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Scandium(III) triflate–TMSCl promoted cyclization of aziridin-1-yl oximes to 5,6-dihydro-4*H*-[1,2,4]oxadiazines

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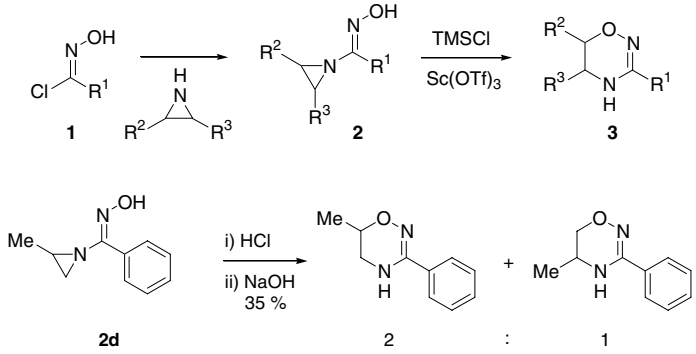
Abstract—A convenient and facile one-pot synthesis of 5,6-dihydro-4*H*-[1,2,4]oxadiazine is described. Treatment of aziridin-1-yl-oximes with Scandium(III) triflate readily afforded 5,6-dihydro-4*H*-[1,2,4]oxadiazine in the presence of chlorotrimethylsilane.

1,2,4-Oxadiazines are of pharmacological relevance and represent useful synthetic building blocks.[1] There have been few reports on the synthesis of 5,6-dihydro-4*H*-[1,2,4]oxadiazines.[2] The literature search revealed that the conventional synthetic methods for [1,2,4]oxadiazines mainly rely on the ring opening of aziridinyl-1-yl oximes mediated by hydrogen chloride and subsequent cyclization of chlorides by NaOH in two steps and low yield.

Rajagopalan and Talaty first reported that 5,6-dihydro-4*H*-[1,2,4]oxadiazine derivatives were synthesized from 1-aroylaziridine oximes.[3] Zen and Harada also reported that oxadiazines were prepared by the reaction of diketones with aliphatic nitro compounds in the presence of acetyl chloride through one-step synthesis.[4] Tabei et al. synthesized the oxadiazine derivatives by the reaction of bromoacetoacetyl bromide with benzamide oximes in low yields.[5] Treatment of aziridinylbenzaldoximes with hydrochloric acid and subsequent treatment with NaOH afforded the oxadiazine derivatives in low yields.[6] Aziridines can be used as important substrates to afford cycloaddition products or ring opened products mediated by Lewis acids.[7] Singh and co-workers[8] performed a successful application of aziridines with alcohols to afford a ring opened product mediated by Lewis acid.

In the course of our research for the preparation of novel protein tyrosine phosphatase 1B (PTP1B) inhibitors,[9]



Scheme 1.

Keywords: Aziridinyl oxime; Oxadiazine; Scandium triflate.
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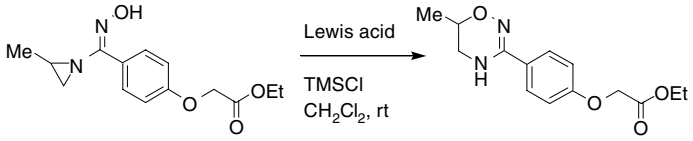
Table 1. Cyclization of aziridinylbenzaldoximes catalyzed by Lewis acid



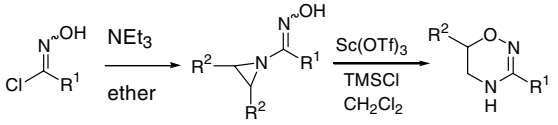
Entry	Lewis acid	Yield (%)
1	$Yb(OTf)_3$	24
2	AgOTf	0
3	$Cu(OTf)_2$	0[a]
4	$BF_3{\cdot}OEt_2$	0[a]
5	$Et_3O{\cdot}BF_4$	0
6	$Sc(OTf)_3$	45[b]
7	$Sc(OTf)_3$	77

[a] No substrate was recovered.
[b] The reaction was performed in the absence of chlorotrimethylsilane.

