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Synthesis of Isoxazoline *N*-Oxides via [Hydroxy(tosyloxy)iodo]benzene (HTIB)-Mediated Oxidative N−O Coupling

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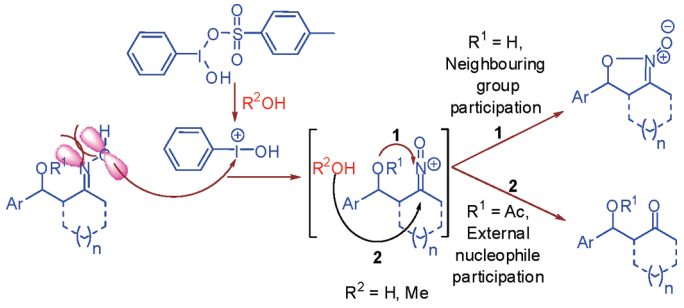

An HTIB mediated oxidative N−O coupling strategy for the synthesis of some isoxazoline *N*-oxide derivatives from *β*-hydroxyketoximes is described, along with a comparative study of the efficiency of N−O coupling in two different solvents. A plausible mechanism for the conversion is proposed.

Introduction

The longstanding goal of "on water" organic transformations, as an economic and environmentally friendly protocol, has been utilized to produce a diverse array of pharmaceutically active and synthetically useful substances.[1] The protocol eliminates the difficulties associated with the workup procedures that arise when homogeneous media are involved and also enhances the rate and selectivity of the reactions.[1c] It is generally believed and has been proven in some situations that a homogeneous medium is the optimal system for chemical transformations. Notwithstanding the possible use of toxic organic solvents, a homogeneous medium is the most frequently utilized medium in organic synthesis.

On the other hand, despite the immense synthetic and medicinal utility of oxa-aza heterocycles with N−O bonds, methods for producing a bond between nitrogen and oxygen atoms remain limited.[2] Examples of N−O bond formation in the literature involve either the displacement of a leaving group, attached to nitrogen, in an S_N2 reaction[2a] or the oxidation of 2-aminoacetophenone,[2e] 2-hydroxyacetophenoneoxime,[3] and glyoxime[2b,c] derivatives. Among these, the oxidation of 2-hydroxyacetophenoneoxime and glyoxime derivatives is the more frequently utilized method, primarily because the starting materials are readily accessible.[2b,c,3] However, in many instances, the oxidation of oximes is accompanied by deoximation.[4] As a result, the selection of a suitable reagent and conditions that

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(4) (a) Zhou, X.-T.; Yuan, Q.-L.; Ji, H.-B. *Tetrahedron Lett.* **2010**, *51*, 613. (b) Sha, X.; Isbell, T. S.; Patel, R. P.; Day, C. S.; King, S. B. *J. Am. Chem. Soc.* **2006**, *128*, 9687. (c) Nath, U.; Das, S. S.; Deb, D.; Das, P. J. *New J. Chem.* **2004**, *28*, 1423. (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **1996**, *96*, 1123. (f) McKillop, A.; Sanderson, W. R *Tetrahedron* **1995**, *51*, 6145 and references therein.

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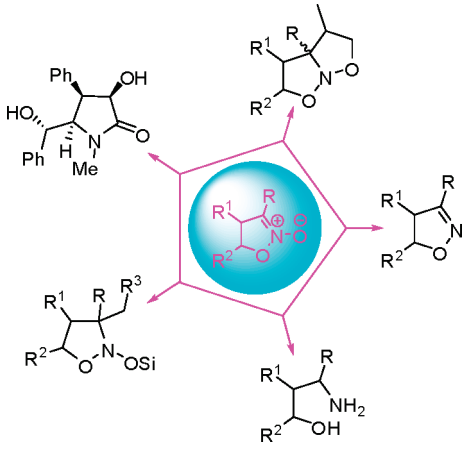

FIGURE 1. Applications of isoxazoline *N*-oxides.

permit the oxidation of oximes to be controlled in favor of N−O bond formation can be a challenge.

In the family of 2,1-oxa-aza heterocycles, isoxazoline *N*-oxides are well-known precursors in the synthesis of a variety of organic compounds of biomedical and synthetic importance (Figure 1).[5] Synthetic applications cover areas that include the synthesis of bicyclic isoxazolines, isoxazolines, amino alcohols, amino acids, and clausenamide derivatives and the asymmetric synthesis of carbanucleosides.[5] In addition, Ioffe and co-workers recently reported on the C−C coupling of isoxazoline *N*-oxide derivatives with silyl ketene acetals.[5d]

In spite of this, only nitroalkanes and nitroalkenes have been utilized as sources of these five-membered nonaromatic nitronates during the past few decades.[5] A wide variety of methods for preparing chiral and achiral isoxazoline *N*-oxide derivatives from these precursors have been documented in the literature.[5] However, all of these protocols involve the use of various organic solvents. Moreover, since the starting materials are similar, the scope of the reaction is limited. Hence, to introduce further diversity and expand this area, a new source of starting materials and a more diverse protocol is needed. In this context, β-hydroxy ketoxime derivatives have the potential to serve as ideal alternative synthons for accessing five-membered cyclic nitronates, since they are readily obtained from β-hydroxy ketones.[6] Although protocols for the synthesis of chiral and achiral derivatives of these ketones have been extensively explored in the literature,[7,8] to the best of our knowledge, they have not been applied to access isoxazoline *N*-oxides. On the other hand, previous studies reported on the synthesis of benzoisoxazole *N*-oxide derivatives from 2-hydroxyacetophenone oximes used either $Pb(OAc)_4$ or $NaBO_3$.[3] The limitation associated with $Pb(OAc)_4$ is that it is a toxic reagent.[11a] In the case of $NaBO_3$, the product yield is poor at room temperature and glacial acetic acid is typically used as the solvent.[3b] One more notable fact is that, in spite of the multifarious utilities of the nitro group as a functional group,[9] isoxazoline *N*-oxide derivatives with nitro functionalities have not been extensively explored. Furthermore, to our knowledge, no general protocol is available in the literature for accessing both isoxazoline *N*-oxides and benzoisoxazole *N*-oxides.

Keeping all these facts in view, in a continuation of our ongoing project on the development of green synthetic protocols based on "on water" concepts,[10] we wish to report herein on the first HTIB-mediated oxidative N−O coupling strategy, leading to the synthesis of both isoxazoline *N*-oxide and benzoisoxazole *N*-oxide derivatives. In addition, we also report on a comparative study of the efficiency of N−O coupling in two different media. It is noteworthy that, as an oxidizing agent, HTIB has a diverse array of applications in synthetic chemistry.[4d,e,10a,11]

Results and Discussion

We recently reported on the HTIB-mediated rapid and mild "on water" oxidation of 2-allyloxy and 2-propargyloxy aldoximes in preparing chromeno isoxazoles and isoxazolines.[10a] At the same time, Patel et al. disclosed a protocol for the oxidation of aldoximes to *N*-hydroxyamides using the same λ^3-iodane.[11a] In the two instances, the substrates have two different environments around the in situ formed nitrile oxide moiety. In our case,

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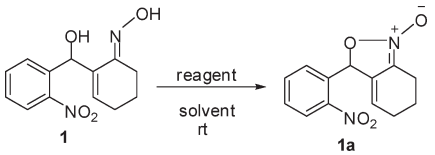
TABLE 1. Optimization of the Reaction with Various Solvents and Reagents



entry	solvent	reagent[a]	time (h)	yield (%)[b]
1	toluene	HTIB	0.50	25
2	CH_2Cl_2	HTIB	0.50	33
3	Et_2O	HTIB	0.50	18
4	CH_3CN	HTIB	0.50	44
5	DMF	HTIB	0.50	52
6	THF	HTIB	0.50	77
7	MeOH	HTIB	0.50	88
8	EtOH	HTIB	0.50	75
9	*t*-BuOH	HTIB	0.50	81
10	H_2O	HTIB	0.75	87
11[c]	H_2O	CAN	24	
12[c]	H_2O	chloramine-T	24	
13[c]	H_2O	iodine	24	
14[c]	H_2O	H_2O_2	24	
15[d]	H_2O	NaOCl	24	18
16[c]	H_2O	DIB	24	
17	H_2O	DIB/CF_3COOH	1	55
18	H_2O	DMP	1.5	trace

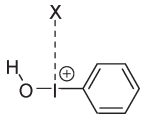
[a]1.1 equiv of reagent was used. [b]Isolated yields. [c]Starting material was recovered. [d]2.5 equiv of NaOCl was used.

the resulting nitrile oxide underwent an intramolecular [3 + 2] cycloaddition due to the presence of a neighboring dienophile. However, in the case of Patel et al., the attack of an external nucleophile occurred on a similar unstable intermediate due to the absence of a neighboring dienophile. Moreover, with respect to hypervalent iodine mediated N−X (X = N, C) bond formation, Dong et al. reported on the oxidative cyclization of 1-carbamoyl-1-oximoylcycloalkanes in the design of spiro-fused pyrazolin-5-one *N*-oxides (N−N bond formation)[12a] and Aggarwal et al. synthesized 2,4-diphenylquinoxaline-1-oxides from benzyl-α-arylimino oximes (N−C bond formation).[12b] Intrigued by these reports, we anticipated the formation of five-membered cyclic nitronates from various *β*-hydroxyketoximes via oxidative N−O coupling.

