# A Synthesis of Oximes from Olefins by Cobalt(II) Porphyrin-Catalyzed Reduction-Nitrosation

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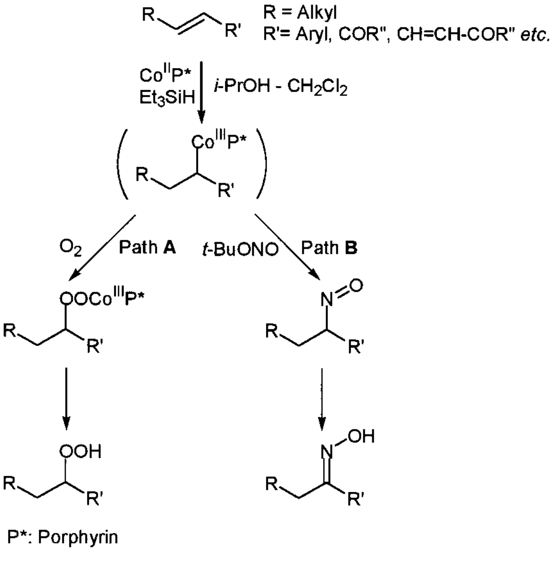
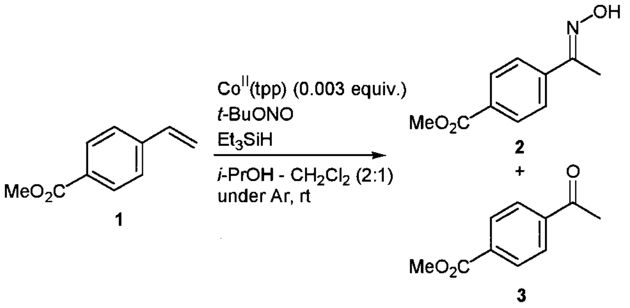
**Abstract**: Various olefins such as styrenes, α,β-unsaturated carbonyl compounds, and α,β,γ,δ-unsaturated carbonyl compounds were directly converted to the corresponding acetophenoximes, α-hydroxyimino carbonyl compounds and γ-hydroxyimino-α,β-unsaturated carbonyl compounds in good or moderate yields by reduction-nitrosation with *t*-butyl nitrite and triethylsilane in the presence of cobalt(II) porphyrin as a catalyst.

The method for preparation of nitroso compounds or oximes from olefins is valuable for synthesis of nitrogen-containing compounds such as amino acids and heterocycles. Okamoto *et al.* first reported that a catalytic reduction-nitrosation of styrenes with ethyl nitrite and tetrahydroborate ion by the use of bis(dimethylglyoximato)cobalt(II) complex afforded the corresponding acetophenoximes.[1)] Mukaiyama *et al.* also reported the conversion of α,β-unsaturated carbonyl compounds by the reaction with nitric monoxide or butyl nitrite and triethylsilane in the presence of *N*,*N*-bis(2-ethoxycarbonyl-3-oxobutylidene) ethylenediaminatocobalt(II) as a catalyst.[2)] However, the reaction substrates seem to be confined to aromatic olefins and α,β-unsaturated carbonyl compounds, respectively, from their reports. Since we previously found a direct and regioselective method for synthesis of hydroperoxy compounds from wide varieties of conjugated olefins by cobalt porphyrin-catalyzed reduction-oxygenation (Path **A** in Scheme 1),[3)] we attempted the reduction-nitrosation of the conjugated olefins by the use of *t*-butyl nitrite instead of oxygen (Path **B** in Scheme 1).



