Synthesis and [3+2] Cycloadditions of 3-Bromo-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxides

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Received 14 September 2009; revised 16 October 2009

Abstract: A number of 3-bromo-5,6-dihydro-4*H*-1,2-oxazine *N*-oxides have been synthesized and subjected to [3+2] cycloaddition with alkenes affording various types of products: 3-vinyloxazolines, isoxazoline *N*-oxides, and 3-functionalized 1,2-oxazine *N*-oxides.

Key words: 1,2-oxazine *N*-oxide, isoxazoline, cycloaddition, nitronates, nitroso acetals

5,6-Dihydro-4*H*-1,2-oxazine *N*-oxides (referred to in the text simply as 1,2-oxazine *N*-oxides) are widely used in organic synthesis.[1] The main practical application of these compounds is their [3+2] cycloaddition with alkenes followed by further reduction (Scheme 1).[2] This strategy was successfully used by Denmark and co-workers in their asymmetrical total syntheses of more than 20 natural compounds.

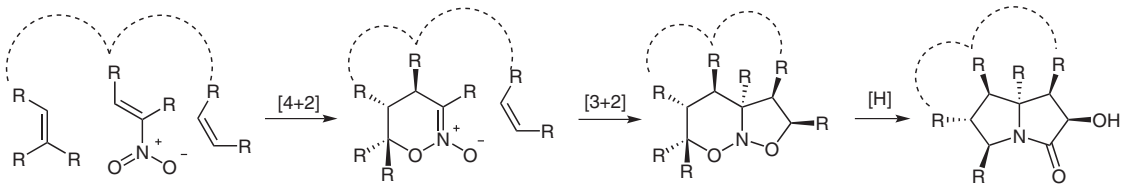
3-Substituted derivatives of 1,2-oxazine *N*-oxides have been, as yet, poorly investigated although the presence of a functional group incorporated directly into the reactive centre of such compounds can significantly alter their chemical properties and subsequently increase their synthetic value.

Between 1970 and 1980, it was reported by Chlenov and co-workers that 3-nitro-1,2-oxazine *N*-oxides undergo [3+2] cycloaddition with alkenes to give the products of various rearrangements of cyclic nitroso acetals[3] (Scheme 2). The reaction was not broadly introduced into organic synthesis due to the poor availability of the required 3-nitro derivatives[4] (5 stages starting from trinitromethane).

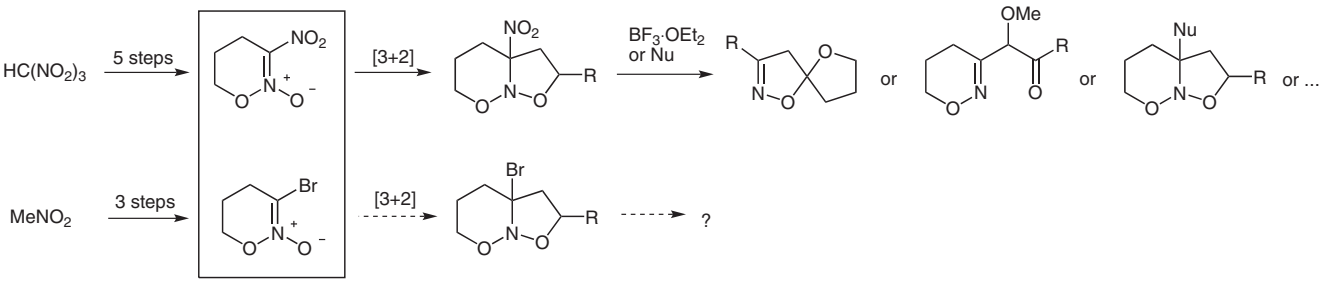
The goal of the current work became the investigation of 3-bromo-1,2-oxazine *N*-oxides, the analogues of previously studied 3-nitro-1,2-oxazine *N*-oxides. Only two representatives of 3-halo-1,2-oxazine *N*-oxides have been previously reported in the literature.[5]

There are two main synthetic approaches to 1,2-oxazine *N*-oxides: intramolecular cyclization and [4+2] cycloaddition of nitroalkenes to olefins.[1] In the current work the latter route was explored as it is easier and more convenient compared to the former (Scheme 3, Table 1). Initial 1-bromo-1-nitroalkenes were obtained from available β-nitrostyrenes in one step.

The configuration of the 3-bromo-1,2-oxazine *N*-oxides **1** obtained was determined by comparison of their spectral

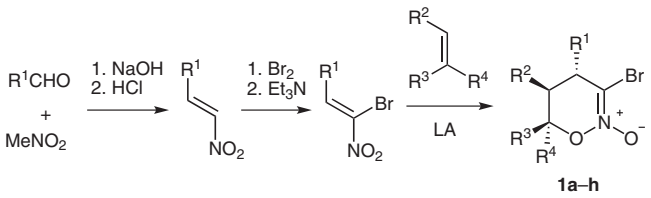


Scheme 1 Synthesis and [3+2] cycloadditions of 1,2-oxazine *N*-oxides



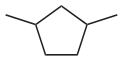
Scheme 2 Synthesis and [3+2] cycloaddition of 3-nitro-1,2-oxazine *N*-oxides

SYNTHESIS 2010, No. 3, pp 0407–0414
Advanced online publication: 07.12.2009
DOI: 10.1055/s-0029-1218594; Art ID: P12709SS



Scheme 3 Synthesis of 3-bromo-1,2-oxazine *N*-oxides **1a**–**h**

Table 1 Synthesis of 3-Bromo-1,2-oxazine *N*-Oxides **1a**–**h** (Scheme 3)

Entry	Product	R^1	R^2	R^3	R^4	Method[a]	Yield (%)
1	**1a**	4-$MeOC_6H_4$	H	Me	Me	A	90
2	**1b**	4-$MeOC_6H_4$	H	OMe	Me	B	97
3	**1c**	4-$MeOC_6H_4$	$-(CH_2)_4-$		H	C	86
4	**1d**	4-$MeOC_6H_4$			H	C	81
5	**1e**	Ph	$-(CH_2)_4-$		OMe	B	61
6	**1f**	4-$O_2NC_6H_4$	$-(CH_2)_4-$		H	D	5
7	**1g**	Ph	H	Me	Me	A	77
8	**1h**	4-$MeOC_6H_4$	H	OEt	H	E	61

