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# Halonium Ion Mediated Synthesis of 2-Halomethylene-3-oxoketoxime Derivatives from Isoxazoline *N*-Oxides

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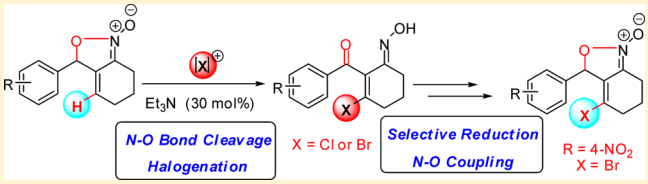
Supporting Information

**ABSTRACT:** A protocol for the *N*-bromosuccinimide (NBS)- and trichloroisocyanuric acid (TCCA)-mediated synthesis of novel 2-halomethylene-3-oxoketoximes via one-pot halogenation/oxidation of isoxazoline *N*-oxide derivatives is described here. The keto functionality of 3-ketoximes was selectively reduced by lithiumaluminum hydride to synthesize an unprecedented type of Baylis−Hillman oxime, which underwent N−O coupling to produce new isoxazoline *N*-oxide derivative.




Despite the rising importance of 3-oxoketoximes as an intermediate, the synthesis of the ketoxime derivatives is an existing challenge.[1] The reported methodologies are plagued by the use of strong bases, complex combination of reagents, multistep reactions, and low productivity.[1] For these reasons, the variation in the 3-oxoketoxime family is limited. Hence, to introduce further diversity and expand this area, a new source of starting material and a more convenient protocol are needed.

On the other hand, although significant progress has been made on the development of new and novel protocols for the synthesis of isoxazoline *N*-oxide derivatives, the utilities of the *N*-oxides are less explored.[2,3] Most of the reports describe the reduction of the *N*-oxides into *β*-hydroxyamines, synthesis of isoxazoline derivatives, 1, 2-addition at the C−N bond, and cycloaddition at the CNO moiety.[2] We also utilized isoxazoline *N*-oxide derivatives to achieve substituted cinnamaldehyde derivative and highly functionalized long-chain diketohalocyano skeletons (**C**, Scheme 1).[3] However, more efforts are necessary to diversify the application of these *N*-oxides. Keeping these points in mind, we report herein the NBS- and TCCA-mediated synthesis of 2-halomethylene-3-oxo-ketoxime derivatives from cyclohexene fused isoxazoline *N*-oxides.

In our recent publication on the halonium ion mediated C−C bond cleavage of isoxazoline *N*-oxide (**A**), we envisaged that the long-chain diketohalocyano skeleton (**C**, Scheme 1) was formed via a nitric oxide intermediate (**B**).[3a] In an attempt to collect further evidence for the formation of the intermediate, we isolated the intermediate **B** (Scheme 1, when R = 4-$NO_2$, X = Br) and passed it through a silica gel column. However, on eluting with a mixture of hexane and ethyl acetate, we did not achieve our desired intermediate. The intermediate was converted into, mainly, diketohalocyano compound (**C**, when R = 4-$NO_2$, X = Br), and in addition to that a minor amount of white solid was obtained as a byproduct (entry 1, Table 1). $^1$H and $^{13}$C NMR, mass, and single-crystal X-ray structures (Figure 1) showed that the white solid is a 2-bromomethylene-substituted 3-oxoketoxime (**D**, R = 4-$NO_2$, X = Br). The product was formed via the removal of the $H^a$ of the intermediate **B** (pathway b, Scheme 1). This result is quite exciting as it demonstrates an unprecedented methodology for the synthesis of 2-halomethylene-substituted 3-oxoketoximes, which are unknown in the literature. In the literature, protocols for the preparation of similar analogues from the corresponding diketones are plagued by the lack of selectivity.[4] It is noteworthy to mention here that the 2-methylene-substituted diketones are well-known precursors for several pharmaceutically active target molecules and natural products.[5] Moreover, our 2-halomethylene-substituted 3-ketoximes have the potential to act as an *α*,*β*-unsaturated ketone, *α*,*β*-unsaturated oxime and vinyl bromide. This result demonstrates an unprecedented utility of isoxazoline *N*-oxide.