**Scheme 1**

**Table 1.** Reduction-nitrosation of 4-carbomethoxystyrene **1** under various conditions.



| Entry | Catalyst[a)] | Time h | *t*-BuONO equiv. | Et$_3$SiH equiv. | Yield / %[b)] 2 | 3 | Recov. %[b)] |
|---|---|---|---|---|---|---|---|
| 1 | Co$^{II}$(tpp) | 24 | 1.5 | 1.5 | 23 | 2 | 62 |
| 2 | Co$^{II}$(tpp) | 24 | 3.0 | 1.5 | 35 | 2 | 50 |
| 3 | Co$^{II}$(tpp) | 24 | 1.5 | 3.0 | 35 | 1 | 57 |
| 4 | Co$^{II}$(tpp) | 24 | 3.0 | 3.0 | 91 | 2 | 0 |
| 5 | Co$^{II}$[t(OMe)pp] | 24 | 3.0 | 3.0 | 96 | 1 | 0 |
| 6 | Co$^{II}$(tmp) | 24 | 3.0 | 3.0 | 18 | 1 | 62 |
| 7 | Co$^{II}$(tdcpp) | 24 | 3.0 | 3.0 | 33 | 2 | 55 |
| 8 | Co$^{II}$(tcmpp) | 24 | 3.0 | 3.0 | 39 | 3 | 59 |
| 9 | Co$^{II}$(tdcpp) | 48 | 3.0 | 3.0 | 85 | 7 | 1 |
| 10 | Mn$^{III}$(tpp)Cl | 24 | 3.0 | 3.0 | 0 | 1 | 78 |
| 11 | Fe$^{III}$(tpp)Cl | 24 | 3.0 | 3.0 | 0 | 0 | 85 |
| 12 | Co$^{II}$(acac)$_2$ | 24 | 3.0 | 3.0 | 2 | 1 | 86 |
| 13 | Co$^{II}$(salen) | 24 | 3.0 | 3.0 | 0 | 0 | 85 |

a) tpp: 5,10,15,20-tetraphenylporphine; Co$^{II}$[t(OMe)pp]: 5,10,15,20-tetrakis(4-methoxyphenyl)porphine; tmp: 5,10,15,20-tetramesitylporphine; tcmpp: 5,10,15,20-tetrakis(4-carbomethoxyphenyl)porphine; tdcpp: 5,10,15,20-tetrakis(2,6-dichlorophenyl)porphine; acac: acetylacetone; salen: *N,N'*-salicylideneethylenediamine.

b) Analyzed by GC.

We first examined the effect of amounts of *t*-butyl nitrite and triethylsilane on the reaction of 4-carbomethoxystyrene **1** in the presence of 0.003 equiv. of 5,10,15,20-tetraphenylporphinatocobalt(II) [Co$^{II}$(tpp)] in *i*-PrOH - CH$_2$Cl$_2$ (1:2) at room temperature for 24 h (Entries 1-4 of Table 1). The combined use of 3.0 equiv. of *t*-butyl nitrite and 3.0 equiv. of triethylsilane for **1** was found to be required for the complete consumption of **1** (Entry 4). Under these conditions, oxime **2** was obtained in 91 % yield along with 2 % yield of ketone **3**. Secondly, the effect of catalyst was investigated under the similar conditions shown in Entry 4, and the results were depicted in Entries 5-13. The abbreviations of metal complexes used as the catalyst were shown in Table 1. Although all cobalt(II) porphyrins could catalyze the reaction, both Co$^{II}$(tpp) and Co$^{II}$[t(OMe)pp] were the most effective catalysts among them (Entries 4 and 5). The low catalytic activity of Co$^{II}$(tmp) compared with those of Co$^{II}$(tpp) and Co$^{II}$[t(OMe)pp] may be accounted for by the steric bulkiness of mesityl groups (Entry 6). The cobalt(II) porphyrins with electron-withdrawing substitutents on the phenyl ring such as Co$^{II}$(tdcpp) and Co$^{II}$(tcmpp) were less active than Co$^{II}$(tpp) on the reaction (Entries 7 and 8). For the completion of the reaction of **1** catalyzed by Co$^{II}$(tdcpp), the elongation of the reaction time was required (Entry 9). Both the other metalloporphyrins [Mn$^{III}$(tpp)Cl and Fe$^{III}$(tpp)Cl] and the other cobalt(II) complexes [Co$^{II}$(acac)$_2$ and Co$^{II}$(salen)] had scarcely or no catalytic activity

(Entries 10-13). Thus we chose commercially available Co$^{II}$(tpp) as the most suitable catalyst on the present reduction-nitrosation, though Co$^{II}$(tpp) was reported to have no catalytic activity on Okamotoís reduction-nitrosation using ethyl nitrite and tetrahydroborate ion as the reagents.[1)]

The progress of the reduction-nitrosation of **1** under the same conditions as described in Entry 4 of Table 1 was followed by the measurement of GC (Fig. 1). The substrate **1** was consumed completely after 24 h. The yield of the oxime **2** increased with the decrease of **1**. In addition, a small amount of ketone **3** was produced increasingly with the elapse of the reaction time. Since oximes were reported to form the corresponding ketones by the reaction with alkyl nitrite by Wieland *et al.*,[4)] the ketone **3** was thought to be gradually formed from the oxime **2** during the reduction-nitrosation. In practice, when the oxime **2** was allowed to react under the same conditons as described in Fig. 1 for 48h, the ketone **3** was additionally obtained in 6 % yield.

