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Intermolecular Cycloaddition of Ethyl Glyoxylate *O-tert*-Butyldimethylsilyloxime with Alkenes

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Abstract: Ethyl glyoxylate *O-tert*-butyldimethylsilyloxime (**12**), on treatment with various alkenes **7** in the presence of 2.2 equiv. of BF₃•OEt₂, generated *C*-ethoxycarbonyl *N*-boranonitrone (**13**), which underwent intermolecular cycloaddition to afford 3-(ethoxycarbonyl)isoxazolidines **14** in moderate to high yields.

Key words: cycloaddition, boron trifluoride, *N*-boranonitrone, alkenes, cycloadducts

Intramolecular oxime-olefin cycloaddition, so called IOOC, appears to be one of the operationally simplest cycloadditions. Thus, heating oximes 1 bearing an olefin moiety in the molecule give N-nonsubstituted isoxazolidines 3 via tautomerization from 1 to NHnitrone 2.^{1,2} However, the cycloaddition often require very high temperature conditions because of the thermodynamically unfavorable tautomerization (Scheme 1).³ In addition, intermolecular oxime-olefin cycloaddition is known to be restricted to reactions of only a few oximes with *N*-methyl or Nphenylmareimides.4



Scheme 1



Scheme 2

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Recently, we reported BF₃-mediated cycloaddition of *O*tert-butyldimethylsilyloximes (*O*-TBS oximes) as an alternative method for the efficient synthesis of isoxazolidines **3**. Treatment of oximes **4** with BF₃•OEt₂ generates *N*-boranonitrones **5**, which undergo intramolecular cycloaddition affording the products **3** after extractive workup (Scheme 2).⁶ This procedure is highly useful for synthesis of isoxazolidine derivatives because the reaction proceeds smoothly at room temperature using the strong N-B and Si-F affinity and is applicable to various substrates giving the corresponding products in good to high yields.

We envisioned the extension of this procedure to the intermolecular counter part, and have now found that exposure of ethyl glyoxylate *O*-TBS oxime **12** to $BF_3 \cdot OEt_2$ in the presence of various alkenes **7** underwent intermolecular cycloaddition to afford cycloadducts **14** in moderate to good yields.^{7,8}

Our investigation began with the simplest extension of the intramolecular cycloaddition to intermolecular version (Scheme 3). When benzaldehyde *O*-TBS oxime **6** was treated with styrene (**7a**) (10 eq.) in the presence of 2.2 eq. of BF₃•OEt₂ in (CH₂Cl)₂ at 60 °C for 24 h, intermolecular cycloaddition proceeded, however, to give only 40% yield of cycloadduct **9**.⁹



Scheme 3

From the viewpoint of the electrophilic nature of *N*-boranonitrone, replacement of the phenyl group in

nitrone **8** by an ester group was examined to activate the intermediary *N*-boranonitrone.¹⁰ The requisite *O*-TBS oxime **12** was readily prepared from chloral hydrate (**10**) which react with hydroxyammonium sulfate in the presence of MgCl₂ in ethanol solution to furnish glyoxylate oxime (**11**)¹¹ (Scheme 4). Silylation of ethyl glyoxylate oxime **11** afforded ethyl glyoxylate *O*-TBS oxime **12** in 86% yield.¹²



The intermolecular cycloadditions of the starting O-TBS oxime 12 with various alkenes 7 were carried out in the presence of 2.2 eq. of BF₃•OEt₂ in (CH₂Cl)₂ under argon at 60 °C. (Scheme 5, Table 1). In contrast to the reaction of benzaldehyde oxime 6, reaction of oxime 12 with styrene (7a) smoothly proceeded to give the corresponding cycloadduct 14a in 71% yield, probably via nitrone **13** as active intermediate (entry 1).¹³ Reaction of aliphatic terminal alkene 7b and 7c also afforded the cycloadduct 14b and 14c in 78% and 61% yields as 77:1 (14b) and 7:1 (14c) mixture of diastereomer respectively (entries 2 and 3). As expected, 1,1-disubstituted alkenes 7d reacted with nitrone 13, giving rise to 5,5-disubstituted isoxazolidine 14d in low yield (entry 4). This low yield may be due to porimerization of alkene **7d** during the reaction. Reactions of 1-methyl cyclopentene (7e) afforded bicyclic products 14e in 79% yields as 3.4:1 mixture of diastereomer (entry 5).