[a] A: $SnCl_4$, alkene (10 equiv), –78 °C, 10 min; B: $SnCl_4$, alkene (2 equiv), –92 °C, 10 min; C: $SnCl_4$, alkene (5 equiv), –30 °C, 1 h; D: $SnCl_4$, alkene (10 equiv), –30 °C, 1 week; E: $TiCl_2(O\textit{i}\text{-}Pr)_2$, alkene (2 equiv), –78 °C, 1 h.

characteristics with those obtained for the 3-methyl- and 3-unsubstituted analogues.[6]

It was found that the stereoselectivity of the [4+2] cycloaddition of 1-bromo-1-nitronates was higher than the selectivity observed for their 3-methyl- and 3-unsubstituted analogues. Thus dichlorodiisopropoxytitanium(IV)-promoted cycloaddition of 4-methoxy-β-methyl-β-nitrostyrene with ethyl vinyl ether provided a mixture of *cis*- and *trans*-isomers in almost equal ratio,[6a] while the reaction of β-bromo-4-methoxy-β-nitrostyrene under similar conditions afforded exclusive formation of the *trans*-adduct **1h** (Table 1 entry 8). A similar result was previously reported by Denmark.[5]

However the rate of [4+2] cycloaddition of 1-bromo-1-nitroalkenes is significantly lower than that observed for 1-methyl-1-nitroalkenes. Therefore, 2-nitro-3-(4-nitrophenyl)prop-1-ene was treated with cyclohexene at –30 °C for one hour[6a] to give the corresponding product in 45% yield (70% conversion); while starting from the analogous 1-bromo-1-nitroalkene afforded the target product **1f** in 5% yield (50% conversion) after one week under the same conditions (Table 1 entry 6).

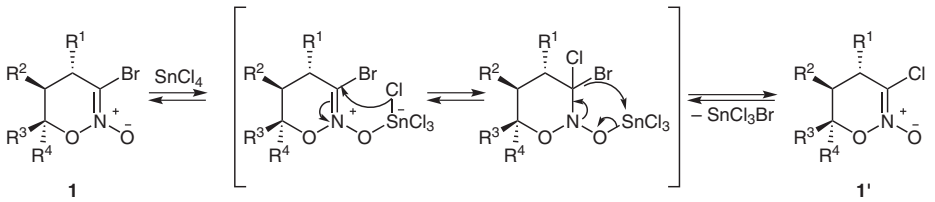
[4+2] Cycloaddition of 1-bromo-1-nitroalkenes is quite sensitive to the reaction conditions. The increase of temperature or exposition time leads to the formation of 3-chloro-1,2-oxazine *N*-oxides **1′** as byproducts (Scheme 4).

An attempt to obtain 3-bromo-1,2-oxazine *N*-oxides **1** from 2-alkyl-1-bromo-1-nitroethenes failed due to their instability under the described reaction conditions.

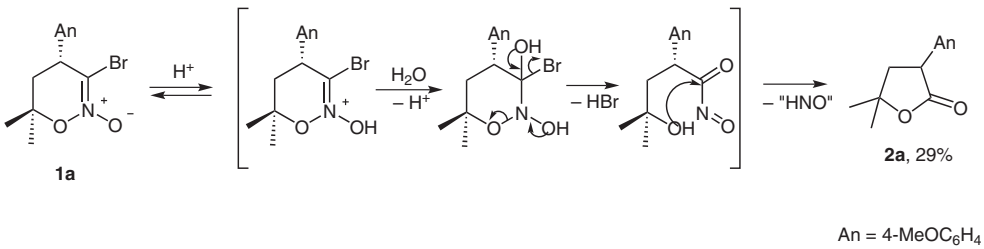
Unlike 3-methyl-1,2-oxazine *N*-oxides, which can be stored at room temperature for long periods, the similar 6-alkoxy-substituted 3-bromo-1,2-oxazine *N*-oxides are very labile products that undergo spontaneous decomposition at room temperature within several hours.

Usually [3+2] cycloaddition of 1,2-oxazine *N*-oxides with alkenes is carried out by stirring the mixture of reagents (possibly at a raised temperature).[7] However an attempt to subject 3-bromo-1,2-oxazine *N*-oxides **1** to this transformation led to intensive resinification of the reaction mixture after addition of the alkene.

The treatment of 3-bromo-1,2-oxazine *N*-oxide **1a** with a 100-fold excess of methyl acrylate at 20 °C afforded lactone **2a** as the sole isolated product in poor yield (29%). Notably the resulting pH of reaction mixture was very acidic. The proposed mechanism of this transformation is presented in Scheme 5.



Scheme 4 Formation of 3-chloro-1,2-oxazine *N*-oxides **1′** in [4+2] cycloadditions



Scheme 5 Hydrolysis of 3-bromo-1,2-oxazine *N*-oxides under standard conditions required for the [3+2]-cycloaddition process

We suggest that methyl acrylate is essential for generation of 'the first molecule' of HBr (see the mechanism for [3+2] cycloaddition, Scheme 7). A low yield of **2a** could be explained by intensive decomposition of **1** on exposure to HBr formed in the course of the reaction.

To avoid hydrolysis of *N*-oxides **1**, a set of experiments was carried out involving the treatment of a model *N*-oxide **1a** with styrene in the presence of various bases (K_2CO_3, NaOMe, $NaHCO_3$, pyridine, Et_3N). It was found that the sole reagent capable of suppressing the polymerization process was triethylamine. However, the reaction afforded almost quantitative formation of 3-vinyloxazine **3b** instead of the expected nitroso acetal **A′** (Scheme 6, Table 2). It was also shown that 3-bromo-1,2-oxazine *N*-oxides **1a**,**g** provided derivatives **3** when treated not only with styrene, but with other donor and acceptor alkenes (Table 2).