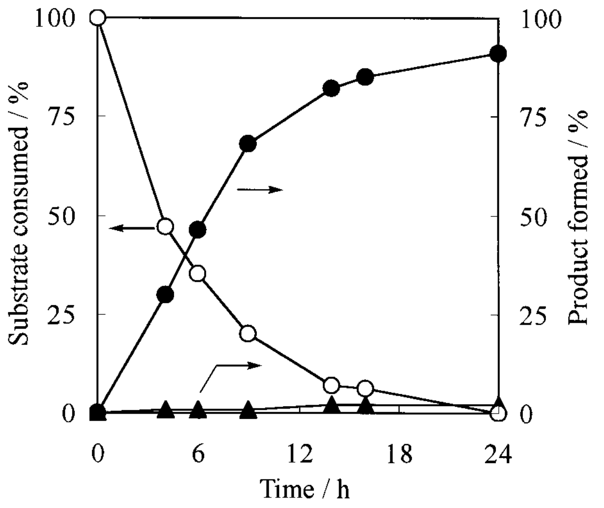


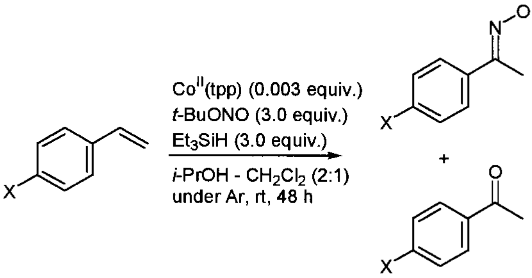
**Fig. 1**. Time course of the reduction-nitrosation of 4-carbomethoxystyrene **1** (1 mmol) with *t*-BuONO (3.0 equiv.) and Et$_3$SiH (3.0 equiv.) catalyzed by Co$^{II}$(tpp) (0.003 equiv.) under Ar at room temperature in *i*-PrOH - CH$_2$Cl$_2$ (1:2) analyzed by GC: 4-carbomethoxystyrene **1** (○); 4-carbomethoxyacetophenoxime **2** (●); 4-carbomethoxyacetophenone **3** (▲).

The reduction-nitrosation of several *p*-substituted styrenes with 3.0 equiv. of *t*-butyl nitrite and triethylsilane in the presence of 0.003 equiv. of Co$^{II}$(tpp) was attempted (Table 2). The reaction of styrenes bearing an electron-withdrawing group such as nitro, carbomethoxy and chloro group afforded the oximes in high yields. On the other hand, the yields of the oximes were moderate for styrene and 4-methylstyrene; the formation of ambigous by-products caused a lowering of the yield of the oxime.

The results of the reduction-nitrosation of α,β-unsaturated carbonyl compounds are summarized in Table 3. From alkenoates, alkenone, and alkenals, the corresponding α-hydroxyimino compounds were produced in good yields (Entries 1-5). However, no reaction exceptionally took place for ethyl cyclohexylideneacetate (Entry 6). The steric hindrance of dialkyl groups on β-position seems to be this cause. It is interesting to point out that the present conditions are mild enough to permit the presence of labile aldehyde on the substrate.

Furthermore, the present reduction-nitrosation could be applied to conjugated dienes (Table 4.). Unfortunately, the reaction of ethyl 2,4-octadienoate gave ethyl 4-hydroxyimino-2-octenoate in 33 % yield and the substrate unchanged in 23 % yield (Entry 1). Moreover, the production of ethyl 2,4-bis(hydroxyimino)octanoate (6 %), which probably arose from over-nitrosation of ethyl 4-hydroxyimino-2-octenoate, was observed. Therefore, we tried to change the substrate to the other esters for the purposes of enhancement of the reactivity and prevention of over-nitrosation (Entries 2-5). For both *N*-benzoyl-*N*-

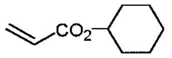
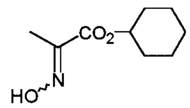
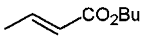
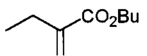
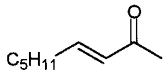
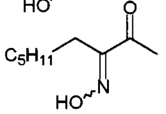
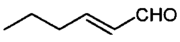
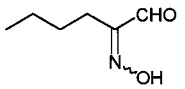
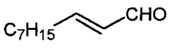
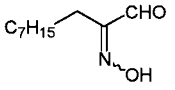
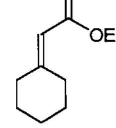
**Table 2.** Reduction-nitrosation of *p*-substituted styrenes



| Entry | Olefin | Yield / %[a)] | | Recov. |
|---|---|---|---|---|
| | | Oxime | Ketone | %[a)] |
| 1 | X = NO$_2$ | 93 | 0 | 0 |
| 2 | X = CO$_2$Me | 87 | 11 | 0 |
| 3 | X = Cl | 70 | 14 | 0 |
| 4 | X = H | 67 | 7 | 0 |
| 5 | X = Me | 57 | 4 | 0 |

