Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9323–9326
Tetrahedron Letters

# Ene reactions of acyl nitroso intermediates with alkenes and their halocyclization

Ahmad Fakhruddin,[a] Seiji Iwasa,[a,*] Hisao Nishiyama[b] and Kazuo Tsutsumi[a]

[a]*School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi, Aichi 441-8580, Japan*
[b]*Graduate School of Engineering, Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya, Aichi 464-8603, Japan*

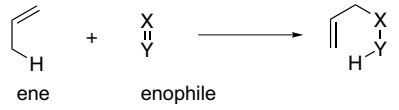
Received 11 September 2004; revised 22 October 2004; accepted 25 October 2004
Available online 6 November 2004

**Abstract**—Highly reactive acyl nitroso intermediates were formed in situ by transition metals-catalyzed hydrogen peroxide oxidation of hydroxamic acids **1a**–**b** and these transient species trapped with alkenes **2a**–**c** to afford the corresponding ene products **3a**–**d** and **4b** up to 91% yield, and halocyclization of **3d** gave substituted oxazolidinone **5a** in 77% yield.


The ene reaction of alkenes and enophiles is one of the useful functionalization protocol of organic molecules. In this regard, alkenes, singlet oxygen,[1] azo compounds,[2] carbonyl functionalities,[3] and nitroso groups[4] have been employed as enophiles in carbon–carbon and carbon–heteroatom transformations with alkenes to afford the corresponding functionalized molecules (Scheme 1).

Nitroso ene reactions are often used as a key step in total syntheses of several natural products.[5] Thus, alkaloids with active antitumor agents such as: crinane, mesembrine, elvesine, and narciclasine are easily available from nitroso ene reactions. Moreover, allylic amines which can be achieved from the nitroso ene products, are versatile building blocks in organic syntheses, as demonstrated in the preparation of carbohydrate derivatives,[6] α- and β-amino acids,[7] and alkaloids.[8]

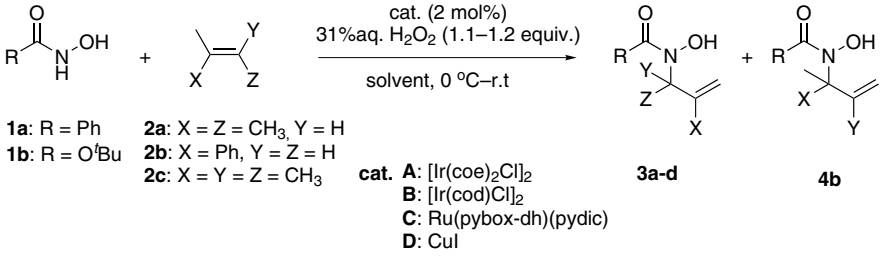
One distinguishing property of the acyl nitroso intermediates is high reactivity, a consequence of the low excitation energy due to a very small HOMO–LUMO energy gap. High reactivity leads to embarrassment in handling, as most of nitroso compounds tend to form dimers.[9] In the case of acyl nitroso intermediates, they are generated in situ. One drawback of the nitroso ene reaction is the labile nature of the products. The reaction products are themselves hydroxamic acids sensitive to the oxidizing conditions used to form the nitrosocarbonyl compounds. So, it is rather challenging to synthesize ene products from the direct oxidation of hydroxamic acids.[10] The hydroxylamines formed tend to undergo further transformations, and often several side products are observed as a result of disproportionation. These include nitrones, amines, azoxy compounds, and nitroxides.[11] However, nitrosocarbonyl compounds may also be generated under mild conditions by thermal dissociation of their cycloadducts with 9,10-dimethylanthracene. The first examples of the intermolecular ene reactions of *C*-nitrosocarbonyl compounds, RCONO, were observed in this way by Kirby and co-workers[10b,c] and Keck et al.[5c] Unfortunately, in the aforementioned methods, the precursors are clumsy to prepare and the alkene partner for the ene reaction must be used in large excess. Therefore, it is very important to design an efficient method for the in situ generation of acyl nitroso enophiles with the utilization of readily available starting materials, for example, the selective oxidation of hydroxamic acids and utilizes this for ene reactions. Adam et al. had prominent success in this direction, since they demonstrated that a simple one-pot procedure, where acyl nitroso ene products can be achieved in good yield under mild conditions from the oxidation of hydroxamic acids by iodosobenzene diacetate or




**Scheme 1.**

*Keywords*: Ene reaction; Ruthenium; Iridium; Copper; Hydrogen peroxide; Acyl nitroso; Halocyclization.
* Corresponding author. Tel.: +81 532446817; fax: +81 532485833; e-mail: iwasa@tutms.tut.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.128