In our attempts to prepare the desired *N*-oxides, our efforts started with 2-(hydroxy(2-nitrophenyl)methyl)cyclohex-2-enone oxime (**1**; Table 1), derived from the corresponding Baylis−Hillman adduct (BHA). We tested our assumption by treating this *β*-hydroxy ketoxime (**1**; Table 1) with HTIB under on water conditions and found that the five-membered cyclic nitronate was formed in excellent yield (entry 10, Table 1). The product was characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135, mass spectral analysis, and elemental analysis. The structure was confirmed by single-crystal X-ray analysis (Figure 2a and the Supporting Information), which showed that the N2−O4 bond length is almost equal to the N−O bond length of a nitro group, whereas the N2−O3 bond is longer than N2−O4. The ^{1}H NMR spectrum (Figure 1b) of the compound showed splitting of the benzylic proton (H^1; Figure 2c) due to both allylic coupling and long-range coupling, as evidenced by COSY and HMQC (Supporting Information).

In general, most organic reactions proceed efficiently in a homogeneous medium.[1c] Hence, in order to compare the efficacy of our reaction in different types of homogeneous and heterogeneous media, we ran the reactions in various organic solvents in addition to water (Table 1). For this purpose, we used nonpolar (CH_2Cl_2, toluene, diethyl ether) as well as polar aprotic (DMF, acetonitrile, THF) and polar protic (methanol, ethanol, *tert*-butyl alcohol) solvents. Poor yields were obtained in all of the nonpolar solvents (entries 1−3). However, when polar aprotic solvents were used, moderate yields were obtained (entries 4−6). Polar protic solvents were found to be the most effective for this conversion (entries 7−10). Water and methanol produced comparable yields (entries 7 and 10). From a mechanistic viewpoint (Scheme 5), the solvent effect can be explained by considering the fact that more polar and coordinating solvents provide better stabilization of the in situ formed hydroxy(phenyl)iodonium ion (PhI^+OH) via coordination (Scheme 1).

SCHEME 1. Coordination of the Solvent Molecule at the Cationic Center of the Active Species



After choosing suitable solvents, we examined a series of mild, moderate, and strong oxidizing agents in order to find a better alternative to HTIB (Table 1). Among the oxidants tested, CAN, chloramine-T, iodine, H_2O_2, and DIB proved to be ineffective for this transformation (entries 11−14 and 16). However, a poor yield of the desired *N*-oxide was obtained with NaOCl (entry 15). On the other hand, in the presence of a catalytic amount of trifluoroacetic acid, DIB produced the isoxazoline *N*-oxide **1a** in moderate yield (entry 17). Only trace amounts of the desired product were obtained when DMP was used (entry 18). On the basis of these results, we concluded that HTIB was the optimal oxidant for this conversion.

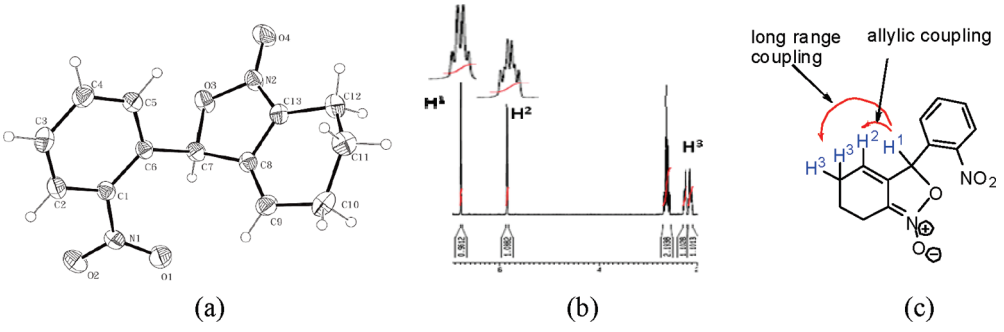
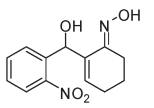
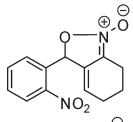
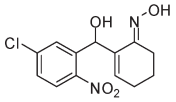
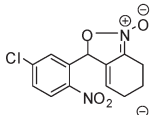
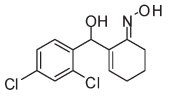
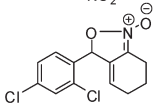
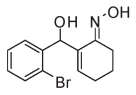
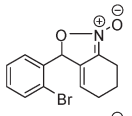
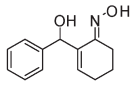
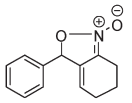
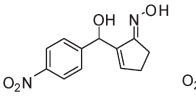
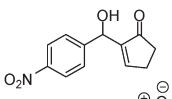
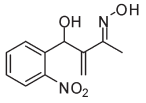
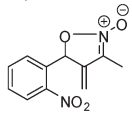


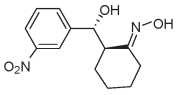
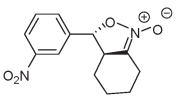
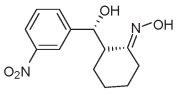
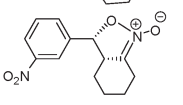
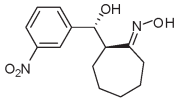
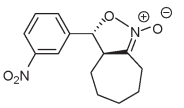
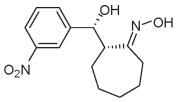
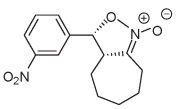
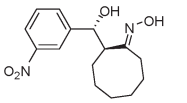
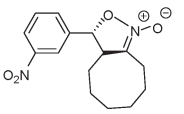
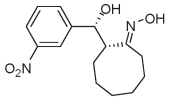
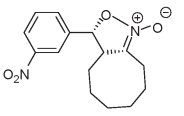
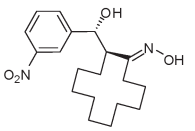
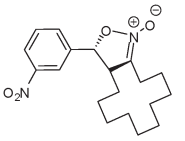
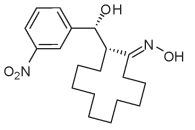
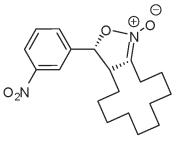
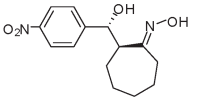
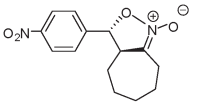
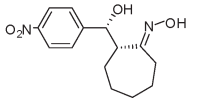
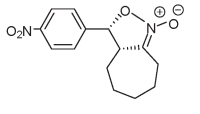
FIGURE 2. (a) Crystal structure, (b) ^{1}H NMR, and (c) type of coupling in the ^{1}H NMR of **1a**.

TABLE 2. Synthesis of Various Carbocycle Fused Isoxazoline *N*-Oxides from Oximes of the Baylis−Hillman Adducts

Entry	Substrate	Product		Yield %[a,b] MeOH	H_2O
1			**1a**	88	87
2[c]			**2a**	81	60
3[d]			**3a**	57	—
4[d]			**4a**	63	—
5			**5a**	55	50
6[d]			**6a**	54	—
7[e]			**7a**	68	61

[a]Reactions performed on a 1.0 mmol scale. [b]Isolated yield. [c]17% of starting material was recovered with water. [d]With water, the starting material was recovered. [e]With MeOH, 10% of β-hydroxy ketone was formed via deoximation. With H_2O, 14% of the starting material was recovered.

TABLE 3. Synthesis of Various Carbocyclic Fused Isoxazoline *N*-Oxides from Oximes of Aldol Adducts

Entry	Substrate	Product		Yield[a,b] MeOH	H_2O
1			**8a**	46	88
2[c]			**9a**	—	37
3			**10a**	90	92
4			**11a**	78	59
5			**12a**	91	70
6			**13a**	69	83
7[d]			**14a**	82	-
8			**15a**	84	62
9			**16a**	92	80
10			**17a**	88	78

[a]Reactions performed on a 0.5 mmol scale. [b]Isolated yield. [c]With MeOH, 76% of the corresponding β-hydroxyketone was formed via deoximation. With H_2O, 44% of the starting material was recovered. [d]With water, starting material was recovered.

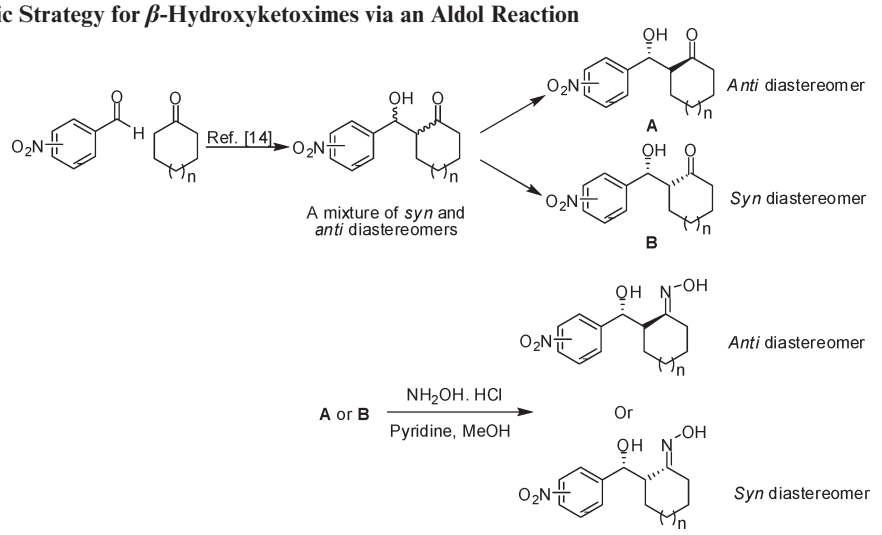
With the optimized conditions in hand, we explored the scope and limitations of our methodology. In this regard, we first focused on oximes derived from Baylis−Hillman adducts (BHAs) (Table 2). The corresponding BHAs were synthesized from substituted or unsubstituted benzaldehydes and different cyclic or acyclic ketones, as previously reported in the literature.[13] In the course of the experiments, we found that the reaction yield varies with the nature of the substituent on the benzene ring, when cyclohex-2-enone oxime derivatives were subjected to HTIB treatment in two different media (entries 1−5). In the homogeneous medium, the presence of a strongly electron withdrawing group such as a nitro group resulted in the formation of the corresponding isoxazoline *N*-oxide derivatives in good yields (entries 1 and 2). Unsubstituted as well as mildly electron withdrawing halide-substituted ketoximes produced moderate yields of the expected product (entries 3−5). Under "on water" conditions, the efficiencies of the reactions were comparable to those for an organic medium in cases of nitro-substituted and unsubstituted ketoximes (entries 1 and 5). However, it is surprising that reactions with halide-substituted ketoximes failed to produce the desired product under "on water" conditions and the starting materials were recovered (entries 3 and 4). While the cyclopent-2-enone oxime derivative was converted into the corresponding β-hydroxy ketones via deoximation in methanol and under "on water" conditions, no conversion was detected (entry 6). On the other hand, the reactions of acyclic ketoxime produced a moderate yield of the product in both methanol and water (entry 7).