we sought to synthesize bioisosteric 5,6-dihydro-4*H*-[1,2,4]oxadiazines to replace the cyclopenta[*d*][1,2]-oxazine skeleton which has limited stability in either acidic or basic medium. Herein, we wish to report a convenient and facile one-pot synthesis of 5,6-dihydro-4*H*-[1,2,4]oxadiazines from aziridin-1-yl oximes mediated by Scandium(III) triflate in the presence of TMSCl. As shown in Scheme 1, the cyclization of aziridinyl oximes **3d** mediated by hydrochloric acid and subsequent treatment of NaOH afforded regioisomeric mixture of [1,2,4]oxadiazines (35%) as inseparable mixture (2:1 ratio) that could be characterized by ^1H and ^{13}C NMR spectra by analogy. For initial assessment, we examined the cyclization of **2** in the presence of various Lewis acids as given in Table 1.

The requisite substrates, aziridinylaldoximes, were prepared by reaction of suitable aziridines with chlorooximes **1**.[10] We observed that suitable aziridinylaldoxoximes were easily derived from their chlorooximes (**1a**–**f**)

Table 2. Synthesis of 1,2,4-oxadiazines



1 **2** **3**

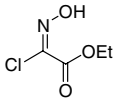
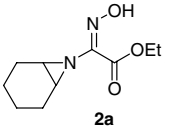
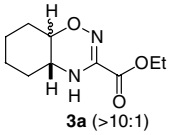
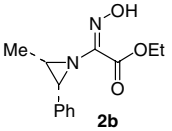
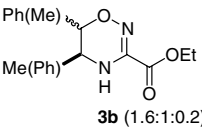
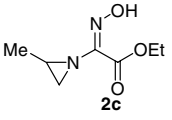
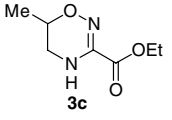
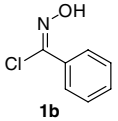
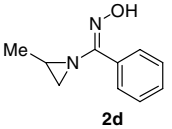
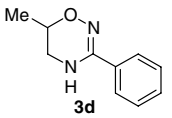
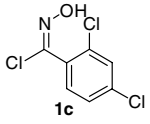
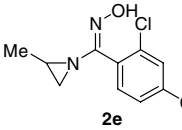
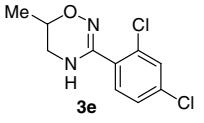
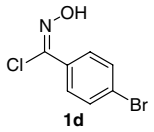
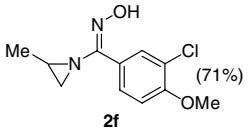
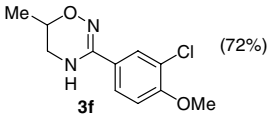
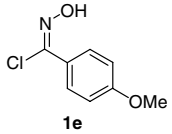
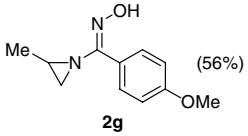
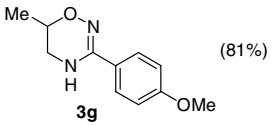
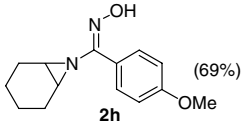
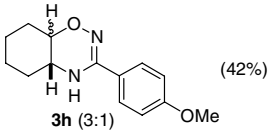
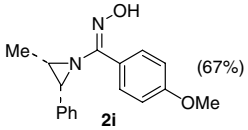
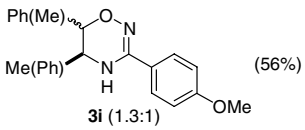
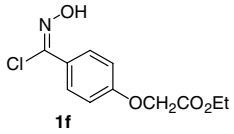
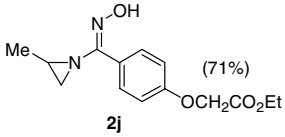
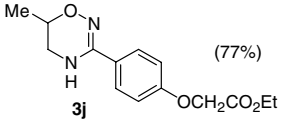
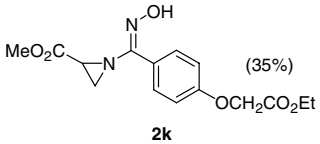
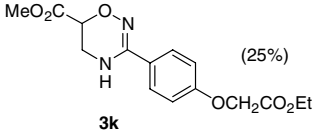
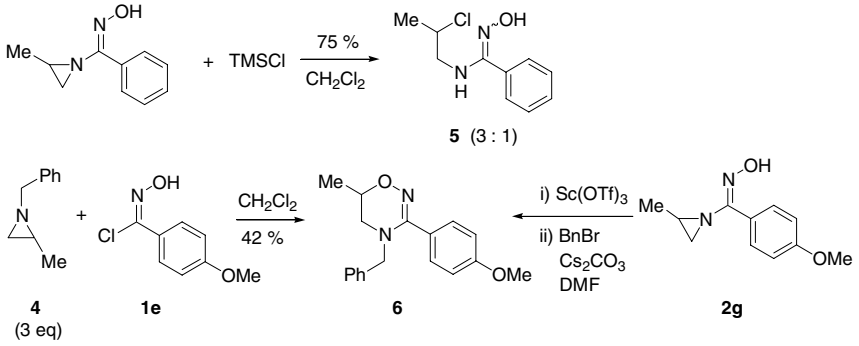
Entry	Chlorooxime	Aziridinyl oxime	[1,2,4]Oxadiazine
1	 **1a**	 (62%) **2a**	 (45%) **3a** (>10:1)
2	**1a**	 (71%) **2b**	 (56%) **3b** (1.6:1:0.2)
3	**1a**	 (81%) **2c**	 (61%) **3c**
4	 **1b**	 (66%) **2d**	 (69%) **3d**
5	 **1c**	 (65%) **2e**	 (65%) **3e**