The data obtained revealed that 3-bromo-1,2-oxazine *N*-oxides undergo cycloaddition under milder conditions compared to the analogous 3-methyl- and 3-unsubstituted derivatives.[8]

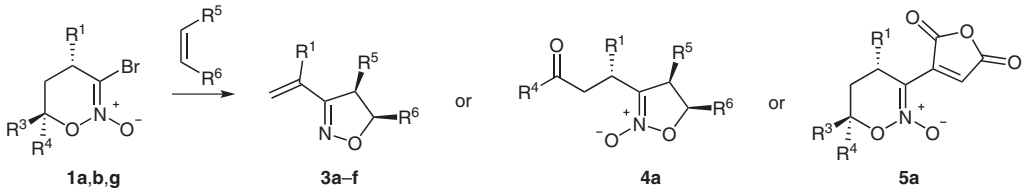
Similarly to the analogous 3-alkyl *N*-oxides, 3-bromo *N*-oxides could not be subjected to intramolecular coupling with internal alkenes such as dimethyl maleate, dimethyl fumarate, and methyl cinnamate. Surprisingly the reaction between 3-bromo *N*-oxide **1a** and maleic anhydride proceeded under mild conditions (toluene, reflux, 1 h) to give *N*-oxide **5a**.

The nature of substituents at the 5th and 6th positions of oxazine cycle has a dramatic effect on the reaction rate and outcome of 3-bromo *N*-oxide [3+2] cycloaddition with alkenes. Thus, treatment of bicyclic derivatives of 3-bromo *N*-oxides **1c–f** with methyl acrylate gave no results even under reflux for one week in toluene. Cycloaddition of 6-methoxy-substituted substrate **1b** and styrene afforded predominantly isoxazoline *N*-oxide **4a** instead of the 3-vinyloxazoline **3b** observed for **1a** (Scheme 6).

The suggested mechanism of the reaction of 3-bromo *N*-oxide **1** with alkenes proceeds through initial formation of bicyclic bromo nitroso acetal **A′** followed by rapid proton elimination to afford derivatives **B** and **C** (Scheme 7). Notably, in all experiments performed, deprotonation was exclusively regioselective. Further fragmentation of **B** or double bond migration in **C** provides the target products **3** and **5**, respectively. The bromo nitroso acetal arising from 6-methoxy derivative **1b** underwent ring opening resulting in the formation of a more stable cation **D**, which subsequently afforded the target nitronate **4a** after hydrolysis.

Cation **A** is suggested to be the key intermediate of the process although we could not trap it with such external nucleophiles as sodium azide, sodium cyanide, or sodium methoxide in methanol. Our attempts to detect the intermediately formed cycloadducts **A′** or cation **A** itself by careful NMR monitoring of the reaction mixture also met with no success.

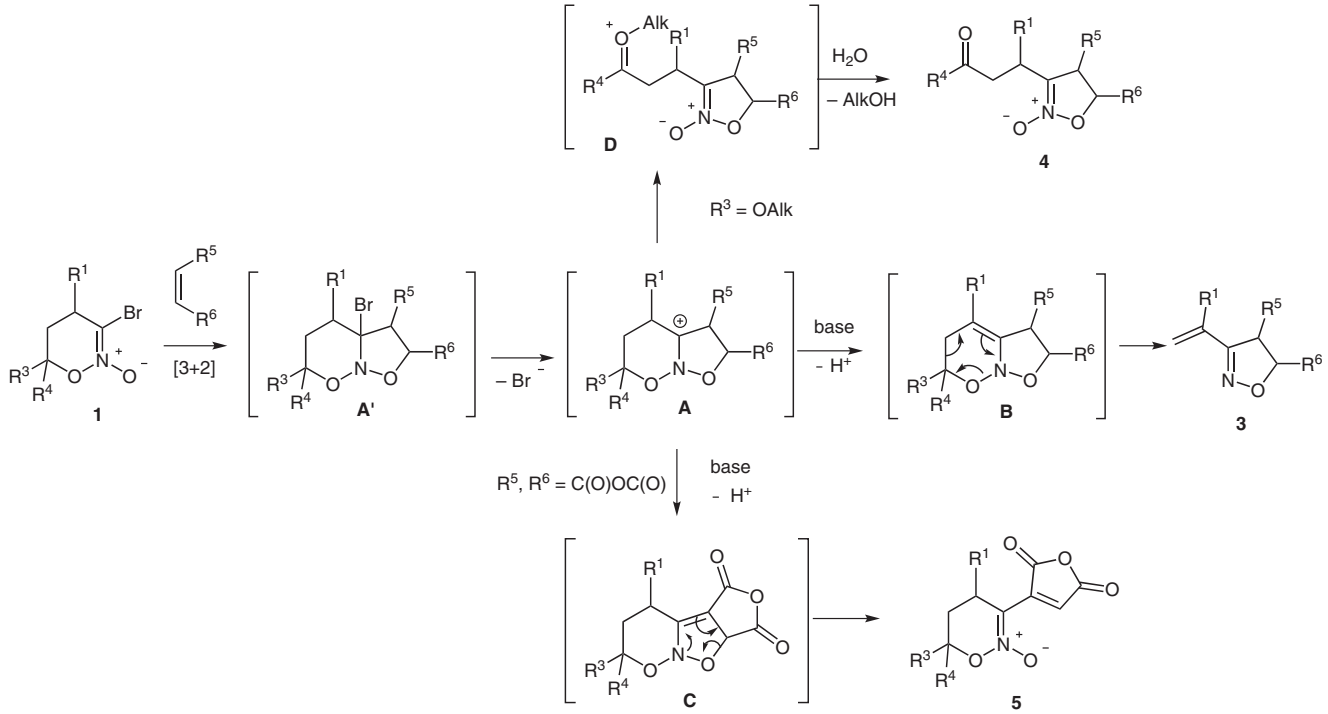
We suggest that removal of anion Br^- proceeds through interaction of the nitrogen atom lone-electron pair with an antibonding orbital of C–Br (Scheme 8),[9] which can be achieved only in the case of '*trans*'-connection of the rings. The isomers of 1,2-oxazine *N*-oxides with '*trans*'- and '*cis*'-fused rings are capable of interconversion by nitrogen atom inversion, which could easily occur under the reaction conditions[10] (110 °C). Thus, the initially formed conformation of nitroso acetal **A′** does not affect the outcome of the reaction (Scheme 8). In the case of tricyclic