Encouraged by the successful syntheses of isoxazoline *N*-oxides from various oximes of Baylis−Hillman adducts, we turned our attention to ketoximes, produced from aldol adducts (Scheme 2). In this particular scheme, our goals were the synthesis of different carbocycle fused isoxazoline *N*-oxide derivatives and the study of the influence of ring size and stereochemistry on N−O coupling. In this regard, we followed the corresponding literature citations in preparing

(12) (a) Wang, K.; Fu, X.; Liu, J.; Liang, Y.; Dong, D. *Org. Lett.* **2009**, *11*, 1015. (b) Aggarwal, R.; Sumran, G.; Saini, A.; Singh, S. P. *Tetrahedron Lett.* **2006**, *47*, 4969.

(13) (a) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555. (b) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedon Lett.* **2002**, *43*, 127.

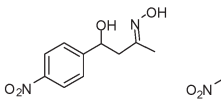
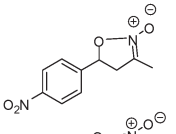
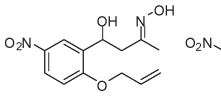
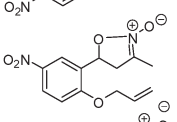
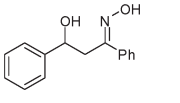
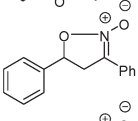
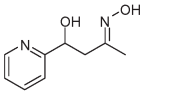
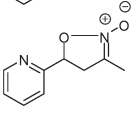
SCHEME 2. Synthetic Strategy for β-Hydroxyketoximes via an Aldol Reaction



the aldol adducts from *m*-nitrobenzaldehyde and different cyclic ketones to produce a mixture of two diastereomers.[14b] These isomers were separated by silica gel column chromatography, and the corresponding ketoximes were then synthesized (Scheme 2 and also the Supporting Information).

The aldol ketoximes were reacted under optimized reaction conditions in both water and methanol, and the results are shown in Table 3. Here, it is noteworthy that, irrespective of ring size, the anti diastereomers were more prone to undergo cyclization than the syn diastereomers. In homogeneous medium (methanol solvent) with cyclohexanone oxime derivatives, the anti diastereomer produced a poor yield of the expected product (entry 1), while the syn diastereomer failed to form the desired *N*-oxide (entry 2). A better result was obtained with the anti isomer when the reaction was carried out under "on water" conditions (entry 1). Under these conditions, the desired product was formed, even in the case of the syn isomer (entry 2). On the other hand, the reaction of the anti isomer of the cycloheptanone oxime derivative produced the corresponding isoxazoline *N*-oxide in excellent yield in both methanol and water (entry 3). However, the syn isomer afforded the cycloheptane fused five-membered cyclic nitronate in lower yield with water than with methanol (entry 4). The reaction of cyclooctanone oxime derivatives resulted in an outcome that was different from those for the other cyclic ketoximes. In methanol, an excellent yield of the *N*-oxide was obtained from the anti isomer (entry 5), while under "on water" conditions a good yield of the desired product was obtained from the syn isomer (entry 6). It is noteworthy that our protocol was even suitable for preparing an isoxazoline *N*-oxide fused with a cyclododecane moiety (entries 7 and 8). Here, methanol was a superior solvent, in comparison to water. The syn and anti diastereomers of an isoxazoline *N*-oxide fused with cycloheptane (**10a** and **11a**) and cyclododecane (**14a** and **15a**) moieties were characterized by single-crystal X-ray analysis (Supporting Information). A close look at the data revealed that the N−O bonds of the isoxazoline ring of the syn isomers is longer than the corresponding bonds for the anti isomers. Presumably, due to the longer bond lengths, the syn isomers were less efficient toward N−O coupling than the anti isomers. In addition to the 3-nitro derivatives, the desired isoxzoline *N*-oxides were obtained in good to excellent yields from the 4-nitro derivatives (entries 9 and 10).

TABLE 4. Synthesis of 3,5-Disubstituted Isoxazoline *N*-Oxides from Oximes of Aldol Adducts

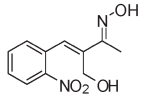
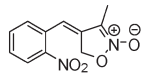
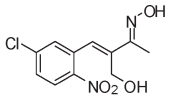
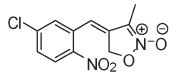
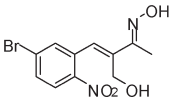
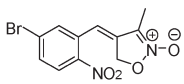
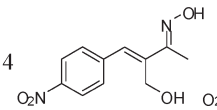
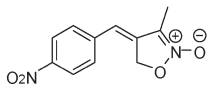
Entry	Substrate	Product		Yield % [a,b] MeOH	Yield % [a,b] H_2O
1[c]			**18a**	75	61
2[d]			**19a**	73	41
3[e]			**20a**	88	61
4[f]			**21a**	-	28

[a]Reactions performed on a 1.0 mmol scale. [b]Isolated yields. [c]Deoximation: 16% with MeOH and 19% with water. [d]Deoximation: 19% with MeOH and 21% with water. 22% of the starting materials was recovered with water. [e]25% of the starting material was recovered with water. [f]23% deoximation with water. The starting material was recovered with methanol.

After successfully accomplishing the preparation of carbocycle fused isoxazoline *N*-oxides from oximes of various aldol adducts of cyclic ketones, we focused our attention on aldol adducts, generated from acyclic ketones (Table 4).[14a] In this category, although the phenyl derivatives underwent efficient cyclization in methanol, the reactions were less efficient in water (entries 1−3). Notably, the reactions of ketoximes, generated from acetone, resulted in the formation of substantial amounts of β-hydroxy ketone via deoximation (entries 1 and 2). This can be attributed to the presence of a sterically less hindered carbonyl center. Under these circumstances, an external nucleophile (solvent) competes with the

(14) (a) Chimni, S. S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019. (b) Dimmock, J. R.; Jha, A.; Kumar, P.; Zello, G. A.; Quail, J. W.; Oloo, E. O.; Oucharek, J. J.; Pasha, M. K.; Seitz, D.; Sharma, R. K.; Allen, T. M.; Santos, C. L.; Manavathu, E. K.; Clercq, E. D.; Balzarini, J.; Stables, J. P. *Eur. J. Med. Chem.* **2002**, *37*, 35.

TABLE 5. Synthesis of 4-Methylene Isoxazoline *N*-Oxide Derivatives

Entry	Substrate	Product		Yield %[a,b] MeOH	H_2O
1			**22a**	89	92
2			**23a**	92	74
3[c]			**24a**	91	49
4			**25a**	90	80

[a]Reaction performed on a 0.5 mmol scale. [b]Isolated yields. [c]With water, 19% of the starting material was recovered.

neighboring group. However, the outcome was interesting in the case of a pyridine derivative (entry 4). Although the reaction failed with methanol, the expected nitronate was obtained in water. In this case, the oxime was solubilized in water after addition of the reagent. The overall result could be explained by considering the fact that water is a better proton donor than methanol.[15] Hence, water would protonate the pyridine, thus preventing the N center of pyridine from coordinating with hydroxy(phenyl)iodonium ion (PhI^+OH).

Except for **9a** and **21a**, the isoxazoline *N*-oxide derivatives described here are stable in air and moisture. However, even on storage in a refrigerator (at 4 °C), compounds **9a** and **21a** decomposed to the corresponding β-hydroxy ketones.

At this point, the oxidative N−O coupling reactions have been confined to β-hydroxy ketoximes, containing a sterically crowded hydroxyl group (Tables 2−4). To observe the effect of the environment at the hydroxyl counterpart, we used primary hydroxyl containing ketoximes in the N−O coupling reaction (Table 5). We prepared 2-acetylcinnamyl alcohol derivatives,[16] and the corresponding ketoximes were then synthesized (Supporting Information). These ketoximes were then subjected to HTIB treatment in water and methanol (Table 5). The results for methanol were excellent in all of the cases (entries 1−4). These efficient N−O couplings are due to the presence of sterically less crowded primary alcohol moieties as the neighboring group. Under "on water" conditions, the outcome was comparable to the results for methanol in cases of mononitro-substituted derivatives (entries 1 and 4). In water, however, the halo-substituted ketoximes were found to be less efficient toward the cyclization than the others (entries 2 and 3). The isoxazoline

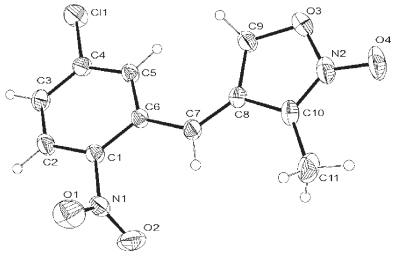
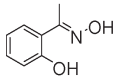
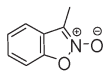
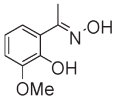
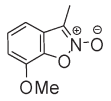
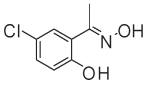
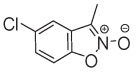


FIGURE 3. Crystal structure of **23a**.