Encouraged by this preliminary observation, we conducted a search for the most favorable conditions for this conversion (Table 1). To pursue this goal, we replaced NBS with TCCA to observe the effect of the halogen atom on this transformation (entry 2). We isolated the intermediate and passed through a silica gel column. In this case, our desired oxoketoxime was obtained as the major product. The increment of the yield from bromo to chloro derivative is probably due to the higher electronegativity of the chlorine atom compared to the bromine atom, and this fact facilitates the removal of the proton ($H^a$, Scheme 1) in the case of the chloro derivative (**B**, X = Cl). Because of the faster removal of the proton, the ketoxime (**D**) derivative was formed at a faster rate than the diketohalocyano (**C**) derivative. Hence, to enhance the rate of removal of the proton, we treated the intermediate (**B**, X = Cl) with the inorganic base, sodium bicarbonate (entry 3). However, the desired product was obtained in moderate yield along with a significant amount of the long-chain diketohalocyano com-

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**Scheme 1. Base-Mediated Formation of the 3-Oxo-ketoxime**

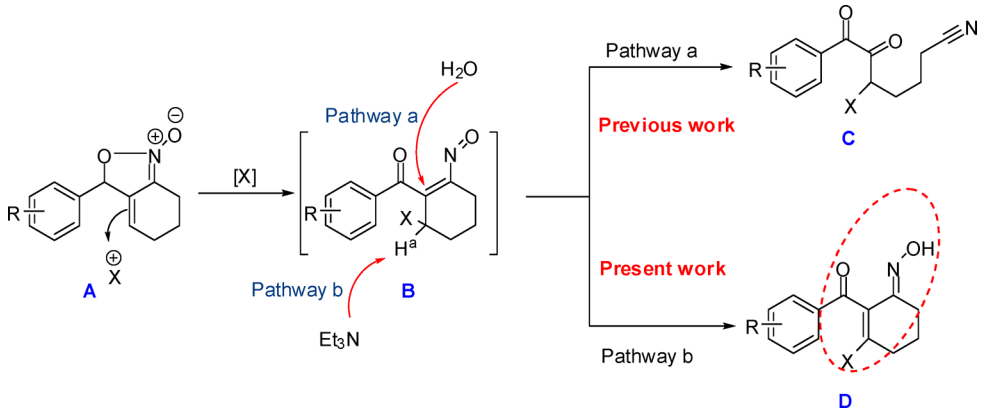
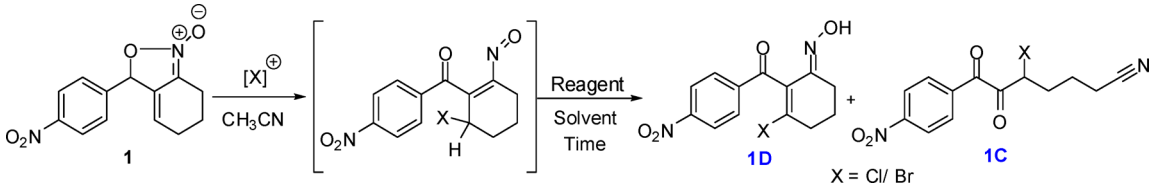



**Table 1. Effect of Different Reagents**




| entry | $[X]^+$ | reagent | solvent | time | yield[a,b] (%) D | yield[a,b] (%) C |
|---|---|---|---|---|---|---|
| 1 | NBS | silica gel[c] | | nd[d] | 27 | 59 |
| 2 | TCCA | silica gel[c] | | nd[d] | 71 | 16 |
| 3 | TCCA | $NaHCO_3$ (0.25 equiv) | $CH_3CN$ | 3.5 h | 55 | 9 |
| 4 | TCCA | $NaHCO_3$(1.10 equiv) | $CH_3CN$ | 3.5 h | 63 | 15 |
| 5 | TCCA | aq. $NaHCO_3$ (0.25 equiv)[e] | $CH_3CN$ | 12 h | 38 | 27 |
| 6 | TCCA | $NaHCO_3$ (0.25 equiv) | MeOH | 7 h | 62 | 7 |
| 7 | TCCA | $NaHCO_3$ (1.0 equiv) | MeOH | 5 h | 61 | nd[d] |
| **8**[f] | **TCCA** | **$Et_3N$ (0.30 equiv)** | **$CH_3CN$** | **5 min** | **83** | |
| **9**[f] | **NBS** | **$Et_3N$ (0.30 equiv)** | **$CH_3CN$** | **5 min** | **89** | |
| 10[g] | NBS | | $CH_3CN$ | 40 h | | 74 |
| 11[g] | NBS | | $CHCl_3$ | 12 h | | 88 |
| 12[g] | TCCA | | $CH_3CN$ | 40 h | | 49 |