Scheme 6 [3+2] Cycloaddition of 3-bromo-1,2-oxazine *N*-oxides

Table 2 Cycloaddition of **1** (Scheme 6)

Entry	Substate	R^1	R^3	R^4	R^5	R^6	Product	Time (h)	Yield (%)
1	**1a**	4-$MeOC_6H_4$	Me	Me	H	CO_2Me	**3a**	0.5	99
2	**1a**	4-$MeOC_6H_4$	Me	Me	H	Ph	**3b**	1	98
3	**1a**	4-$MeOC_6H_4$	Me	Me	H	OBu	**3c**	1	98
4	**1g**	Ph	Me	Me	H	CH_2OH	**3d**	1.3	95
5	**1g**	Ph	Me	Me	H	CO_2Me	**3e**	0.5	99
6	**1g**	Ph	Me	Me	H	COMe	**3f**	3	93
7	**1b**	4-$MeOC_6H_4$	OMe	Me	H	Ph	**3b** + **4a**	3	10 (**3b**) 58 (**4a**)
8	**1a**	4-$MeOC_6H_4$	Me	Me	C(O)OC(O)		**5a**	1	61



Scheme 7 Proposed mechanism for [3+2] cycloaddition of **1**

nitroso acetals previously synthesized by Denmark, by contrast, the initially conformer formed cannot be interconverted to give one with an antiperiplanar orientation of the nitrogen atom lone-electron pair and C–Br bond due to the rigidity of their cycle structure. Consequently, these compounds cannot produce cation **A** to undergo subsequent rearrangements and thereby are quite stable and can be isolated from the reaction mixture in a pure state.

Various compounds bearing the 3-vinyloxazoline fragment possess significant biological activity. For example, compounds related to **6** (Figure 1) represent human β-adrenergic receptor agonists and antagonists (β-AR), with potential use in cardiovascular (coronary heart disease, cardiac insufficiency) and respiratory therapy.[11] In recent years, active development of drugs against diabetes and obesity based on β-AR has been carried out. The data library of agents inhibiting Xa factor (preventing thrombosis formation) was created using compounds related to **7**.

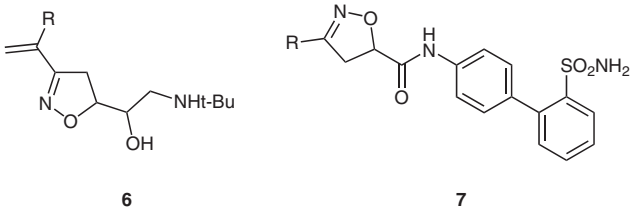
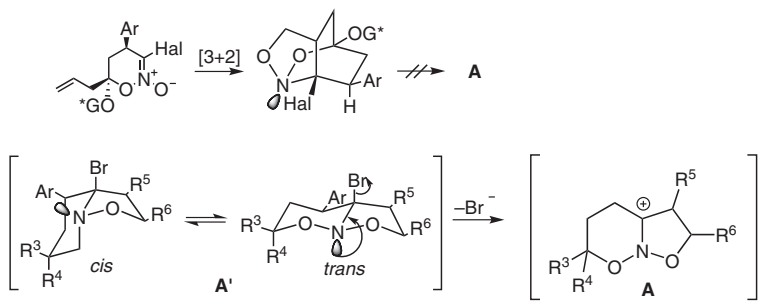


Figure 1 Pharmacologically active analogues of isoxazolines **3**

In conclusion, the present report describes a new synthesis of 3-bromo-1,2-oxazine *N*-oxides via a [4+2]-cycloaddition reaction and a thorough investigation of their [3+2] cycloadditions with alkenes has been carried out.

All [4+2]-cycloaddition reactions were performed in oven-dried (150 °C) glassware under an argon atmosphere. Melting points were determined on a Koffler melting point apparatus. Chromatographic separations were performed on silica gel (Merck Kieselgel 230–400 mesh) with analytical grade solvents. Analytical TLC was per-



Scheme 8 Structure of the earlier obtained bicyclic and tricyclic α-halo nitroso acetals

formed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light and/or anisaldehyde–MeOH–H_2SO_4 and/or ninhydrin. NMR spectras were recorded on an NMR spectrometer AM-300 (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz) for $CDCl_3$ solns with residual solvent peak as an internal standard. Elemental analyses were performed by the analytical center of N. D. Zelinsky Institute of Organic Chemistry.

Hexane, EtOAc, toluene, Et_2O, EtOH, and MeOH were distilled without drying agents. The following reaction solvents and reagents were distilled from the indicated drying agents: CH_2Cl_2, Et_3N, $SnCl_4$ (CaH_2), $CHCl_3$ (P_2O_5). The following chemicals were purchased from the indicated sources: 2-methoxypropene, ethyl vinyl ether, methyl acrylate, cyclopentene, butyl vinyl ether, $TiCl_4$, Ti(O*i*-Pr)$_4$, MVK, cyclohexene, styrene, maleic anhydride, allyl alcohol (Acros), isobutylene, norbornene (Aldrich). β-Nitrostyrene, and *p*-nitro-β-nitrostyrene were prepared according to the literature procedure for β-nitrostyrene.[12] Brine refers to sat. aq NaCl soln.