TABLE 6. Synthesis of Benzoisoxazole *N*-Oxides

Entry	Substrate	Product		Yield %[a,b] MeOH	H_2O
1			**26a**	80	81
2			**27a**	72	77
3			**28a**	92	89

[a]Reaction performed on a 1.0 mmol scale. [b]Isolated yields.

counterparts of these types of molecules have already been reported,[17] but to the best of our knowledge the *N*-oxide derivatives are the new entities in the isoxazoline *N*-oxide family. The structure of compound **23a** was confirmed by single-crystal X-ray analysis (Figure 3).

In addition to isoxazoline *N*-oxide derivatives, our protocol has also proved to be suitable for the synthesis of benzoisoxazole *N*-oxide derivatives (Table 6). Various 2-hydroxyacetophenone oximes underwent smooth cyclization with good yields in both water and methanol (entries 1−3). A substrate with an electron-donating group (entry 2) produced lower yields than a substrate with an electron-withdrawing group (entry 3).

The effect of medium appeared to be more important in the case of a bis-oxime (**29**; Scheme 3). Here, methanol, being a better nucleophile than water, produced a mixture of three products, two of which were produced by deoximation (**29b**, **c**). The yield of the desired nitronate was poor (38% of **29a**). In contrast, under "on water" conditions, the desired bis benzoisoxazole *N*-oxide (**29a**) was obtained as the sole product in good yield.

In order to extend the scope of our methodology further, we utilized 3-acetyl-4-hydroxyquinolone oxime (**30**; Scheme 4) to synthesize a quinoline fused isoxazole derivative (**31**). The desired product was not produced, and the starting material was recovered. This may be because 3-acetyl-4-hydroxyquinolone oxime (**30**) is hyperconjugated and generates a more nucleophilic substituted hydroxylamine center and the oxygen of this hydroxylamine attacks the cationic active species more quickly than the oxime oxygen.

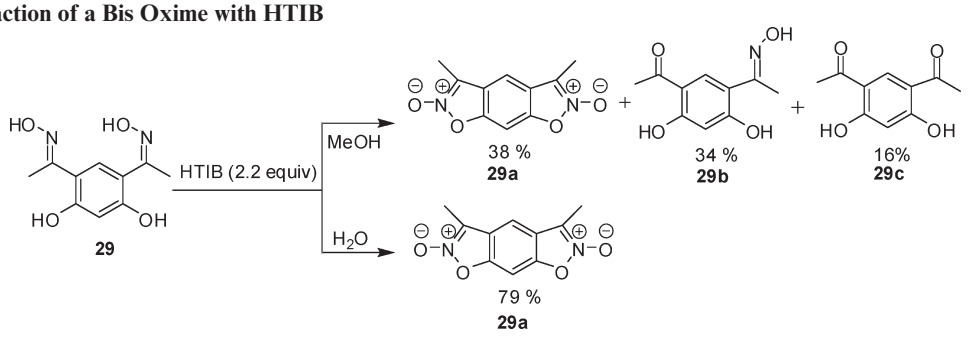
(15) (a) Tarnopolsky, A.; Hoz, S. *Org. Biomol. Chem.* **2007**, *5*, 3801. (b) Nurminen, E.; Lönnberg, H. *J. Phys. Org. Chem.* **2004**, *17*, 1.

(16) (a) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385. (b) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613. (c) Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630. (d) To be submitted for publication.

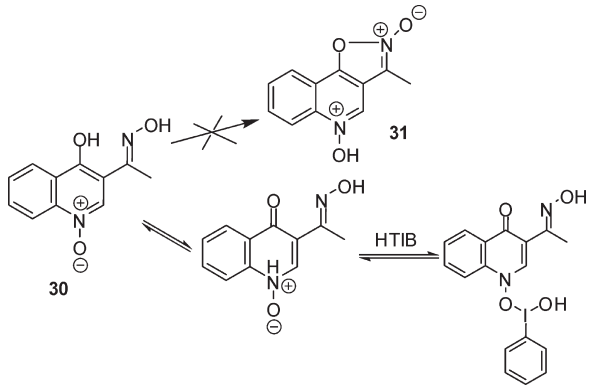
(17) (a) Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P.; Sridharan, V.; Pett, M. T. *Chem. Commun.* **2001**, 1968. (b) Broggini, G.; Rosa, C. L.; Zecchi, G. *Synlett* **1995**, 1208.

(18) (a) Dale, T. J., Jr.; Rebek, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7850. (b) Ren, Y.; Yamataka, H. *J. Org. Chem.* **2007**, *72*, 5660. (c) Richter, H. W.; Cherry, B. R.; Zook, T. Z.; Koser, G. F. *J. Am. Chem. Soc.* **1997**, *119*, 9614. (d) Klopman, G.; Tsuda, K.; Louis, J. B.; Davis, R. E. *Tetrahedron* **1970**, *26*, 4549. (e) Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16. (f) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 1778.

SCHEME 3. Reaction of a Bis Oxime with HTIB

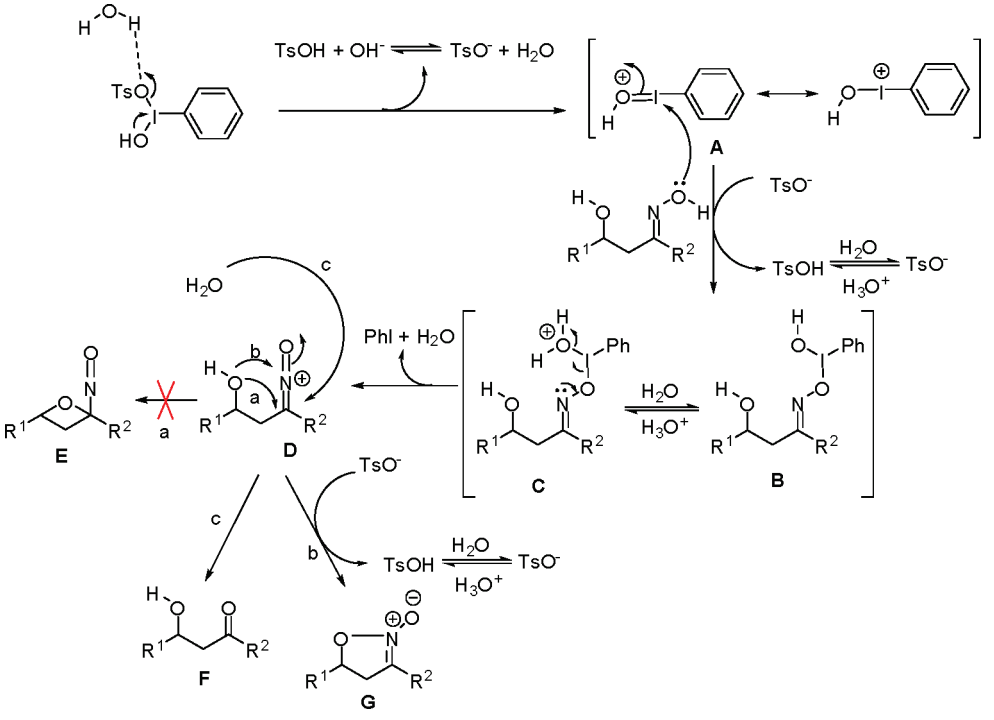


SCHEME 4. Probable Explanation for the Failure of the Reaction between 3-Acetyl-4-hydroxyquinolone Oxime and HTIB

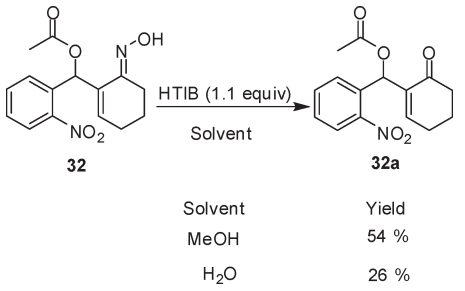


After examining the scope and limitations of our protocol, we focused our attention on possible mechanisms for the reaction. In our previous report, we proposed a mechanism for the HTIB-mediated oxidation of an aldoxime into a nitrile oxide.[10a] On the basis of our earlier results[10a] and literature reports,[18] we envisage that the hydroxyphenyliodonium ion ($PhI^{+}OH$) acts as an active species in the oxidative N−O coupling reactions (Scheme 5). Here, we assume that the initiation of the reaction may occur in a manner similar to our previous proposal to form intermediate **B** and the mechanism is similar up to the formation of intermediate **D**. It should be noted that the formation of an *N*-oxonitrenium ion (**D**) from an oxime was postulated earlier by Dong et al., in explaining the formation of an N−N bond, mediated by PIFA/TFA in dichloromethane.[12a] As this ion (intermediate **D**) possesses a nucleophilic alcoholic oxygen at the β-position, we assume an N−O coupling. Actually, in this circumstance, there are two electrophillic centers available for the neighboring alcoholic oxygen. Those electrophilic centers are the carbon and nitrogen centers of the *N*-oxonitrenium ion moiety. If the neighboring nucleophile attacks the carbon center (pathway a), then an unstable four-membered ring (**E**) would be formed, whereas if it attacks the nitrogen center (pathway b) the result would be the formation of a stable five-membered ring (**G**). This would drive the reaction toward N−O coupling (pathway b). The formation of the deoximation product can be rationa-

SCHEME 5. Plausible Mechanistic Pathway for the Formation of Isoxazoline *N*-Oxide Derivatives



SCHEME 6. Reaction of (6-(Hydroxyimino)cyclohex-1-enyl)-(2-nitrophenyl)methyl Acetate with HTIB[a,b]



[a]1.1 equiv of reagent used. [b]Isolateyield.

lized by considering the participation of an external nucleophile (pathway c).