**Scheme 2.**

**Table 1.** Catalytic hydrogen peroxide oxidation of hydroxamic acids (**la** and **b**) and their subsequent ene reactions with alkenes (**2a–c**)[a]

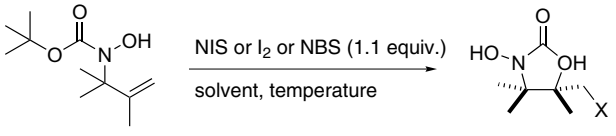
| Entry | H.a | Alkene | Cat. | $H_2O_2$ (equiv) | Solvent | Time (h) | Product | Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **A** | 1.1 | THF | 40 | **3a** | 38 |
| 2 | **1a** | **2a** | **B** | 1.1 | THF | 24 | **3a** | 40 |
| 3 | **1a** | **2a** | **C** | 1.1 | THF | 24 | **3a** | 29 |
| 4 | **1a** | **2a** | **C** | 1.1 | MeOH | 72 | **3a** | 32 |
| 5 | **1a** | **2a** | **D** | 1.2 | THF | 24 | **3a** | 0 |
| 6 | **1a** | **2a** | **D** | 1.2 | MeOH | 24 | **3a** | 0 |
| 7 | **1b** | **2a** | **A** | 1.1 | THF | 24 | **3b + 4b**(4:1)[b] | 76 |
| 8 | **1b** | **2a** | **B** | 1.1 | THF | 24 | **3b + 4b**(3:1)[b] | 84 |
| 9 | **1b** | **2a** | **C** | 1.1 | THF | 24 | **3b + 4b**(8:1)[b] | 50 |
| 10 | **1b** | **2a** | **C** | 1.1 | MeOH | 24 | **3b + 4b**(8:1)[b] | 86 |
| 11 | **1b** | **2a** | **D** | 1.2 | THF | 3 | **3b + 4b**(4:1)[b] | 83 |
| 12 | **1b** | **2b** | **A** | 1.2 | THF | 48 | **3c** | 30 |
| 13 | **1b** | **2b** | **B** | 1.1 | THF | 16 | **3c** | 31 |
| 14 | **1b** | **2b** | **C** | 1.1 | THF | 48 | **3c** | 26 |
| 15 | **1b** | **2b** | **C** | 1.1 | MeOH | 24 | **3c** | 12 |
| 16 | **1b** | **2b** | **C** | 1.2 | MeOH | 48 | **3c** | 17 |
| 17 | **1b** | **2b** | **D** | 1.2 | MeOH | 5 | **3c** | 78 |
| 18 | **1b** | **2b** | **D** | 1.2 | THF | 4 | **3c** | 75 |
| 19 | **1b** | **2c** | **A** | 1.2 | THF | 24 | **3d** | 73 |
| 20 | **1b** | **2c** | **B** | 1.2 | THF | 8 | **3d** | 87 |
| 21 | **1b** | **2c** | **C** | 1.2 | THF | 24 | **3d** | 56 |
| 22 | **1b** | **2c** | **D** | 1.2 | THF | 4 | **3d** | 91 |

[a] All the reactions were carried out at 0.5 mmol of hydroxamic acid (H.a) and 1.5 equiv of olefin with 2 mol% catalyst loading and 1.0 mL of solvent.
[b] The ratios of regioisomers were determined by $^1$H NMR.
[c] The yields are isolated products; and the yields of entries 7–11 represent the combined yields of the regioisomers.

iodosobenzene as an oxidant with 3 equiv of the alkene.[12] But, this method still has some drawbacks due to the use of a stoichiometric amount of traditional oxidants and large excess of olefins.

In this context, here, we report a simple one-pot procedure for the ene reactions with alkenes, involving Ru(II)- or Ir(I)- or Cu(I)-catalyzed oxidation of hydroxamic acids with 31% aqueous hydrogen peroxide (Scheme 2, Table 1) and the halocyclization of ene product (Scheme 3, Table 2). During our ongoing research, we have planned to apply our transition metal-catalyzed hydrogen peroxide system[13] to the ene reactions. In this regard, aliphatic alkenes bearing allylic hydrogens were chosen as allylic-H source and in situ generation of acyl nitroso species as enophiles to get the products through C–N bond formation.