Table 2 (*continued*)

Entry	Chlorooxime	Aziridinyl oxime	[1,2,4]Oxadiazine
6	 **1d**	 (71%) **2f**	 (72%) **3f**
7	 **1e**	 (56%) **2g**	 (81%) **3g**
8	**1e**	 (69%) **2h**	 (42%) **3h** (3:1)
9	**1e**	 (67%) **2i**	 (56%) **3i** (1.3:1)
10	 **1f**	 (71%) **2j**	 (77%) **3j**
11	**1f**	 (35%) **2k**	 (25%) **3k**

as given in Table 2. Chlorooximes **1** were easily derived from their aldehydes.[11] To evaluate the possibility of effecting Lewis acid-promoted cyclization of **2**, a representative selection of Lewis acids including $Yb(OTf)_3$, AgOTf, $Cu(OTf)_2$, $BF_3{\cdot}OEt_2$, and $Sc(OTf)_3$ were tested in their ability to form [1,2,4]oxadiazines **3**. Treatment of aziridinylaldoximes with optimal Lewis acid smoothly afforded dihydro-4*H*-[1,2,4]oxadiazines **3** in the presence of chlorotrimethylsilane. All experiments were run at room temperature with Lewis acid (1.1 equiv) in the presence of chlorotrimethylsilane (1.1 equiv).[12] In the preliminary experiments, $Sc(OTf)_3$ and $Yb(OTf)_3$ were found to facilitate the cyclization of aziridinylaldoxime to oxadiazines, but the reaction yields were unsatisfactory. The reaction gave only a ring opened product when chlorotrimethylsilane was used in the absence of Lewis acid within 30 min at room temperature, and the reaction did not proceed below 0 °C (Scheme 2). No substrate was recovered when boron trifluoride-diethyl etherate or copper triflate was used. (entries 4 and 5). The reaction was unsatisfactory when other Lewis acids were tested (entries 2 and 3).



Scheme 2.

Resubjection of ring opened product **5** in the presence of TMSCl or $Sc(OTf)_3$–TMSCl did not give rise to cyclized product with only the recovered starting material.

Reaction yields were significantly improved by the addition of chlorotrimethylsilane (1.1 equiv) to the reaction mixture, presumably because of preventing the formation of complex between Lewis acid and hydroxyl group.[13] The desired product **3d** was produced by use of either TMSOTf or TfOH in place of $Sc(OTf)_3$–TMSCl in low yield, 29% and 35% of the cyclized product, respectively. Treatment of aziridinylaldoximes (**2a**–**k**) with Scandium(III) triflate in the presence of chlorotrimethylsilane readily afforded [1,2,4]oxadiazine derivatives (**3a**–**k**) in moderate to excellent yields.