In order to support our assumption, we carried out an NMR experiment in D_2O and the outcome was similar to that in a previous report (see Supporting Information).[10a] Moreover, when we blocked the β-hydroxy group of the ketoxime with an acetyl group (**32**), the ketone (**32a**) was obtained as the predominant product (Scheme 6). The reason for this is the unavailability of a neighboring group. In this situation, the external nucleophile attacks at the carbonyl center, resulting in the formation of the deoximation product. Methanol, being more nucleophilic than water, results in a better yield of the deoximation product than an aqueous medium. This result indirectly supports an intramolecular N−O coupling at the last step (pathway b, Scheme 5) and rules out the possibility of an S_N2 substitution after oxidation of the oxime to a nitro functionality.[4f] In addition, it also proves that the solvent methanol is more prone to cause deoximation than water. Notably, under "on water" conditions, a significant amount of the starting oxime was recovered.

Once we explored the scope, limitations, and a plausible mechanism for the N−O coupling strategy, we evaluated the utility of our novel types of isoxazoline *N*-oxides (Scheme 7). In this context, (*Z*)-3-methyl-4-(2-nitrobenzylidene)-4,5-dihydroisoxazole 2-oxide (**22a**) was transformed into (2*Z*)-3-(hydroxyimino)-2-(2-nitrobenzylidene)butanal (**33**) on treatment with triethylamine in DMSO. Compound **33** was obtained as a mixture of syn and anti oximes in a ratio of 2:1. The acyl-substituted *o*-nitrocinnamaldehyde derivative **33** is a new compound and is quite unique, in that it contains a ketoxime group as well as a free aldehyde group. Later, considering the diverse utility of conjugated enones in synthetic chemistry,[19] we conducted a Knoevenagel condensation of this cinamaldehyde derivative with 5,5-dimethyl-1,3-cyclohexanedione under "on water" conditions to prepare a conjugated enone (**34**). Additional applications of isoxazoline *N*-oxide derivatives will be reported in due course.

Conclusions

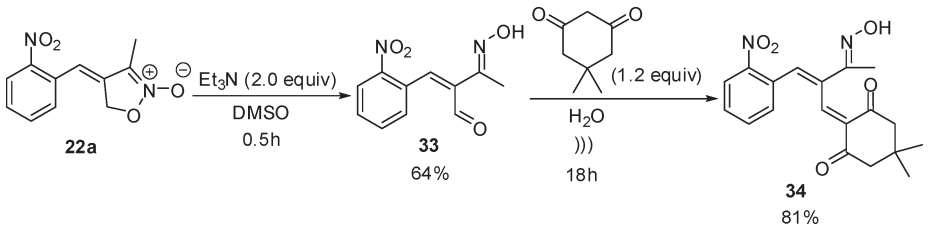
In summary, we have described a novel route to the synthesisis of isoxazoline *N*-oxides via oxidative intramolecular N−O coupling and verified that this methodology is also applicable to the synthesis of benzoisoxazole *N*-oxide derivatives. This is the first report of an "on water" protocol for the synthesis of the five-membered cyclic nitronates. Our protocol is mild and efficient, and the substrates are easily accessible. In most cases, the product is insoluble in both water and methanol and hence is precipitated at the bottom of the reaction vessel. A simple filtration is sufficient to isolate the pure product in such cases. A mechanism for the oxidative N−O coupling, which is supported by experimental evidence as well as literature reports, is proposed. The utility of these new types of isoxazoline *N*-oxides was further explored by synthesizing a substituted cinnamaldehyde derivative. Finally, we conclude that, apart from the existing nitroalkane- and nitroalkene-oriented protocols, the oxidation of ketoximes has the potential to serve as an equally sustainable alternative route to accessing a wide range of new and novel nitronates.

Experimental Section

General Information. Reagents and solvents were purchased from various commercial sources and used directly without any further purification unless otherwise stated. Column chromatography was performed on 63−200 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (δ) using TMS as an internal standard, and coupling constants are expressed in hertz. IR spectra were recorded on an FT-IR spectrometer and are reported in cm^{-1}. Melting points were recorded using an Electro Thermal capillary melting point apparatus and are uncorrected. Sonication was conducted at 42 kHz with a power of 100 W. **26a** and **28a** are known compounds.[3b,d,e]

General Procedure for the Oxidative N−O Coupling. Procedure A. To a 50 mL beaker containing the oxime derivative (0.5 mmol) in 5 mL of methanol was added [hydroxy(tosyloxy)-iodo]benzene (0.55 mmol) in small portions with continuous stirring over a period of 25 min, and the stirring was then continued for an additional 5 min. An equal amount of water was then added. If the solid product precipitated at the bottom of the beaker, the precipitate was isolated on the filter and washed with 60% methanol in water to give the pure product. In cases where the product did not precipitate, an additional 10 mL of water was added to the reaction mixture and the organic compound was isolated by extraction with ethyl acetate (15 mL × 3). The combined organic layers were dried over magnesium sulfate and

SCHEME 7. Synthesis of Conjugated Enone[a]



[a]Isolated yield.

concentrated under vacuum. The resulting residue was further purified by flash column chromatography.

Procedure B. To a 50 mL beaker containing the oxime derivative (0.5 mmol) in 5 mL of water was added [hydroxy(tosyloxy)-iodo]benzene (0.55 mmol) in small portions with continuous stirring over a period of 45 min. After the completion of the addition, the stirring was continued for an additional 5 min. The precipitated crude product was isolated by filtration and washed with water. In the case of an oily product, the reaction mixture was extracted with ethyl acetate (2 × 10 mL). The organic layers were separated, dried over magnesium sulfate, and concentrated under vacuum. The resulting residue was further purified by flash column chromatography.

3-(2-Nitrophenyl)-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-Oxide (1a). Pale yellow solid, mp 156−158 °C. IR (KBr, cm^{-1}): 3079, 2928, 2835, 1652, 1628, 1524, 1435, 1353, 1269, 1246, 1188, 1165. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.0 Hz, 1H), 7.75−7.69 (m, 2H), 7.57−7.51 (m, 1H), 6.80−6.79 (m, 1H), 5.87 (dd, J = 6.8, 4.4 Hz, 1H), 2.71−2.56 (m, 2H), 2.31−2.23 (m, 1H), 2.18−2.11 (m, 1H), 1.89−1.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 136.2, 134.8, 134.5, 129.4, 128.2, 125.2, 123.2, 115.2, 75.3, 25.1, 21.2, 20.4. MS (m/z (relative intensity)): 261 (M^+ + 1, 12), 260 (M^+, 100), 231 (16), 214 (48), 197 (61), 182 (14), 168 (20), 158 (22). HRMS (m/z): calcd for $C_{13}H_{12}N_2O_4$ (M^+) 260.0792, found 260.0807. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.96; H, 4.63; N, 10.72.

3-(2-Nitro-5-chlorophenyl)-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-Oxide (2a). Yellow solid, mp 172−174 °C. IR (KBr, cm^{-1}): 3099, 2947, 2864, 1656, 1628, 1527, 1343, 1270, 1256, 1183, 1110. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 8.8, 2.3 Hz, 1H), 6.83 (dd, J = 5.6, 2.8 Hz, 1H), 5.88−5.85 (m, 1H), 2.71−2.58 (m, 2H), 2.31−2.18 (m, 1H), 2.18−2.11 (m, 1H), 1.87−1.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 141.6, 136.9, 135.8, 129.7, 128.3, 126.9, 123.7, 114.9, 74.8, 25.2, 21.3, 20.4. MS (m/z (relative intensity)): 296 (M^++2, 23), 294 (M^+, 83), 248 (100), 231 (73), 192 (26), 167 (18), 126 (8), 95 (4). HRMS (m/z): calcd for $C_{13}H_{11}ClN_2O_4$ (M^+) 294.0402, found 294.0416 and calcd for $C_{13}H_{11}{}^{37}ClN_2O_4$ (M^+) 296.0372, found 296.0389.

3-(2,4-Dichlorophenyl)-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-Oxide (3a). Brown solid, mp 63−65 °C. IR (KBr, cm^{-1}): 3070, 2945, 2834, 1657, 1624, 1587, 1561, 1472, 1451, 1381, 1355, 1263. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 1.8 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.30 (dd, J = 8.4, 1.8 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 5.80 (d, J = 2.4, 1H), 2.65−2.61 (m, 2H), 2.29−2.19 (m, 2H), 1.86−1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.3, 135.0, 133.2, 129.9, 129.0, 128.0, 121.9, 115.6, 76.5, 24.9, 21.2, 20.5. MS (m/z (relative intensity)): 283 (M^+, 100), 248 (17), 218 (5), 173 (13), 159 (2). HRMS (m/z): calcd for $C_{13}H_{11}{}^{35}Cl_2NO_2$ (M^+) 283.0161, found 283.0164 and calcd for $C_{13}H_{11}Cl_1{}^{37}ClNO_2$ (M^+) 285.0132, found 285.0136.