The *N*-boranonitrone **13** was found to react with 2-substituted acrylate (Scheme 6). When oxime **12** was treated with ethyl acrylate (**7g**) in the presence of BF₃•OEt₂ in (CH₂Cl)₂ at 60 °C for 15 h, cycloadduct **14g** was obtained in 53% yield as a 7:1 mixture of diastereomers. This reaction would be applicable for syntheses of naturally occurring 4-hydroxy-4-substituted glutamic acids.¹⁴

Scheme 6

In conclusion, we have developed a novel intermolecular cycloaddition of *O*-TBS oxime **12** with various alkenes **7** via *N*-boranonitrone **13** as active intermediate, giving the

Scheme 5

Table 1. Intermolecular Cycloaddition of *O*-TBS oxime **12** with Alkenes **7a-e** in the presence of BF₃•OEt₂^a





^a All reactions were carried out with 2.2 equiv of $BF_3 \bullet OEt_2$ in $(CH_2Cl)_2$ at 60 °C.

corresponding isoxazolidines 14. To the best of our knowledge, the present reaction is the first example of intermolecular cycloaddition of oxime derivatives that can react with various alkenes. Further work will be devoted to the extension of the procedure to the other functionalized oximes and alkenes, as well as to the application of the procedure in natural product synthesis.

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- (9) For completion of the cycloaddition, two equiv. of BF₃•OEt₂ are essential. See ref 6.
- (10) During study on the intramolecular cycloaddition of *N*boranonitrone, we observed the tendency that electronrich carbon atom in the olefin attacks the nitrone-carbon. For example, reaction of oxime **15a** with BF₃•OEt₂ afforded cycloadduct **16** bearing bicyclo[3.3.0] system whereas a similar reaction of oxime **15b** afforded cycloadduct **17** having bicyclo[3.2.1] system. See ref 6b.



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- Preparation of ethyl 2-[tert-butyldimethylsilyloxy-(12)imino]acetate (12): The mixture of ethyl 2-hydroxyiminoacetate (11) 11 (0.91 g, 7.8 mmol), *tert*butylchlorodimethylsilane (1.77 g, 11.8 mmol), and imidazole (1.60 g, 23.5 mmol) in DMF (12 ml) was stirred at room temperature for 46 h. The reaction mixture was poured into water and extracted with Et₂O. The combined organic phases were washed with brine and dried with MgSO₄. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography on silica gel with hexane-OEt2 (20:1) to afford 12 (1.77 g, 98%) as a colorless oil. IR 2934, 1749, 1728 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.62 (1H, s), 4.30 (2H, J = 7.1 Hz), 1.33 (3H, t, J = 7.1 Hz), 0.95 (9H, s), 0.23 (6H, s); ¹³C NMR (75 MHz, CDCl₃) & 162.3, 146.1, 61.3, 25.7, 18.0, 14.0, -5.4; LRMS 231.14; HRMS (EI): calcd for C10H21NO3Si 231.1291, found 231.1270.
- (13) Typical procedure for the cycloaddition: To a solution of 12 (300 mg, 1.3 mmol) in (CH₂Cl)₂ (10 mL) was added

7e (1.1 mL, 13 mmol) and BF₃•OEt₂ (310 µL, 2.9 mmol) at room temperature, and then the mixture was heated at 60 °C for 2 h (The reaction was monitored by thin layer chromatography). After cooling, the reaction mixture was poured into saturated NaHCO3 solution and was extracted with CHCl₃. The combined organic layer were washed with brine and dried with MgSO₄. The residue was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with hexane-AcOEt (3:2) to give two diastereomers, 14e (160 mg, 61%) and 14e' (47 mg, 18%) as light brown oil. IR (neat) 1733 cm⁻¹; **14e**: ¹H NMR (300 MHz, CDCl₃) δ 5.90 (1H, br s), 4.23 (1H, q, J = 7.1 Hz), 4.12 (1H, d, J = 7.5 Hz), 2.73 (1H, dd, J = 14.5, 7.0 Hz), 1.77 (4H, m), 1.50 (2H, m), 1.40 (3H, s), 1.29 (1H, t, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 164.4, 95.5, 66.0, 61.1, 55.7, 39.5, 28.2, 26.4, 24.8, 14.2; LRMS 199.10; found HRMS (EI) calcd for C₁₀H₁₇NO₃ 199.1208, found 221.1187; **14e'**: ¹H NMR (300 MHz, CDCl₃) δ 5.93 (1H, br s), 4.23 (1H, q, J = 7.1 Hz), 3.56 (1H, d, J = 6.6 Hz), 2.49 (1H, s), 1.60 (6H, m), 1.37 (3H, m), 1.29 (3H, d, J = 7.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.3, 96.1, 70.2, 61.4, 59.5, 38.5, 32.2, 24.4, 23.5, 14.1;

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Graphic Abstract



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