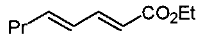
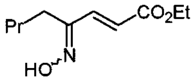
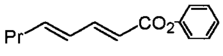
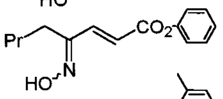
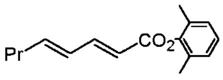
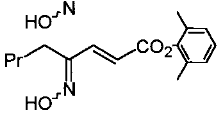
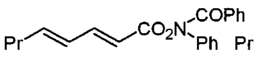
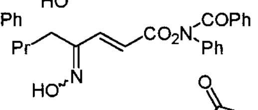
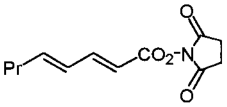
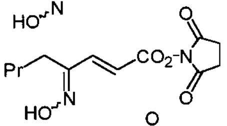
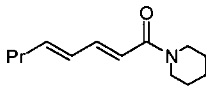
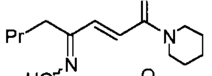
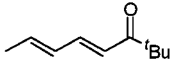
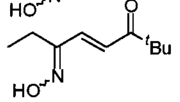
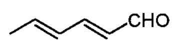
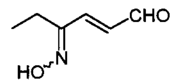
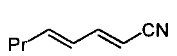
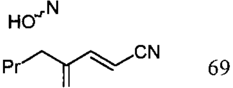
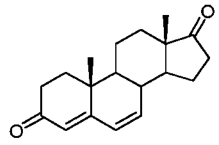
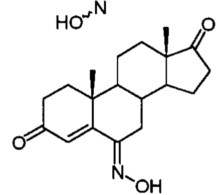
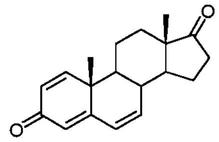
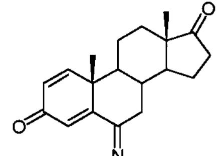
a) Isolated yield.

**Table 3.** Reduction-nitrosation of α,β-unsaturated carbonyl compounds[a)]

| Entry | Substrate | Product | Yield %[b)] | Recov. %[b)] |
|---|---|---|---|---|
| 1 |  |  | 94 | 0 |
| 2 |  |  | 64 | 14 |
| 3 |  |  | 92 | 0 |
| 4 |  |  | 69 | 0 |
| 5 |  |  | 61 | 38 |
| 6 |  | No Reaction | | |

a) Conditions: substrate (1 mmol), Co$^{II}$(tpp) (0.003 equiv.), Et$_3$SiH (3.0 equiv.), *t*-BuONO (3.0 equiv.), *i*-PrOH - CH$_2$Cl$_2$ (7.5 cm$^3$, 1:2) under Ar at room temperature for 48 h.
b) Isolated yield.

**Table 4.** Reduction-nitrosation of α,β,γ,δ-unsaturated carbonyl compounds[a)]

| Entry | Substrate | Product | Yield %[b)] | Recov. %[b)] |
|---|---|---|---|---|
| 1 |  |  | 33 | 23 |
| 2 |  |  | 54 | 0 |
| 3 |  |  | 69 | 0 |
| 4 |  |  | 92 | 0 |
| 5 |  |  | 94 | 0 |
| 6 |  |  | 38 | 28 |
| 7 |  |  | 39 | 12 |
| 8 |  |  | 55 | 0 |
| 9 |  |  | 69 | 0 |
| 10 |  |  | 31 | 53 |
| 11 |  |  | 68 | 21 |

a) Conditions: substrate (1 mmol), $Co^{II}$(tpp) (0.003 equiv.), $Et_3SiH$ (3.0 equiv.), *t*-BuONO (3.0 equiv.), *i*-PrOH - $CH_2Cl_2$ (7.5 $cm^3$, 1:2) under Ar at room temperature for 48 h.
b) Isolated yield.