3-(2-Bromophenyl)-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-Oxide (4a). Colorless solid, mp 93−95 °C. IR (KBr, cm^{-1}): 3063, 2930, 2834, 1657, 1628, 1469, 1439, 1355, 1266. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 7.8, 1.4 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.24−7.20 (m, 1H), 6.49 (dd, J = 5.8, 2.9 Hz, 1H), 5.84 (dd, J = 7.2, 4.4 Hz, 1H), 2.70−2.57 (m, 2H), 2.30−2.12 (m, 2H), 1.87−1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 136.7, 133.4, 130.4, 128.3, 128.2, 122.1, 121.8, 115.8, 79.1, 25.0, 21.2, 20.6. MS (m/z (relative intensity)): 296 (M^+ + 3, 13), 293 (M^+, 100), 215 (4), 214 (20), 183 (26), 156 (17). HRMS (m/z): calcd for $C_{13}H_{12}{}^{79}BrNO_2$ (M^+) 293.0046, found 293.0028 and calcd for $C_{13}H_{12}{}^{81}BrNO_2$ (M^+) 295.0025, found 295.0004.

3-Phenyl-3,5,6,7-tetrahydrobenzo[*c*]isoxazole 1-Oxide (5a). Yellow gummy solid. IR (KBr, cm^{-1}): 3063, 3033, 2945, 1653, 1631, 1451, 1355, 1266. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.35 (m, 5H), 6.02 (m, 1H), 5.60 (dd, J = 6.9, 4.3 Hz, 1H), 2.64 (t, J = 6.6 Hz, 2H), 2.31−2.14 (m, 2H), 1.91−1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 137.5, 129.1, 129.0, 126.9, 121.2, 116.2, 80.6, 24.9, 21.1, 20.7. MS (m/z (relative intensity)): 216 (M^+ + 1, 45), 215 (M^+, 100), 198 (9), 185 (5), 169 (22), 157 (14), 141 (22), 129 (10), 105 (33). HRMS (m/z): calcd for $C_{13}H_{13}NO_2$ (M^+) 215.0941, found 215.0948.

3-Methyl-4-methylene-5-(2-nitrophenyl)-4,5-dihydroisoxazole 2-Oxide (7a). Yellow solid, mp 115−117 °C. IR (KBr, cm^{-1}): 3077, 2863, 1646, 1606, 1528, 1351, 1263. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 8.2 Hz, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 6.83 (t, J = 2.5 Hz, 1H), 5.13 (m, 2H), 2.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 144.7, 134.4, 133.8, 129.9, 128.7, 125.2, 115.6, 106.8, 75.7, 8.9. MS (m/z (relative intensity)): 235 (M^+ + 1, 11), 234 (M^+, 100), 203 (5), 187 (17), 171 (5), 158 (38), 130 (33), 103 (45), 93 (14), 79 (36), 76 (23). HRMS (m/z): calcd for $C_{11}H_{10}N_2O_4$ (M^+) 234.0635, found 234.0639.

3-(3-Nitrophenyl)-3,3a,4,5,6,7-hexahydrobenzo[*c*]isoxazole 1-Oxide (Anti) (8a). Colorless solid, mp 152−154 °C. IR (KBr, cm^{-1}): 3080, 2930, 2855, 1655, 1532, 1345, 1270, 1236. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 5.20 (d, J = 9.4 Hz, 1H), 3.19−3.13 (m, 1H), 2.81 (dd, J = 15.7, 4.3 Hz, 1H), 2.22−2.14 (m, 2H), 1.99−1.90 (m, 2H), 1.56−1.41 (m, 2H), 1.40−1.27 (m 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 140.2, 132.1, 130.2, 123.8, 121.1, 116.7, 82.4, 51.6, 30.9, 24.0, 23.9, 23.6. MS (m/z (relative intensity)): 262 (M^+, 52), 245 (45), 170 (1), 150 (15), 111 (28), 81 (100). HRMS (m/z): calcd for $C_{13}H_{14}N_2O_4$ (M^+) 262.0948, found 262.0960.

3-(3-Nitrophenyl)-3,3a,4,5,6,7-hexahydrobenzo[*c*]isoxazole 1-Oxide (Syn) (9a). Colorless gummy solid. IR (KBr, cm^{-1}): 2934, 2860, 1703, 1661, 1530, 1448, 1350, 1282, 1231. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J = 8.2 Hz, 1H), 8.14 (s, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.60 (t, J = 7.9 Hz, 1H), 5.82 (d, J = 10.2 Hz, 1H), 3.70−3.62 (m, 1H), 2.88−2.83 (m, 1H), 2.25−2.18 (m, 1H), 1.92−1.88 (m, 1H), 1.80−1.73 (m, 1H), 1.55−1.50 (m, 1H), 1.32−1.19 (m, 2H), 0.76−0.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 138.9, 131.9, 130.1, 123.5, 121.1, 115.4, 77.2, 47.9, 28.4, 24.4, 24.1, 24.0.

3-(3-Nitrophenyl)-3a,4,5,6,7,8-hexahydro-3*H*-cyclohepta[*c*]isoxazole 1-Oxide (Anti) (10a). Pale yellow solid, mp 101−103 °C. IR (KBr, cm^{-1}): 3077, 2930, 2856, 1639, 1532, 1451, 1347, 1274, 1241, 1211. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 5.16 (d, J = 8.1 Hz, 1H), 3.35−3.30 (m, 1H), 2.70−2.65 (m, 1H), 2.57−2.49 (m, 1H), 2.04−1.92 (m, 4H), 1.79−1.68 (m, 1H), 1.52−1.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 140.6, 132.2, 130.3, 123.9, 121.3, 120.3, 81.6, 55.5, 32.9, 30.2, 28.9, 27.7, 25.3. MS (m/z (relative intensity)): 276 (M^+, 37), 259 (25), 176 (2), 150 (11), 125 (13), 95 (100). HRMS (m/z): calcd for $C_{14}H_{16}N_2O_4$ (M^+) 276.1105, found 276.1114.

3-(3-Nitrophenyl)-3a,4,5,6,7,8-hexahydro-3*H*-cyclohepta[*c*]isoxazole 1-Oxide (Syn) (11a). Pale yellow solid, mp 105−107 °C. IR (KBr, cm^{-1}): 2930, 2856, 1639, 1532, 1451, 1351, 1277, 1218, 1203. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8.2 Hz, 1H), 8.18 (s, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 5.77 (d, J = 9.0 Hz, 1H), 3.64−3.59 (m, 1H), 2.74−2.69 (m, 1H), 2.58−2.49 (m, 1H), 2.05−1.94 (m, 2H), 1.82−1.79 (m, 1H), 1.50−1.47 (m, 1H), 1.30−1.26 (m, 1H), 1.22−1.13 (m, 2H), 1.12−1.05 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 137.6, 132.5, 130.0, 123.6, 121.6, 120.8, 79.0, 50.4, 30.2, 29.6, 29.1, 27.5, 25.3.

(19) For selected recent publications, see: (a) Basavaiah, D.; Aravindu, K.; Kumar, K. S.; Reddy, K. R. *Eur. J. Org. Chem.* **2010**, 1843. (b) Goswami, P.; Das, B. *Tetrahedron Lett.* **2009**, *50*, 897. (c) Basavaiah, D.; Aravindu, K. *Org. Lett.* **2007**, *9*, 2453. (d) Guo, H.-C.; Ma, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (e) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779.

MS (*m*/*z* (relative intensity)): 276 (M^+, 39), 259 (20), 231 (4), 176 (3), 150 (9), 125 (14), 95 (100), 67 (17). HRMS (*m*/*z*): calcd for $C_{14}H_{16}N_2O_4$ (M^+) 276.1105, found 276.1112.

3-(3-Nitrophenyl)-3,3a,4,5,6,7,8,9-octahydrocycloocta[*c*]isoxazole 1-Oxide (Anti) (12a). Colorless solid, mp 98−100 °C. IR (KBr, cm^{-1}): 3085, 2922, 2863, 1635, 1532, 1462, 1347, 1292. ^1H NMR (400 MHz, $CDCl_3$): δ 8.24−8.22 (m, 2H), 7.80 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 8.6 Hz, 1H), 5.29 (d, J = 6.8 Hz, 1H), 3.30 (dd, J = 11.5, 7.2 Hz, 1H), 2.76−2.69 (m, 1H), 2.34−2.27 (m, 1H), 2.09−2.05 (m, 1H), 1.92−1.84 (m, 4H), 1.71−1.66 (m, 2H), 1.63−1.57 (m, 1H), 1.55−1.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 141.3, 131.7, 130.3, 123.8, 120.8, 119.2, 79.9, 53.9, 29.2, 26.3, 25.6, 25.5, 24.0, 23.6. MS (*m*/*z* (relative intensity)): 290 (M^+, 44), 273 (14), 244 (5), 162 (3), 150 (9), 109 (100), 67 (57). HRMS (*m*/*z*): calcd for $C_{15}H_{18}N_2O_4$ (M^+) 290.1261, found 290.1269.