When Ru(II)- or Ir(I)-catalyzed oxidation of hydroxamic acid (**1a**) was carried out in the presence of trisubstituted alkene **2a**, subsequent ene product **3a** was formed in low yield (29–40%) (entries 1–4) and no regioisomer was detected. Surprisingly, it was noticed that the



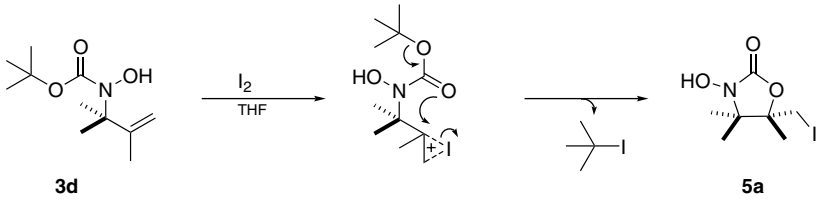

**Scheme 3.**

Cu(I)-catalyst completely failed to produce any ene product in this case (entries 5 and 6). The reactions of

**Table 2.** Halocyclization of ene product

| Entry | Halogen source[a] | Solvent | Temp. | Time | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | NIS | $Et_2O$ | rt | 40 min | 57 |
| 2 | NIS | $Et_2O$ | 0 °C–rt | 4 h | 70 |
| 3 | NIS | THF | rt | 4 h | 77 |
| 4 | $I_2$ | $Et_2O$ | rt | 4 h | 77 |
| 5 | NBS | THF | rt | 4 h | 46 |

[a] NIS: *N*-iodosuccinimide, NBS: *N*-bromosuccinimide.
[b] Isolated yield after silica gel column chromatography.




**Scheme 4.**

the same alkene with another hydroxamic acid **1b** gave excellent results with good to moderate regioselectivity (entries 7–11). Allylic hydrogen was abstracted from more substituted side of the alkene and generated major regioisomer, and the best result was found in the case of Ru(II)-catalyst, 86% yield as well as 8:1 regioselectivity in MeOH (entry 10). Consequently, hydroxamic acid **1b** responded well compared to **1a** in the aforementioned ene reaction. Ru(II)- or Ir(I)-catalyzed oxidation of hydroxamic acid (**1b**) showed poor yield with alkene **2b**, only 12–31% yield was observed (entries 12–16), but Cu(I)-catalyst generated good ene product **3c** in both MeOH (78%) and THF (75%) (entries 17 and 18). Good catalytic ene reactions were observed in the case of tetrasubstituted alkene **2c** and the Ir(I)- and Cu(I)-catalyzed ene reactions produced good yields 73–91% (entries 19, 20, and 22).

Halocyclization is an interesting transformation in organic syntheses and very recently Galeazzi et al. demonstrated the stereoselective iodocyclization of amides.[14] This can also be employed to produce cyclic compounds from acyclic ene products. As a test experiment, we have chosen compound **3d**, which was obtained from the transition metal-catalyzed hydrogen peroxide oxidation of hydroxamic acid **1b** with alkene **2c** (Scheme 3, Table 2). Both $Et_2O$ and THF are effective as solvent for present halocyclization (Table 2, entries 1–5). In the presence of NIS or $I_2$, iodolactonization took place and produced **5a** with 77% yield (entries 3 and 4) and when NBS is used bromolactonization occurred and **5b** was formed in 46% yield. The double bond of vinyl group in compound **3d** can originate a cycle with the oxygen of carbonyl group and thereby formed 3-hydroxy-5-iodomethyl-4,4,5-trimethyl oxazolidine-2-one, **5a** and 3-hydroxy-5-bromomethyl-4,4,5-trimethyl oxazolidine-2-one, **5b** (Scheme 4).

In conclusion, we have demonstrated a simple one-pot method for the acyl nitroso ene reactions. Ene products can be achieved in good yield under environmentally friendly oxidation condition and further transformation of the ene product leads to afford *N*-hydroxy halosubstituted oxazolidinone in good yield. In this reaction although the enophile is unsymmetrical only one mode of addition is observed, reaction always leading to the formation of a C–N bond and generation of a N–OH compound. Nevertheless, the nitroso ene reaction potentially can be an efficient method for carbon–nitrogen bond formation. Understanding the mechanism and overcoming troublesome aspects of this reaction is present interest.[15]

