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

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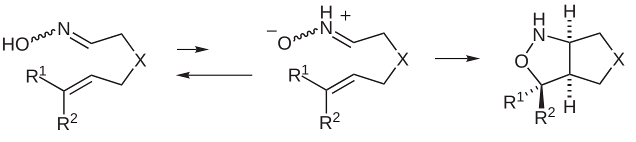
Abstract: Ethyl glyoxylate *O-tert*-butyldimethylsilyloxime, on treatment with various alkenes in the presence of $BF_3{\cdot}OEt_2$, generated a *C*-ethoxycarbonyl *N*-boranonitrone intermediate, which underwent intermolecular cycloaddition to afford 3-(ethoxycarbonyl)isoxazolidines in moderate to high yields.

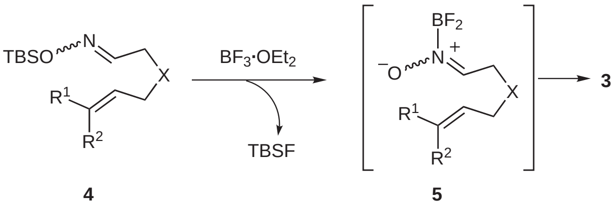
Key words: cycloaddition, boron trifluoride, *N*-boranonitrone, alkenes, cycloadducts

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-unsubstituted isoxazolidines **3** via tautomerization from **1** to NH-nitrone **2**.[1,2] However, the cycloaddition often requires 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 *N*-phenylmaleimides.[4,5]



Scheme 1

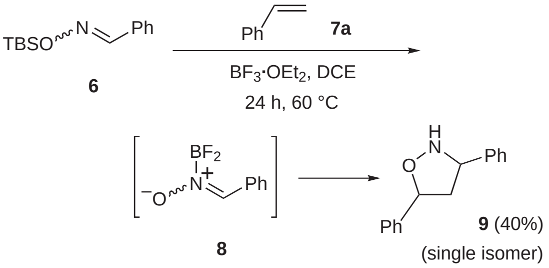
Recently, we reported BF_3-mediated cycloaddition of *O-tert*-butyldimethylsilyloximes (*O*-TBS oximes) as an alternative method for the efficient synthesis of isoxazolidines **3**. Treatment of oximes **4** with $BF_3{\cdot}OEt_2$ generates *N*-boranonitrones **5**, which undergo intramolecular cycloaddition 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.



Scheme 2

We envisioned the extension of this procedure to the intermolecular counterpart, 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** resulted in the 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 equiv) in the presence of $BF_3{\cdot}OEt_2$ (2.2 equiv) in 1,2-dichloroethane (DCE) at 60 °C for 24 hours, 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 reacted with hydroxyammonium sulfate in the presence of $MgCl_2$ in ethanol solution to furnish glyoxylate oxime **11**[11]

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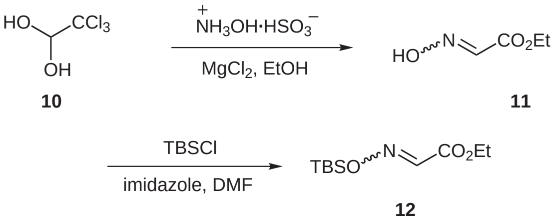
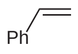
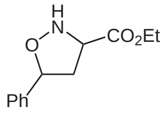
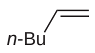
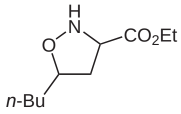
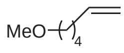
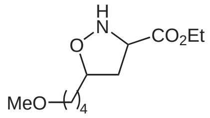
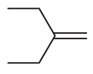
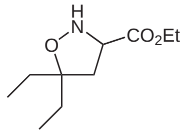
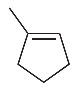
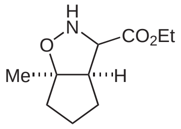


Scheme 4

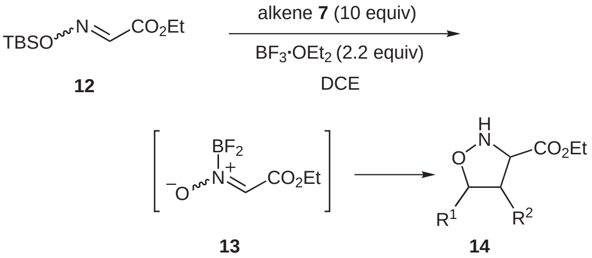
(Scheme 4). Silylation of ethyl glyoxylate oxime (**11**) afforded ethyl glyoxylate *O*-TBS oxime (**12**) in 86% yield.[12]

The intermolecular cycloadditions of the starting *O*-TBS oxime **12** with various alkenes **7** were carried out in the presence of 2.2 equivalents of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane 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 alkenes **7b** and **7c** also afforded the cycloadducts **14b** and **14c** in 78% and 61% yields as 77:1 (**14b**) and 7:1 (**14c**) mixture of diastereomers, respectively (entries 2 and 3). As expected, 1,1-disubstituted alkene **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 polymerization of alkene **7d** during the reaction. Reaction of 1-methylcyclopentene (**7e**) afforded bicyclic product **14e** in 79% yields as 3.4:1 mixture of diastereomers (entry 5).