1-(2-Bromo-2-nitrovinyl)-4-methoxybenzene

To a stirred soln of *p*-methoxy-β-nitrostyrene (15.57 g, 87 mmol) in $CHCl_3$ (100 mL), Br_2 (4.5 mL, 88 mmol) was added at r.t. within 5 min. The mixture was refluxed for 20 min. The temperature was decreased to 8 °C and soln of Et_3N (15.7 mL, 113 mmol) was added dropwise during 20 min. The mixture was maintained for 10 min and poured into a mixture of EtOAc (300 mL) and H_2O (300 mL). The organic layer was washed with, H_2O (200 mL), brine (2 × 150 mL) and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was recrystallized (EtOH) to give the product (20.4 g, 91%) as yellow crystals; R_f = 0.76 (hexane–EtOAc, 1:1) (UV); mp 60–62 °C (EtOH) (Lit.[13] 67–68 °C).

1-(2-Bromo-2-nitrovinyl)benzene

To a stirred soln of β-nitrostyrene (42.9 g, 0.288 mol) in $CHCl_3$ (300 mL) was added a soln of Br_2 (14.9 mL, 0.29 mol) in $CHCl_3$ (10 mL) at r.t. over 5 min; the mixture was refluxed for 35 min. The temperature was decreased to 8 °C and soln of Et_3N (52.0 mL, 0.374 mol) in $CHCl_3$ (50 mL) was added dropwise over 30 min. The mixture was maintained for 15 min and poured into a mixture of $CHCl_3$ (100 mL) and H_2O (400 mL). The organic layer was washed with H_2O (400 mL) and brine (2 × 250 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized (EtOH) to give the product (49.9 g, 76%) as yellow crystals; mp 67 °C (EtOH) (Lit.[13] 67 °C); R_f = 0.62 (hexane–EtOAc, 1:1) (UV).

1-(2-Bromo-2-nitrovinyl)-4-nitrobenzene

To a stirred soln of *p*-nitro-β-nitrostyrene (6.53 g, 34.0 mmol) in CH_2Cl_2 (150 mL) was added Br_2 (1.73 mL, 34 mmol) at r.t. over 2 min. The mixture was refluxed for 3 h. The temperature was decreased to 8 °C and soln of Et_3N (6.12 mL, 43.9 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 30 min. The mixture was maintained for 15 min and poured into a mixture of EtOAc (250 mL) and H_2O (300 mL). The organic layer was washed with H_2O (200 mL) and brine (2 × 200 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was recrystallized (EtOH) to give the product (5.66 g, 61%) as yellow crystals; mp 130–134 °C (EtOH) (Lit.[14] 134–136 °C); R_f = 0.63 (hexane–EtOAc, 1:1) (UV).

3-Bromo-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxides 1; General Procedure

$SnCl_4$ (0.65 mL, 5.5 mmol) was added to a stirred soln of nitroalkene (5 mmol) in CH_2Cl_2 (25 mL) at –78 °C in dry argon and the mixture stirred at this temperature for 5 min. The alkene (see Table 1) was added dropwise at the temperature indicated in Table 1 and stirred for the indicated time; it was then poured into EtOAc (150 mL) and sat. aq $NaHCO_3$ (100 mL). The organic layer was washed with sat. aq $NaHCO_3$ (50 mL), H_2O (100 mL), and brine (2 × 50 mL) and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was recrystallized (hexane–EtOAc, 3:1) to give colorless crystals.

(*R*/*S*)-3-Bromo-4-(4-methoxyphenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (1a)

Mp 124–125 °C (Et_2O); R_f = 0.37 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.42 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 2.18 (m, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 3.99 (dd, *J* = 11.1, 8.4 Hz, 1 H, CH), 6.88 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.10 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 22.2, 27.4 (CH_3), 43.4 (CH_2), 46.7 (Ar-*C*H), 55.4 (OCH_3), 83.3 (C), 111.2 (C=N), 114.5, 129.0 (CH_{Ar}), 131.9 (C_{Ar}), 159.3 (*C*OCH_3).

Anal. Calcd for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46. Found: C, 49.75; H, 5.18; N, 4.43.

***rel*-(4*R*,6*R*)-3-Bromo-6-methoxy-4-(4-methoxyphenyl)-6-methyl-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (1b)**

Mp 57–61 °C (Et_2O); R_f = 0.44 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.55 (s, 3 H, CH_3), 2.18 (dd, *J* = 11.8, 13.8 Hz, 1 H, CH_2), 2.41 (dd, *J* = 7.2, 13.8 Hz, 1 H, CH_2), 3.51 (s, 3 H, OCH_3), 3.81 (s, 3 H, Ar-OCH_3), 4.14 (dd, *J* = 7.2, 11.8 Hz, 1 H, CH), 6.89 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.12 (d, *J* = 8.5, 2 H, CH_{Ar}).

^{13}C NMR: δ = 20.4 (CH_3), 42.2 (CH_2), 45.5 (Ar-*C*H), 50.6 (OCH_3), 55.3 (Ar-OCH_3), 105.4 (C), 112.2 (C=N), 114.5, 129.2 (CH_{Ar}), 131.8 (C_{Ar}), 159.3 (*C*OCH_3).

Anal. Calcd for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24. Found: C, 47.35; H, 4.77; N, 4.15.

***rel*-(4*R*,4a*S*,8a*S*)-3-Bromo-4-(4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine *N*-Oxide (1c)**

Mp 123–124 °C (Et_2O); R_f = 0.47 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.13–2.18 (m, 9 H, CH, CH_2), 3.76 (s, 1 H, Ar-CH), 3.81 (s, 3 H, OCH_3), 4.75 (br s, 1 H, OCH), 6.91 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.12 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 19.9, 24.5, 27.4, 28.6 (CH_2), 42.1 (Ar-*C*H), 53.8 (CH), 55.3 (OCH_3), 77.2 (OCH), 107.6 (C=N), 114.5, 128.6 (CH_{Ar}), 132.9 (C_{Ar}), 159.2 (*C*OCH_3).

Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.96; H, 5.33; N, 4.12. Found: C, 52.56; H, 5.29; N, 4.04.