phenylhydroxylaminyl ester and *N*-hydroxysuccinimidyl ester, the desired hydroxyimino compounds were obtained in high yields (Entries 4 and 5). The yield of the hydroxyimino compounds seemed to increase in order of increasing electron-negativity of the ester moiety. The results of reduction-nitrosation of α,β,γ,δ-unsaturated amide and ketone were similar to that of Entry 1, that is, the moderate yields of the hydroxyimino esters and the recovery of the substrates unaltered were observed (Entries 6 and 7). On the other hand, the reaction of 2,4-hexadienal and 2,4-octadienonitrile afforded 4-hydroxyimino-2-hexenal and 4-hydroxyimino-2-octenonitrile, respectively, in fairly good yields (Entries 8 and 9). In Entries 2, 3 and 6-9, the formation of various by-products such as the ketone and the bis(hydroxyimino) compound as described above resulted in the decrease of the desired oximes. In addition, (*E*)-6-hydroxyiminoandrost-4-ene-3,17-dione and (*E*)-6-hydroxyiminoandrosta-1,4-diene-3,17-dione, which were known as novel types of aromatase inhibitors,[5)] could be synthesized in one step from easily available androstane derivatives[6)] by the present reduction-nitrosation (Entries 10 and 11). To our knowledge, the present reaction enables firstly the direct conversion of α,β,γ,δ-unsaturated carbonyl compounds into γ-hydroxyimino-α,β-unsaturated ones.

Thus, a widely applicable method for the preparation of oximes from conjugated olefins by cobalt(II) porphyrin-catalyzed reduction-nitrosation was established.

### References and Notes

(1) Okamoto, T.; Kobayashi, K.; Oka, S.; Tanimoto, S. *J. Org. Chem.* **1987,** *52*, 5089. Okamoto, T.; Kobayashi, K.; Oka, S.; Tanimoto, S. *J. Org. Chem.* **1988**, *53*, 4897.

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(3) Matsushita, Y.; Matsui, T.; Sugamoto, K. *Chem. Lett.* **1992**, 1381. Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* **1992**, 2165. Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* **1993**, 925. Matsushita, Y.; Sugamoto, K.; Nakama, T.; Sakamoto, T.; Matsui, T. *Tetrahedron Lett.* **1995**, *36*, 1879. Matsushita, Y.; Sugamoto, K.; Nakama, T.; Matsui, T. *J. Chem. Soc., Chem. Commun.* **1995**, 567.

(4) Wieland, T.; Grimm, D. *Ber.* **1963**, *96*, 275.

(5) Holland, H. L.; Kumaresan, S.; Tan, L.; Njar, V. C. O. *J. Chem. Soc., Perkin Trans 1* **1992**, 585. In this work, (*E*)-6-hydroxyiminoandrosta-4-ene-3,17-dione and (*E*)-6-hydroxyiminoandrosta-1,4-diene-3,17-dione were synthesized from $\Delta^5$-androstene-3β,17β-diacetate by multi-step procedures.

(6) Androsta-4,6-diene-3,17-dione and androsta-1,4,6-triene-3,17-dione were prepared form $\Delta^4$-androstene-3,17-dione in 64 % and 41 % yields, respectively, according to the following literature. Pradhan, S. K.; Ringold, H. J. *J. Org. Chem.* **1964**, *29*, 601.

(7) **Typical procedure for the reaction of 4-carbomethoxystyrene 1**: The reaction was carried out under Ar in order to prevent any contamination from $O_2$. **1** (162 mg, 1 mmol) and $Co^{II}$(tpp) (2.02 mg, 0.003 mmol) were dissolved in 3 $cm^3$ of $CH_2Cl_2$ in a 50 $cm^3$ kjeldahl flask equipped with three-way cock. The atmosphere in the flask was replaced with Ar by bubbling for 15 min at O °C, and then an Ar balloon was attached to the flask through the three-way stopcock. Triethylsilane (0.48 $cm^3$, 3 mmol) and *t*-butyl nitrite (0.36 $cm^3$, 3 mmol) were dissolved in 2.0 $cm^3$ of $CH_2Cl_2$ and 2.5 $cm^3$ of *i*-PrOH followed by the replacement with Ar by bubbling for 15 min at O °C. The thus obtained mixture was added to the solution of **1** and $Co^{II}$(tpp), and then the mixture was stirred at room temperature for 48 h. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography with *n*-hexane / ethyl acetate (20/1 - 9/1 v/v) to afford 4-carbomethoxyacetophenoxime **2** (169 mg, 87 %) and 4-carbomethoxyacetophenone **3** (19.2 mg, 11 %).