown in Table 2. Although the addition of styrene to a solution of **2** (method A) gave cycloadduct **3** in 57% yield, the addition of a solution of **2** to styrene (method B) gave **3** in only 20% yield and a significant amount of styrene polymer (ca. 80% based on styrene) was formed presumably because of the higher initial concentration of styrene. The simultaneous addition of two reaction components (method C) gave essentially the same results as method A. However, micromixing[13] gave rise to a significant increase in the yield of **3** (79%) at the expense of the amount of the polymer (ca. 20% based on styrene). The efficient 1:1 mixing by a micromixer might cause intermediate **4** to be formed at a very low concentration of styrene, which leads to the effective intramolecular reaction to give **3**. Similar mixing effects were also observed for *p*-chloro and *p*-methylstyrenes. It should be emphasized that the cation pool method is intrinsically suitable for the study of the mixing effect, because it enables the use of a solution of cation as a starting material, whereas in the conventional method, cations are gradually formed in situ during the course of reaction.

To test the generality of the present cycloaddition, we examined the reaction of **2** with other dienophiles. As summarized in Table 1, the corresponding cycloadducts were successfully obtained in the reactions with cyclohexene, vinylsilane, and vinyl acetate. Compound **2** also reacted with 1,3-cyclohexadinene to give the adduct, where the diene behaved as a 2π component. It is synthetically advantageous that alkynes such as alkyl-, aryl-, and silyl-substituted acetylenes could also be utilized to obtain the corresponding cycloadducts having a carbon−carbon double bond.

In conclusion, the *N*-acyliminium ion pool was found to undergo cycloaddition reaction with a variety of dienophiles such as alkenes and alkynes. The reaction mechanism depends on the nature of the dienophile. A concerted mechanism seems to be most likely for alkyl-substituted alkenes as suggested by the DFT calculations in the gas phase, whereas a stepwise mechanism plays the major role for aryl-substituted alkenes. It is also noteworthy that the present study demonstrates the potential of the combination of the cation pool method and the micromixing in both mechanistic and synthetic aspects. The efficient 1:1 mixing favors the intramolecular reaction over the intermolecular reaction. We are currently investigating further mechanistic aspects and synthetic applications of these intriguing cycloaddition reactions.

Acknowledgment. This research was partially supported by a Grant-in-Aid for Scientific Research from Monbukagakusho and the Highly Efficient Micro Chemical Process Technology Project of NEDO.

Supporting Information Available: Experimental procedures and spectroscopic and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For selective oxidative cleavage of the trimethylsilyl group on the carbon alpha to the nitrogen of carbamates to generate *N*-acyliminium cation, see: (a) Yoshida, J.; Isoe, S. *Tetrahedron Lett.* **1987**, *28*, 6621. (b) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824.

(12) Brocherieux-Lanoy, S.; Dhimane, H.; Poupon, J.-C.; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163.

(13) Efficient mixing using a micromixer: (a) Ehrfeld, W.; Golbig, K.; Hessel, V.; Löwe, H.; Richter, T. *Ind. Eng. Chem. Res.* **1999**, *38*, 1075. (b) Kakuta, M.; Bessoth, F. G.; Manz, A. *Chem. Rec.* **2001**, *1*, 395. (c) Stroock, A. D.; Dertinger, S. K. W.; Ajdari, A.; Mezić, I.; Stone, H. A.; Whitesides, G. M. *Science* **2002**, *295*, 647. (d) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354.