3-(3-Nitrophenyl)-3,3a,4,5,6,7,8,9-octahydrocycloocta[*c*]isoxazole 1-Oxide (Syn) (13a). Pale yellow solid, mp 130−132 °C. IR (KBr, cm^{-1}): 3092, 2929, 2858, 1630, 1529, 1463, 1443, 1349. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 7.3 Hz, 1H), 8.20 (s, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.62−7.58 (m, 1H), 5.82 (d, J = 7.9 Hz, 1H), 3.45−3.39 (m, 1H), 2.68−2.58 (m, 2H), 2.04−1.99 (m, 1H), 1.72−1.61 (m, 2H), 1.58−1.46 (m, 3H), 1.32−1.26 (m, 3H), 1.18−1.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 136.9, 132.3, 129.9, 123.5, 121.9, 121.4, 80.3, 48.9, 28.7, 27.5, 26.1, 25.9, 23.9, 22.7. MS (*m*/*z* (relative intensity)): 290 (M^+, 39), 273 (48), 150 (100), 109 (65). HRMS (*m*/*z*): calcd for $C_{15}H_{18}N_2O_4$ (M^+) 290.1267, found 290.1262.

3-(3-Nitrophenyl)-3,3a,4,5,6,7,8,9,10,11,12,13-dodecahydrocyclododeca[*c*]isoxazole 1-Oxide (Anti) (14a). Colorless solid, mp 113−115 °C. IR (KBr, cm^{-1}): 2932, 2863, 1637, 1531, 1469, 1444, 1351. ^1H NMR (400 MHz, $CDCl_3$): δ 8.22−8.20 (m, 2H), 7.76 (d, J = 7.7 Hz, 1H), 7.63−7.58 (m, 1H), 5.29 (d, J = 5.6 Hz, 1H), 3.32 (dd, J = 10.0, 4.8 Hz, 1H), 2.53−2.46 (m, 1H), 2.43−2.36 (m, 1H), 1.94−1.75 (m, 3H), 1.61−1.46 (m, 5H), 1.46−1.25 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 142.2, 131.5, 130.4, 123.8, 120.6, 117.2, 79.3, 54.6, 29.7, 25.7, 25.1, 24.3, 24.2, 23.6, 23.3, 23.2, 22.3. MS (*m*/*z* (relative intensity)): 346 (M^+, 100), 329 (53), 299 (34), 230 (5), 216 (9), 202 (14), 163 (23), 150 (15), 95 (30), 83 (55). HRMS (*m*/*z*): calcd for $C_{19}H_{26}N_2O_4$ (M^+) 346.1893, found 346.1885.

3-(3-Nitrophenyl)-3,3a,4,5,6,7,8,9,10,11,12,13-dodecahydrocyclododeca[*c*]isoxazole 1-Oxide (Syn) (15a). Colorless solid, mp 118−120 °C. IR (KBr, cm^{-1}): 3091, 2934, 2864, 1651, 1634, 1538, 1531, 1469, 1445, 1348. ^1H NMR (400 MHz, $CDCl_3$): δ 8.23−8.20 (m, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 5.79 (d, J = 8.6 Hz, 1H), 3.59 (dd, J = 13.6, 5.8 Hz, 1H), 2.63−2.55 (m, 1H), 2.47−2.40 (m, 1H), 1.76−1.70 (m, 1H), 1.68−1.62 (m, 1H), 1.53−1.47 (m, 2H), 1.43−1.35 (m, 7H), 1.29−1.20 (m, 4H), 1.18−1.11 (m, 2H), 1.01−0.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.5, 137.2, 132.4, 129.9, 123.6, 121.6, 120.4, 79.1, 48.2, 25.9, 25.8, 24.5, 24.2, 23.7, 23.6, 23.4, 22.9, 22.8. MS (*m*/*z* (relative intensity)): 346 (M^+, 100), 329 (77), 298 (11), 228 (3), 222 (8), 178 (11), 163 (20), 95 (30), 83 (61). HRMS (*m*/*z*): calcd for $C_{19}H_{26}N_2O_4$ (M^+) 346.1893, found 346.1885.

3-(4-Nitrophenyl)-3a,4,5,6,7,8-hexahydro-3*H*-cyclohepta[*c*]isoxazole 1-Oxide (Anti) (16a). Colorless solid, mp 135−137 °C. IR (KBr, cm^{-1}): 3079, 2928, 2855, 1640, 1607, 1521, 1451, 1349, 1275. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28−8.25 (m, 2H), 7.62−7.59 (m, 2H), 5.16 (d, J = 7.8 Hz, 1H), 3.30−3.25 (m, 1H), 2.67−2.62 (m, 1H), 2.57−2.49 (m, 1H), 1.99−1.91 (m, 4H), 1.79−1.70 (m, 1H), 1.47−1.40 (m, 1H), 1.36−1.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 145.7, 126.9, 124.4, 120.1, 81.5, 55.6, 33.2, 30.1, 28.9, 27.7, 25.3. MS (*m*/*z* (relative intensity)): 276 (M^+, 39), 259 (6), 230 (2), 176 (2), 125 (14), 95 (100), 67 (10). HRMS (*m*/*z*): calcd for $C_{14}H_{16}N_2O_4$ (M^+) 276.1105, found 276.1111.

3-(4-Nitrophenyl)-3a,4,5,6,7,8-hexahydro-3*H*-cyclohepta[*c*]isoxazole 1-Oxide (Syn) (17a). Colorless solid, mp 95−97 °C. IR (KBr, cm^{-1}): 3079, 2929, 2855, 1640, 1606, 1519, 1451, 1382, 1348, 1278. ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 5.75 (d, J = 9.0 Hz, 1H), 3.65−3.59 (m, 1H), 2.73−2.68 (m, 1H), 2.57−2.48 (m, 1H), 2.03−1.94 (m, 2H), 1.81−1.78 (m, 1H), 1.53−1.44 (m, 1H), 1.29−1.21 (m, 1H), 1.16 (dd, J = 22.6, 11.4 Hz, 2H), 1.10−0.99 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 142.7, 127.5, 124.0, 120.7, 79.0, 50.5, 30.1, 29.6, 29.2, 27.5, 25.3. MS (*m*/*z* (relative intensity)): 276 (M^+, 46), 259 (16), 184 (5), 150 (8), 125 (14), 95 (100), 67 (13). HRMS (*m*/*z*): calcd for $C_{14}H_{16}N_2O_4$ (M^+) 276.1105, found 276.1102.

3-Methyl-5-(4-nitrophenyl)-4,5-dihydroisoxazole 2-Oxide (18a). Colorless solid, mp 123−125 °C. IR (KBr, cm^{-1}): 3107, 2922, 2849, 1653, 1598, 1513, 1351. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 5.69 (dd, J = 9.4, 7.1 Hz, 1H), 3.63 (dd, J = 17.0, 9.8 Hz, 1H), 3.03 (dd, J = 17.0, 6.6 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 146.6, 126.4, 124.5, 111.1, 73.9, 42.5, 11.9. MS (*m*/*z* (relative intensity)): 223 (M^+ + 1, 23), 222 (M^+, 100), 205 (7), 175 (18), 150 (44), 146 (7), 84 (4), 71 (39), 55 (7). HRMS (*m*/*z*): calcd for $C_{10}H_{10}N_2O_4$ (M^+) 222.0635, found 222.0644.

5-(2-(Allyloxy)-5-nitrophenyl)-3-methyl-4,5-dihydroisoxazole 2-Oxide (19a). Yellow solid, mp 85−87 °C. IR (KBr, cm^{-1}): 3086, 2923, 1659, 1652, 1613, 1593, 1520, 1488, 1338, 1271. ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 2.7 Hz, 1H), 8.22 (dd, J = 9.0, 2.8 Hz, 1H), 6.98 (d, J = 9.1 Hz, 1H), 6.09−5.99 (m, 1H), 5.81 (dd, J = 10.0, 2.8 Hz, 1H), 5.45−5.37 (m, 2H), 4.74−4.65 (m, 2H), 3.65−3.57 (m, 1H), 3.00−2.94 (m, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 141.7, 131.6, 129.4, 125.8, 122.1, 119.3, 111.9, 111.7, 70.6, 70.0, 41.3, 11.9. MS (*m*/*z* (relative intensity)): 278 (M^+, 5), 261 (8), 221 (7), 209 (11), 206 (100), 191 (39), 166 (20), 96 (10), 73 (8). HRMS (*m*/*z*): calcd for $C_{13}H_{14}N_2O_5$ (M^+) 278.0897, found 278.0887.

3,5-Diphenyl-4,5-dihydroisoxazole 2-Oxide (20a). Colorless solid, mp 76−78 °C. IR (KBr, cm^{-1}): 3048, 2937, 1613, 1591, 1498, 1447, 1384, 1226. ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 7.7 Hz, 2H), 7.46−7.35 (m, 8H), 5.73 (t, J = 8.5 Hz, 1H), 3.92 (dd, J = 16.2, 9.5 Hz, 1H), 3.55 (dd, J = 16.2, 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 129.7, 129.2, 129.1, 128.9, 126.9, 126.4, 125.9, 114.1, 75.9, 40.5. MS (*m*/*z* (relative intensity)): 239 (M^+, 100), 192 (10), 117 (4), 105 (12), 103 (18). HRMS (*m*/*z*): calcd for $C_{15}H_{13}N_1O_2$ (M^+) 239.0941, found 239.0944.