***rel*-(4*R*,4a*S*,5*S*,8a*S*)-3-Bromo-4-(4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-5,8-methano-1,2-benzoxazine *N*-Oxide (1d)**

Mp 134–136 °C (Et_2O); R_f = 0.51 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.03–1.76 (m, 6 H, CH_2), 2.03 (br s, 1 H, CH_2CH), 2.43 (dd, *J* = 10.5, 6.6 Hz, 1 H, CH), 2.56 (d, *J* = 5.3 Hz, 1 H, CH_2CH), 3.71 (d, *J* = 10.5 Hz, 1 H, Ar-CH), 3.83 (s, 3 H, OCH_3), 4.57 (d, *J* = 6.6 Hz, 1 H, OCH), 6.89 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.13 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 24.1, 28.5, 33.0 (CH_2), 39.9, 41.5 (*C*HCH_2), 49.6 (Ar-*C*H), 55.3 (OCH_3), 56.6 (CH), 89.1 (OCH), 114.1 (CH_{Ar}), 115.6 (C=N), 129.8 (CH_{Ar}), 130.9 (C_{Ar}), 159.5 (*C*OCH_3).

Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; Br, 3.98. Found: C, 54.37; H, 5.26; N, 3.91.

***rel*-(4*R*,4a*S*,8a*S*)-3-Bromo-8a-methoxy-4-phenyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine *N*-Oxide (1e)**

Mp 121–125 °C (Et_2O); R_f = 0.50 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.10–1.79 (m, 8 H, CH_2), 2.20–2.35 (m, 1 H, CH), 3.48 (s, 3 H, OCH_3), 3.70 (d, *J* = 11.2 Hz, 1 H, Ph-CH), 7.1–7.44 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 22.0, 24.7, 26.5, 28.45 (CH_2), 48.1, 49.5 (Ph*C*H), 52.0 (OCH_3), 108.6 (C=N), 111.6 (CO), 127.0 (*p*-C_{Ph}), 128.6, 128.9 (CH_{Ph}), 139.1 (C_{Ph}).

Anal. Calcd for $C_{15}H_{18}BrNO_3$: C, 52.96; H, 5.33; N, 4.12. Found: C, 52.99; H, 5.78; N, 4.15.

***rel*-(4*R*,4a*S*,8a*S*)-3-Bromo-4-(4-nitrophenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine *N*-Oxide (1f)**

Mp 147–153 °C (Et_2O); R_f = 0.57 (hexane–EtOAc, 5:1) (UV).

^{1}H NMR: δ = 1.21–2.19 (m, 9 H, CH, CH_2), 3.95 (s, 1 H, Ar-CH), 4.72 (s, 1 H, OCH), 7.41 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 8.26 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 19.8, 24.4, 27.6, 28.5 (CH_2), 41.9 (CH), 53.4 (Ar-*C*H), 77.3 (OCH), 105.4 (C=N), 124.5, 128.6 (CH_{Ar}), 147.6, 147.8 (C_{Ar}).

Anal. Calcd for $C_{14}H_{15}BrN_2O_4$: C, 47.34; H, 4.26; N, 7.89. Found: C, 47.43; H, 4.60; N, 8.00.

(*R*/*S*)-3-Bromo-6,6-dimethyl-4-phenyl-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (1g)

Mp 125–126 °C (Et_2O); R_f = 0.41 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.40 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 2.15 (m, 2 H, CH_2), 3.69 (dd, *J* = 11.0, 8.3 Hz, 1 H, Ar-CH), 7.09–7.40 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 22.1, 27.3 (CH_3), 43.1 (CH_2), 48.0 (Ph*C*H), 83.4 (C), 110.6 (C=N), 126.1, 127.5, 126.4 (CH_{Ph}), 138.9 (C_{Ph}).

Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.81; H, 5.13; N, 4.72.

***rel*-(4*R*,6*R*)-3-Bromo-6-ethoxy-4-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (1h)**

Mp 105–107 °C (Et_2O); R_f = 0.44 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.30 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 2.34 (m, 2 H, CH_2), 3.74 (dd, *J* = 9.8, 7.1 Hz, 1 H, CH_2CH_3), 3.81 (s, 3 H, OCH_3), 4.08 (dd, *J* = 9.8, 7.1 Hz, 1 H, CH_2CH_3), 4.16 (dd, *J* = 11.0, 8.1 Hz, 1 H, Ar-CH), 5.46 (br s, 1 H, OCH), 6.88 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.12 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 15.1 (CH_2CH_3), 36.3 (CH_2), 44.4 (Ar-*C*H), 55.3 (OCH_3), 65.4 (CH_2CH_3), 102.0 (CO), 111.5 (C=N), 114.5, 129.1 (CH_{Ar}), 131.9 (C_{Ar}), 159.3 ($COCH_3$).

Anal. Calcd for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24. Found: C, 47.19; H, 5.20; N, 4.33.

***rel*-(4*R*,6*R*)-3-Bromo-6-ethoxy-4-(4-methoxyphenyl)-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (1h) Using $TiCl_2$(O*i*-Pr)$_2$**

To a stirred soln of 1-(2-bromo-2-nitrovinyl)-4-methoxybenzene (3.10 g, 12.0 mmol) and ethyl vinyl ether (2.3 mL, 24.0 mmol) in CH_2Cl_2 (36 mL) was added a soln of Ti(O*i*-Pr)$_2Cl_2$ (11.38 g, 48.0 mmol) in CH_2Cl_2 (30 mL) at –78 °C under an argon atmosphere. The mixture was maintained at –78 °C for 1 h and then quenched with 0.5 M NaOH in MeOH (96 mL) and poured into a mixture of CH_2Cl_2 (200 mL), sat. aq Na_2CO_3 (150 mL), and aq 0.1 M NaOH (200 mL). The organic layer was washed with aq 0.1 M NaOH (150 mL). The aqueous layer was washed with CH_2Cl_2 (150 mL). The combined organic layers were washed with aq 0.1 M NaOH (100 mL), sat. aq $NaHCO_3$ (2 × 150 mL), and brine (3 × 150 mL) and dried (Na_2SO_4). The solvents were removed in vacuo to give **1h** as white crystals.