The functional group, such as carboethoxy (**3a**– **c**), was well tolerated in the reaction and aziridinyl oximes were readily cyclized into oxadiazines, regioselectively. In addition, fused (**3a**,**h**) and disubstituted oxadiazines (**3b**,**i**) were readily prepared from their corresponding aziridinyl oximes. We performed the reaction with aziridinylaldoximes (**2a**,**b**,**h**,**i**), and the corresponding [1,2,4]oxadiazines (**3a**,**b**,**h**,**i**) were produced with no diastereofacial selectivity presumably because of undergoing via carbocation formation. For **3b** and **3i**, the other possible isomers were not identified. We observed that the yields of **3h** and **3k** were very low presumably because of the steric and electronic environment of carboethoxy group. The regiochemical description of the product was unequivocally determined by decoupling experiment (^{1}H TOCSY) and characteristic splitting patterns of cyclized product.[14]

As an extended study, a novel cycloaddition of aziridine **4** and chlorooxime **1e** afforded oxadiazine in low yield (42%), along with by-products as inseparable mixture (Scheme 2). The structure of cycloaddition product **6** was conformed by the same compound derived from the cyclization of azridinyl oxime **2g** and subsequent treatment of benzyl bromide.

In summary, we performed a convenient and facile cyclization of aziridinyl oxime to 5,6-dihydro-4*H*-[1,2,4]-oxadiazines mediated by Scandium(III) triflate in the presence of chlorotrimethylsilane.

Acknowledgment

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12. *Typical procedure*: To a stirred solution of phenyl chlorooxime (1.3 g, 8.33 mmol) in diethyl ether (10 mL) was added 2-methylaziridine (1.7 mL, 24.9 mmol) in ether (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The resulting mixture was poured into water (15 mL) and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to afford **2d** (0.97 g, 66%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (m, 2H), 7.39 (m, 3H), 2.46 (m, 1H), 2.24 (d, $J = 6.0$ Hz, 1H), 2.18 (d, $J = 6.0$ Hz, 1H), 1.41 (d, $J = 5.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.4, 133.6, 129.4, 128.5, 126.8, 36.7, 36.3, 18.0; MS *m*/*e* (relative intensity) 176 (M^+, 83), 130 (4), 104 (100), 77 (45). Compound (**3d**): To a stirred solution of **2d** (100 mg, 0.57 mmol), $Sc(OTf)_3$ (307 mg, 0.62 mmol) in dichloromethane (3 mL) was added TMSCl (0.62 mmol, 80 μL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The resulting mixture was poured into water (10 mL) and neutralized with $NaHCO_3$ to pH = 7. The resulting mixture was extracted with ethyl acetate (20 mL) and the organic layer was dried over $MgSO_4$. The organic layer was concentrated under reduced pressure and purified by column chromatography to afford **3d** (69 mg, 69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.42 (m, 3H), 4.74 (br s, 1H), 3.85 (ddq, $J = 8.6$, 6.2, 2.8 Hz, 1H), 3.52 (ddd, $J = 11.5$, 8.6, 1.8 Hz, 1H), 3.27 (ddd, $J = 11.5$, 5.5, 2.8 Hz, 1H), 1.34 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 152.3, 133.0, 130.0, 128.5, 125.9, 67.6, 46.4, 17.4; MS *m*/*e* (relative intensity) 176 (M^+, 100), 159 (22), 146 (7), 130 (13), 117 (28), 104 (99), 77 (97).
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14. NMR spectra were taken on a Bruker DRX-300 instrument fitted with a 5 mm 1H/broadband gradient probe with inverse geometry (proton coils closest to the sample). The 1D TOCSY increment of **3d** (3.85 ppm) appeared when it was irradiated with methyl (1.34 ppm). The connectivity of carbon was also conformed by the ^{1}H homo-decoupling experiment of each peak by irradiation and the coupling constant was determined as described below in the typical procedure of this article.