General procedure is as follows (Table 1, entry 22): To a solution of hydroxamic acid **1b** (68.0 mg, 0.5 mmol) and 2,3-dimethyl-2-butene **2c** (93 μL, 0.75 mmol) in THF (1.0 mL) was added a solid of CuI (2.0 mg, 0.01 mmol) at 0 °C and followed by addition of hydrogen peroxide (31%, 65 μL, 0.6 mmoL). The resulting greenish-yellow mixture was stirred for 4 h at room temperature. The organic phase was extracted with $CH_2Cl_2$, and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give the ene product **3d** (98.0 mg) in 91% isolated yield. **3d**: pale pink liquid; $R_f$ (hexane:EtOAc = 4:1) = 0.44; IR (NaCl): 3225, 2978, 2930, 1694, 1651, 1645, 1471, 1463, 1455, 1393, 1372, 1254, 1158, 1111 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 6.62 (s, 1H), 4.82 (br s, 1H), 4.73–4.72 (m, 1H), 1.79 (d, $J$ = 0.55 Hz, 3H), 1.48 (br s, 15H) ppm; $^{13}C$ NMR ($CDCl_3$, 75 MHz): $\delta$ 158.28, 150.58, 108.73, 82.71, 65.58, 28.35, 25.34, 19.27 ppm.

General procedure is as follows (Table 2, entry 3): To a solution of ene product **3d** (47.3 mg, 0.22 mmol) in THF (1.5 mL) was added NIS (54.0 mg, 0.24 mmol) at room temperature. The resulting mixture was stirred for 4 h. Then saturated $Na_2S_2O_3$ solution was added dropwise until the iodine color disappeared. The organic phase was extracted with $CH_2Cl_2$, and dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to give the cyclic product **5a** (48.6 mg) in 77% isolated yield. **5a**: yellow liquid; $R_f$ (hexane:EtOAc = 2:1) = 0.20; IR (NaCl): 3261, 2981, 2941, 1759, 1470, 1454, 1383, 1333, 1187, 1124, 1057, 1038 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz): $\delta$ 7.72–7.50 (br s, 1H), 3.49 (d, $J$ = 10.71 Hz, 1H), 3.32 (d, $J$ = 10.71 Hz, 1H), 1.59 (s, 3H), 1.37 (d, $J$ = 12.63 Hz, 6H) ppm; $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 158.45, 82.77, 65.68, 21.96, 20.71, 18.48, 7.78 ppm; Anal. Calcd for $C_7H_{12}NO_3I$: C, 29.98; H, 4.19; N, 4.51. Found: C, 29.49; H, 4.24; N, 4.91.

## Acknowledgements

S.I. thanks the Ministry of Education, Culture, Sports, Science and Technology for partial financial support.

## References and notes

1. Stratakis, M.; Orfanopoulos, M.; Foote, C. S. *J. Org. Chem.* **1998**, *63*, 1315.

2. Stratakis, M.; Hatzimarinaki, M.; Froudakis, G. E.; Orfanopoulos, M.; Foote, C. S. *J. Org. Chem.* **2001**, *66*, 3682.
3. (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021; (b) Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **1998**, *63*, 1315; (c) Yamanaka, M.; Mikami, K. *Helv. Chim. Acta* **2002**, *85*, 4264.
4. Wanner, M. J.; Koomen, G.-J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1908.
5. (a) Keck, G. E.; Webb, R. *Tetrahedron Lett.* **1979**, *20*, 1185; (b) Keck, G. E.; Webb, R. R., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173; (c) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007; (d) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302.
6. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
7. Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301.
8. Trost, B. M. *Angew. Chem.* **1989**, *101*, 1119.
9. Stowell, J. C. *J. Org. Chem.* **1971**, *36*, 3055.
10. (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1; (b) Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 883; (c) Kirby, G. W.; McGuigan, H.; McLean, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1961.
11. (a) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689; (b) Knight, G. T.; Pepper, B. *Tetrahedron* **1971**, *27*, 6201; (c) Knight, G. T.; Loadman, M. J. R. *J. Chem. Soc. B* **1971**, 2107.
12. Adam, W.; Krebs, O.; Orfanopoulos, M.; Stratakis, M. *J. Org. Chem.* **2002**, *67*, 8395.
13. (a) Iwasa, S.; Tajima, K.; Tsushima, S.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 5897; (b) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *Chem. Commun.* **2001**, 1812; (c) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2058; (d) Iwasa, S.; Fakhruddin, A.; Tsukamoto, Y.; Kameyama, M.; Nishiyama, H. *Tetrahedron Lett.* **2002**, *43*, 6159.
14. Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Org. Lett.* **2004**, *6*, 2571.
15. (a) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131; (b) Leach, A. G.; Houk, K. N. *Org. Biomol. Chem.* **2003**, *1*, 1389; (c) Xin, L. *Org. Lett.* **2004**, *6*, 2813.