3-(4-Methoxyphenyl)-5,5-dimethyldihydrofuran-2(3*H*)-one (2a)

The soln of **1a** (0.314 g, 1 mmol) in methyl acrylate (9.05 mL, 100 mmol) was stirred for 1 d. The mixture was poured into a mixture of EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 40 mL) and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was recrystallized (Et_2O) to give **2a** (0.064 g, 29%) as a white solid; mp 60–62 °C; R_f = 0.51 (EtOAc–MeOH, 2:1).

^{1}H NMR: δ = 1.46, 1.52 (2 s, 6 H, CH_3), 2.18 (t, *J* = 12.6 Hz, 1 H, CH_2), 2.54 (dd, *J* = 12.6, 9.2 Hz, 1 H, CH_2), 3.78 (s, 3 H, OCH_3), 3.97 (dd, *J* = 11.7, 9.2 Hz, 1 H, CH), 6.88 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.19 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 26.8, 28.9 (CH_3), 44.1 (CH), 46.0 (CH_2), 55.2 (OCH_3), 81.8 [$C(CH_3)_2$], 114.2 (CHAr), 128.9 (C_{Ar}), 129.0 (CH_{Ar}), 158.8 ($COCH_3$), 176.7 (C=O).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; Found: C, 70.66; H, 7.24.

3-Vinylisoxazolines 3; General Procedure

A soln of 1,2-oxazine *N*-oxide **1** (1 mmol), Et_3N (0.42 mL, 3 mmol), and alkene (5 mmol) in toluene (10 mL) was refluxed for the time indicated in Table 2. The mixture was poured into a mixture of EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 40 mL) and dried (Na_2SO_4). Solvents were removed in vacuo and the residue was subjected to column chromatography (hexane–EtOAc, from 10:1 to 1:1).

Methyl (*R*/*S*)-3-[1-(4-Methoxyphenyl)vinyl]-4,5-dihydroisoxazole-5-carboxylate (3a)

Yellowish oil; R_f = 0.59 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 3.53 (d, *J* = 9.2 Hz, 2 H, CH_2), 3.81 (s, 3 H, OCH_3), 3.82 (s, 3 H, Ar-OCH_3), 5.14 (t, *J* = 9.2 Hz, 1 H, CH), 5.49, 5.60 (2 s, 2 H, H_2C=), 6.88 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.40 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 39.4 (CH_2), 52.9 (OCH_3), 55.3 (Ar-OCH_3), 78.7 (CH), 113.6 (CH_{Ar}), 121.0 (CH_2=), 129.8 (CH_{Ar}), 130.0 (C_{Ar}), 139.0 (C=), 157.4 ($COCH_3$), 163.1 (C=N), 170.7 (CO_2CH_3).

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.66; H, 5.93; N, 5.76.

(*R*/*S*)-3-[1-(4-Methoxyphenyl)vinyl]-5-phenyl-4,5-dihydroisoxazole (3b)

Yellowish oil; R_f = 0.65 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 3.23 (dd, *J* = 16.2, 8.1 Hz, 1 H, CH_2), 3.69 (dd, *J* = 16.2, 11.0 Hz, 1 H, CH_2), 3.82 (s, 3 H, OCH_3), 5.49, 5.60 (2 s, 2 H, H_2C=), 5.71 (dd, *J* = 11.0, 8.1 Hz, 1 H, CH), 6.92 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.46 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.28–7.42 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 29.8 (CH_2), 55.3 (OCH_3), 82.7 (CH), 113.5 (CH_{Ar}), 120.2 (CH_2=), 125.8, 128.1, 128.7, 129.8, 130.4, 130.5 (C_{Ar}), 139.8 (C=), 157.4 ($COCH_3$), 159.6 (C=N).

Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.09; H, 6–15; N, 4.89.

(*R*/*S*)-5-Butoxy-3-[1-(4-methoxyphenyl)vinyl]-4,5-dihydroisoxazole (3c)

Yellowish oil; R_f = 0.51 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 0.92 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.23–1.60 (m, 4 H, $CH_2CH_2CH_3$), 3.10 (dd, *J* = 17.1, 1.3 Hz, 1 H, CH_2), 3.32 (dd, *J* = 17.1, 6.6 Hz, 1 H, CH_2), 3.53 (m, 1 H, OCH_2), 3.82 (s, 3 H, OCH_3), 3.85 (m, 1 H, OCH_2), 5.50, 5.59 (2 s, 2 H, H_2C=), 5.62 (dd, *J* = 6.6, 1.3 Hz, 1 H, CH), 6.89 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.42 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}).

^{13}C NMR: δ = 13.9 (CH_3), 19.3 (CH_2CH_3), 31.6 ($CH_2CH_2CH_3$), 41.9 (CH_2), 55.4 (OCH_3), 68.2 (OCH_2), 103.3 (CH), 113.6 (CH_{Ar}),

120.5 (H_2C=), 129.8 (CH_{Ar}), 131.8 (C_{Ar}), 139.7 (C=), 158.3 (*C*OCH_3), 164.4 (C=N).

Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.03; H, 7.93; N, 4.90.

(*R*/*S*)-[3-(1-Phenylvinyl)-4,5-dihydroisoxazol-5-yl]methanol (3d)

Yellowish oil; R_f = 0.27 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 2.57 (br s, 1 H, OH), 3.20 (m, 2 H, CH_2O), 3.62 (dd, *J* = 11.8, 4.6 Hz, 1 H, CH_2), 3.79 (dd, *J* = 11.8, 3.3 Hz, 1 H, CH_2), 4.77 (m, 1 H, CH), 5.53 (s, 1 H, HC=), 5.60 (s, 1 H, HC=), 7.23–7.48 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 36.9 (CH_2), 63.7 (CH_2O), 81.5 (CH), 121.5 (C=), 128.3, 128.62, 129.1 (CH_{Ph}), 138.1 (C_{Ph}), 139.0 (C=), 163.0 (C=N).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.19; H, 6.67; N, 6.70.