3-Methyl-5-(pyridin-2-yl)-4,5-dihydroisoxazole 2-Oxide (21a). Brown oil. IR (KBr, cm^{-1}): 3057, 3012, 2922, 1713, 1652, 1593, 1573, 1475, 1438, 1395, 1352, 1259. ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 4.2 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.29−7.26 (m, 1H), 5.64 (dd, J = 9.9, 5.4 Hz, 1H), 3.63−3.56 (m, 1H), 3.39 (dd, J = 17.4, 4.0 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 149.8, 137.4, 123.6, 120.6, 112.4, 74.9, 40.3, 11.9.

3-Methyl-4-(2-nitrobenzylidene)-4,5-dihydroisoxazole 2-Oxide (22a). Yellow solid, mp 128−130 °C. IR (KBr, cm^{-1}): 1641, 1595, 1509, 1361, 1269. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, J = 8.2, 1.1 Hz, 1H), 7.66−7.62 (m, 1H), 7.47−7.43 (m, 1H), 7.27 (d, J = 7.6, 1H), 6.78 (t, J = 3.1 Hz, 1H), 5.29 (d, J = 3.1 Hz, 2H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 138.5, 133.5, 130.4, 128.8, 128.5, 125.6, 117.5, 113.6, 68.3, 9.1. MS (*m*/*z* (relative intensity)): 235 (M^+ + 1, 12), 234 (M^+, 100), 158 (15), 146 (11), 130 (11), 119 (22), 104 (6), 92 (36). HRMS (*m*/*z*): calcd for $C_{11}H_{10}N_2O_4$ (M^+) 234.0635, found 234.0640.

3-Methyl-4-(5-chloro-2-nitrobenzylidene)-4,5-dihydroisoxazole 2-Oxide (23a). Yellow solid, mp 129−131 °C. IR (KBr, cm^{-1}): 3109, 3070, 2923, 1644, 1600, 1578, 1517, 1334, 1279. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 7.22 (d, J = 1.7 Hz, 1H), 6.74 (t, J = 3.0 Hz, 1H), 5.31 (d, J = 3.0 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 139.9, 139.8, 132.4, 128.6, 128.4, 127.2, 117.4, 112.4, 68.1, 9.2. MS (*m*/*z* (relative intensity)): 270 (M^+ + 2, 25),

268 (M^+, 100), 208 (6), 192 (20), 153 (38), 125 (46), 90 (6), 55 (6). HRMS (*m*/*z*): calcd for $C_{11}H_9ClN_2O_4$ (M^+) 268.0245, found 268.0257 and calcd for $C_{11}H_9{}^{37}ClN_2O_4$ (M^+) 270.0216, found 270.0225.

3-Methyl-4-(5-bromo-2-nitrobenzylidene)-4,5-dihydroisoxazole 2-Oxide (24a). Yellow solid, mp 125−127 °C. IR (KBr, cm^{-1}): 3092, 3070, 1642, 1580, 1517, 1336, 1274. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 8.7, 1.9 Hz, 1H), 7.39 (d, J = 1.7 Hz, 1H), 6.73 (t, J = 3.1 Hz, 1H), 5.30 (d, J = 3.1 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 139.8, 132.4, 131.6, 131.4, 128.4, 127.2, 117.4, 112.3, 68.1, 9.2. MS (*m*/*z* (relative intensity)): 314 ($M^+ + 2$, 81), 312 (M^+, 100), 297 (3), 266 (8), 210 (36), 199 (52), 171 (72), 145 (13), 130 (7), 90 (18), 55 (13). HRMS (*m*/*z*): calcd for $C_{11}H_9BrN_2O_4$ (M^+) 311.9740, found 311.9745 and calcd for $C_{11}H_9{}^{81}BrN_2O_4$ (M^+) 313.9720, found 313.9728.

3-Methyl-4-(4-nitrobenzylidene)-4,5-dihydroisoxazole 2-Oxide (25a). Yellow solid, mp 184−186 °C. IR (KBr, cm^{-1}): 1635, 1603, 1570, 1508, 1340, 1273. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 6.38 (t, J = 3.1 Hz, 1H), 5.44 (d, J = 3.0 Hz, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 142.1, 139.1, 128.8, 124.6, 117.6, 116.5, 69.0, 9.2. MS (*m*/*z* (relative intensity)): 235 ($M^+ + 1$, 11), 234 (M^+, 100), 205 (5), 176 (8), 150 (5), 130 (4), 84 (5). HRMS (*m*/*z*): calcd for $C_{11}H_{10}N_2O_4$ (M^+) 234.0635, found 234.0643.

6-Methoxy-3-methylbenzo[*d*]isoxazole 2-Oxide (27a). Colorless solid, mp 113−115 °C. IR (KBr, cm^{-1}): 2974, 2834, 1599, 1504, 1427. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.5 Hz, 1H), 6.88 (dd, J = 8.6, 2.2 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 3.86 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 151.6, 119.9, 116.3, 113.8, 112.9, 92.2, 55.9, 9.5. MS (*m*/*z* (relative intensity)): 179 (M^+, 100), 150 (4), 149 (54), 121 (52), 91 (5), 77 (4). HRMS (*m*/*z*): calcd for $C_9H_9NO_3$ (M^+) 179.0577, found 179.0587.

Bis Isoxazoline *N*-Oxide Derivative 29a. Colorless solid, mp 176−178 °C. IR (KBr, cm^{-1}): 1601, 1459, 1412, 1365, 1259, 1220. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.03 (d, J = 0.4 Hz, 1H), 2.48 (s, 6H). ^{13}C NMR (100 MHz, DMSO): δ 150.2, 117.9, 115.2, 111.5, 86.9, 9.1. MS (*m*/*z* (relative intensity)): 220 (M^+, 100), 190 (9), 148 (13), 131 (16), 122(13). HRMS (*m*/*z*): calcd for $C_{10}H_8N_2O_4$ (M^+) 220.0484, found 220.0483.

Preparation of (2*Z*)-3-(Methylimino)-2-(2-nitrobenzylidene)-butanal (33). To a stirred solution of 3-methyl-4-(2-nitrobenzylidene)-4,5-dihydroisoxazole 2-oxide (2 mmol) in 1.6 mL of DMSO was added triethylamine (4.4 mmol), and the reaction was monitored by TLC. After 0.5 h, the reaction mixture was transferred into 50 mL of water in a beaker and the solution extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with a brine solution (50 mL × 2), dried over magnesium sulfate, and concentrated under vacuum. The resulting residue was further purified by flash column chromatography (15% EA in hexane). The product was obtained as a nonseparable mixture of syn and anti oximes in a ratio of 2:1 as a yellow solid; mp 130−132 °C. IR (KBr, cm^{-1}): 3276, 2922, 2849, 1686, 1522, 1342. ^{1}H NMR (400 MHz, $CDCl_3$): δ (for major peaks) 9.76 (s, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.69 (dd, J = 16.2, 7.36 Hz, 1H), 7.65−7.56 (m, 1H), 7.41 (d, J = 7.6 Hz, 1H), 1.89 (s, 3H); δ (for minor peaks) 9.76 (s, 1H), 8.27 (d, J = 8.1 Hz, 1H), 7.99 (s, 1H), 7.98 (s, 1H), 7.69 (dd, J = 16.2, 7.36 Hz, 1H), 7.65−7.56 (m, 1H), 7.41 (d, J = 7.6 Hz, 1H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (for major peaks) 191.8, 151.6, 147.5, 147.4, 139.5, 134.1, 133.3, 130.6, 129.9, 125.2, 13.1; δ (for minor peaks) 190.5, 154.7, 147.4, 143.3, 137.5, 133.8, 133.3, 130.9, 129.9, 125.6, 15.1. MS (*m*/*z* (relative intensity)): 233 ($M^+ - 1$, 14), 205 (44), 170 (55), 130 (100), 103 (92). HRMS (*m*/*z*): calcd for $C_{11}H_9N_2O_4$ ($M^+ - 1$) 233.0562, found 233.0563.

Synthesis of 2-(3-(Hydroxyimino)-2-(2-nitrobenzylidene)butylidene)-5,5-dimethylcyclohexane-1,3-dione (34). To (2*Z*)-3-(methylimino)-2-(2-nitrobenzylidene)butanal (0.5 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (0.6 mmol) in a 20 mL vial was added 5 mL of water, and the mixture was stirred for 5 min. It was then sonicated for 18 h. The solid was isolated on a filter, and the resulting residue was further purified by flash column chromatography to give a yellow solid; mp 212−214 °C. IR (KBr, cm^{-1}): 3284, 2959, 2871, 1630, 1590, 1531, 1399, 1359, 1264. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.7 Hz, 1H), 7.51−7.43 (d, 3H), 7.35 (d, J = 7.5 Hz, 1H), 7.16 (s, 2H), 2.35−2.17 (m, 4H), 2.09 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 171.5, 153.8, 149.3, 132.9, 129.8, 129.1, 124.6, 122.9, 118.9, 110.9, 72.4, 50.5, 42.1, 32.6, 29.3, 27.6, 9.5. MS (*m*/*z* (relative intensity)): 358 ($M^+ + 2$, 2), 356 (M^+, 56), 339 (66), 293 (64), 292 (45), 280 (16), 235 (5), 222 (30), 188 (35), 169 (100), 158 (43), 83 (16). HRMS (*m*/*z*): calcd for $C_{19}H_{20}N_2O_5$ (M^+) 356.1372, found 356.1376.

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Supporting Information Available: Text, figures, and tables giving experimental procedures and spectroscopic data for all compounds and tables, figures, and CIF files giving crystal structure data for **1a**, **10a**, **11a**, **14a**, **15a**, and **23a**. This material is available free of charge via the Internet at http://pubs.acs.org.