Table 1 Intermolecular Cycloaddition of *O*-TBS Oxime **12** with Alkenes **7a**–**e** in the Presence of $BF_3{\cdot}OEt_2$[a]

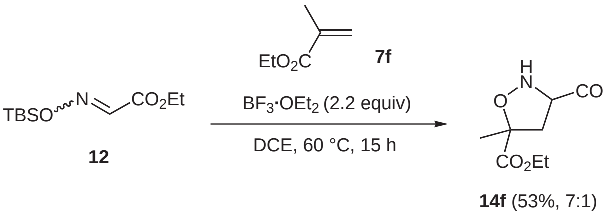
Entry	Alkene **7**	Time	Product **14**	Yield (%)
1	 **7a**	2 h	 **14a**	71 (5:1)
2	 **7b**	18 h	 **14b**	78 (77:1)
3	 **7c**	22 h	 **14c**	61 (7:1)
4	 **7d**	3 h	 **14d**	28
5	 **7e**	2 h	 **14e**	79 (3.4:1)

[a] All reactions were carried out with $BF_3{\cdot}OEt_2$ (2.2 equiv) in 1,2-dichloroethane at 60 °C.



Scheme 5

The *N*-boranonitrone **13** was found to react with 2-substituted acrylate (Scheme 6). When oxime **12** was treated with ethyl acrylate **7f** in the presence of $BF_3{\cdot}OEt_2$ in 1,2-dichloroethane at 60 °C for 15 hours, cycloadduct **14f** 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 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.

Acknowledgment

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References and Notes

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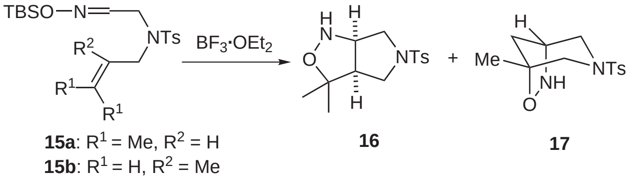
(9) For completion of the cycloaddition, 2 equiv of $BF_3{\cdot}OEt_2$ are essential. See ref. 6.

(10) During study on the intramolecular cycloaddition of *N*-boranonitrone, we observed the tendency that electron-rich carbon atom in the olefin attacks the nitrone-carbon. For example, reaction of oxime **15a** with $BF_3{\cdot}OEt_2$ afforded cycloadduct **16** bearing a bicyclo[3.3.0] system, whereas a similar reaction of oxime **15b** afforded cycloadduct **17** having a bicyclo[3.2.1] system (Scheme 7). See ref 6b.



Scheme 7

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(12) **Preparation of Ethyl 2-[*tert*-Butyldimethylsilyl-oxyimino]acetate (12)**: The mixture of ethyl 2-hydroxy-iminoacetate (**11**;[11] 0.91 g, 7.8 mmol), *tert*-butylchloro-dimethylsilane (1.77 g, 11.8 mmol), and imidazole (1.60 g, 23.5 mmol) in DMF (12 mL) was stirred at r.t. for 46 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The combined organic phases were washed with brine and dried with $MgSO_4$. The solvent was removed by rotary evaporation and the crude product was purified by column chromatography on silica gel with hexane–Et_2O (20:1) to afford **12** (1.77 g, 98%) as a colorless oil. IR: 2934, 1749, 1728 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.62$ (s, 1 H), 4.30 (q, $J = 7.1$ Hz, 2 H), 1.33 (t, $J = 7.1$ Hz, 3 H), 0.95 (s, 9 H), 0.23 (s, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.3$, 146.1, 61.3, 25.7, 18.0, 14.0, –5.4. LRMS: $m/z = 231.14$. HRMS (EI): m/z calcd for $C_{10}H_{21}NO_3Si$: 231.1291; found: 231.1270.

(13) **Typical Procedure for the Cycloaddition**: To a solution of **12** (300 mg, 1.3 mmol) in DCE (10 mL) were added **7e** (1.1 mL, 13 mmol) and $BF_3{\cdot}OEt_2$ (310 μL, 2.9 mmol) at r.t., and then the mixture was heated at 60 °C for 2 h. The reaction was monitored by TLC. After cooling, the reaction mixture was poured into sat. $NaHCO_3$ solution and was extracted with $CHCl_3$. The combined organic layers were washed with brine and dried with $MgSO_4$. The residue was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with hexane–EtOAc (3:2) to give two diastereomers, **14e** (160 mg, 61%) and **14e′** (47 mg, 18%) as light brown oils. **14e**: IR (neat): 1733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.90$ (br s, 1 H), 4.23 (q, $J = 7.1$ Hz, 2 H), 4.12 (d, $J = 7.5$ Hz, 1 H), 2.73 (dd, $J = 7.0$, 14.5 Hz, 1 H), 1.82–1.72 (m, 4 H), 1.59–1.45 (m, 2 H), 1.40 (s, 3 H), 1.29 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.4$, 95.5, 66.0, 61.1, 55.7, 39.5, 28.2, 26.4, 24.8, 14.2. LRMS: $m/z = 199$. HRMS (EI): m/z calcd for $C_{10}H_{17}NO_3$: 199.1208; found: 199.1187. **14e′**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.93$ (br s, 1 H), 4.23 (q, $J = 7.1$ Hz, 2 H), 3.56 (d, $J = 6.6$ Hz, 1 H), 2.49 (br s, 1 H), 1.92–1.65 (m, 6 H), 1.45–1.32 (m, 3 H), 1.29 (t, $J = 7.1$ Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.3$, 96.1, 70.2, 61.4, 59.5, 38.5, 32.2, 24.4, 23.5, 14.1.

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