Methyl (*R*/*S*)-3-(1-Phenylvinyl)-4,5-dihydroisoxazole-5-carboxylate (3e)

Yellowish oil; R_f = 0.59 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 3.51 (d, *J* = 9.2 Hz, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 5.13 (t, *J* = 9.2 Hz, 1 H, CH), 5.51, 5.62 (2 s, 2 H, H_2C=), 7.21–7.43 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 39.9 (CH_2), 53.4 (OCH_3), 78.7 (CH), 121.0 (CH_2=), 128.9, 129.2, 130.0 (CH_{Ph}), 138.6 (C_{Ph}), 160.1 (C=N), 171.0 (C=O).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.52; H, 5.90; N, 5.89.

***rel*-(*S*)-1-[3-(1-Phenylvinyl)-4,5-dihydroisoxazol-5-yl]ethanone (3f)**

Yellowish oil; R_f = 0.63 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 2.33 (s, 3 H, CH_3), 3.38 (dd, *J* = 16.9, 11.7 Hz, 1 H, CH_2), 3.52 (dd, *J* = 16.9, 6.2 Hz, 1 H, CH_2), 4.98 (dd, *J* = 11.7, 6.2 Hz, 1 H, CH), 5.57, 5.64 (2 s, 2 H, H_2C=), 7.30–7.46 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 26.3 (CH_3), 37.2 (CH_2), 84.5 (CH), 122.2 (CH_2=), 128.1, 128.2, 128.4 (CH_{Ph}), 137.7 (C_{Ph}), 139.7 (C=), 157.6 (C=N), 207.1 (C=O).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.64; H, 6.35; N, 6.57.

(*R*/*S*)-3-[1-(4-Methoxyphenyl)vinyl]-5-phenyl-4,5-dihydroisoxazole (3b) and 3-[1-(4-Methoxyphenyl)-3-oxobutyl]-5-phenyl-4,5-dihydroisoxazole 2-Oxide (4a)

The soln of 1,2-oxazine *N*-oxide **1b** (0.33 g, 1 mmol), K_2CO_3 (0.14 g, 1 mmol), and styrene (0.57 mL, 5 mmol) in DMF (10 mL) was kept for 3 h. The mixture was poured into a mixture of EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 40 mL) and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was subjected to column chromatography (hexane–EtOAc, from 10:1 to 1:1) to give **3b** (0.028 g, 10%) and **4a** (0.19 g, 58%) as a colorless oil; R_f = 0.31 (hexane–EtOAc, 1:1) (UV).

Isoxazole *N*-oxide 4a

^{1}H NMR: δ = 2.18 (s, 3 H, CH_3), 2.96 (dd, *J* = 17.7, 5.9 Hz, 1 H, CH_2), 3.06 (dd, *J* = 16.6, 7.8 Hz, 1 H, isoxazole-CH_2), 3.38 (dd, *J* = 16.6, 8.5 Hz, 1 H, isoxazole-CH_2), 3.38 (dd, *J* = 17.7, 9.2 Hz, 1 H, CH_2), 3.75 (s, 3 H, OCH_3), 4.14 (dd, *J* = 9.2, 5.9 Hz, 1 H, Ar-CH), 4.14 (dd, *J* = 7.8, 8.5 Hz, 1 H, OCH), 6.82 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.20 (d, *J* = 8.5 Hz, 2 H, CH_{Ar}), 7.30 (m, 5 H, CH_{Ph}).

^{13}C NMR: δ = 29.7 (CH_3), 37.7 (*C*HAr), 41.1 (isoxazole-CH_2), 45.0 (CH_2), 55.3 (OCH_3), 76.3 (OCH), 114.2, 128.7 (CH_{Ar}), 117.2 (C=N), 126.0, 128.8, 128.9 (CH_{Ar}), 130.5 (C_{Ph}), 138.7 (C_{Ar}), 159.2 (*C*OCH_3), 206.2 (C=O).

^{14}N NMR: δ = –72.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.46; H, 6.07; N, 4.12.

3-(2,5-Dioxo-2,5-dihydrofuran-3-yl)-4-(4-methoxyphenyl)-6,6-dimethyl-5,6-dihydro-4*H*-1,2-oxazine *N*-Oxide (5a)

The soln of **1a** (0.314 g, 1 mmol), Et_3N (0.28 mL, 2 mmol), and maleic anhydride (0.294 g, 3 mmol) in toluene (10 mL) was refluxed for 2 h. The mixture was poured into a mixture of EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with H_2O (2 × 50 mL) and brine (2 × 40 mL) and dried (Na_2SO_4). The solvents were removed in vacuo and the residue was subjected to column chromatography (hexane–EtOAc, from 10:1 to 1:1) to give **5a** (0.20 g, 61%) as a yellowish oil; R_f = 0.55 (hexane–EtOAc, 1:1) (UV).

^{1}H NMR: δ = 1.46, 1.52 (2 s, 6 H, 2 CH_3), 2.05 (dd, *J* = 14.3, 9.9 Hz, 1 H, CH_2), 3.36 (dd, *J* = 14.3, 8.8 Hz, 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 4.84 (t, *J* = 9.2 Hz, 1 H, CH), 6.81 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.07 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.74 (s, 1 H, HC=).

^{13}C NMR: δ = 22.2, 27.6 (2 CH_3), 37.9, 42.2 (CH, CH_2), 55.3 (OCH_3), 85.2 [*C*$(CH_3)_2$], 114.6 (CH_{Ar}), 119.3 (C=N), 128.8 (CH_{Ar}), 132.7 (C_{Ar}), 136.5, 137.8 (C=, CH=), 158.7 (*C*OCH_3), 163.8 (C=O).

Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23. Found: C, 61.88; H, 5.28; N, 4.03.

Acknowledgment

This work was supported by RFFI (#06-03-32607).

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