[a]Yields refer to isolated and purified compounds. [b]Unless otherwise stated, standard reaction conditions: **1** (0.5 mmol), NBS (1.1 equiv) or TCCA (0.37 equiv), solvent (3 mL), rt, 3 min then base was added. [c]The reaction was quenched with water and extracted with ethyl acetate. The intermediate was passed through a silica gel column. [d]nd = not determined. [e]1 M aq solution of $NaHCO_3$ was used. [f]Compound **B** was not found in the crude $^1H$ NMR. [g]Reference 3a.

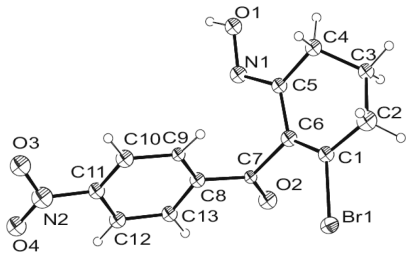



**Figure 1.** Single-crystal X-RD structure of **1a**.

pound (**C**). The result was not improved on varying the amount of base (entries 4 and 5) or by changing the solvent from acetonitrile to methanol (entries 6 and 7). Then, we used the organic base triethylamine and observed a dramatic increment of the product yield (entry 8). Similar results were attained in the case of bromo derivative as well (entry 9). Hence, the scope of the methodology was evaluated by using triethylamine as base and acetonitrile as solvent.

With the optimized conditions in hand, we explored the scope of the methodology with NBS and TCCA. To pursue this goal, we examined the effect of substitution on the phenyl ring (Table 2). In the case of NBS treatment, the products were obtained in good to excellent yields in the presence of an electron-withdrawing group at the *para*- and *meta*-positions of the phenyl ring (entries 1, 3, and 5). However, when the phenyl ring contains *o*-$NO_2$ functionality, the desired 3-oxoketoximes were acquired in fewer yields (entries 11 and 13). The products were obtained in moderate yields in the casess of halo-substituted derivatives (entries 7, 13, 15, and 17). The isoxazoline *N*-oxide with unsubstituted phenyl ring also produced the expected ketoxime in moderate yield (entry 9). In contrast to NBS treatment of isoxazoline *N*-oxides, a slight different trend was observed with TCCA. The *o*- (entry 2) and *p*-$NO_2$ derivatives (entry 12) afforded the desired products in good yields. However, the reaction offered the products in lower yields in the cases of *m*-$NO_2$ and *p*-CN derivatives (entries 4 and 6). In the presence of halo substitution, the


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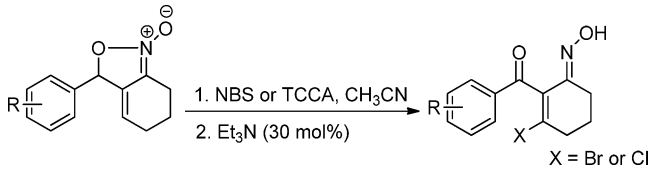
**Table 2. NBS and TCCA Treatment of Different Cyclohexene-Fused Isoxazoline *N*-Oxide Derivatives**



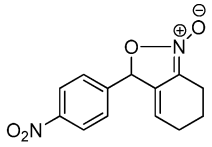
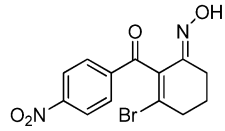
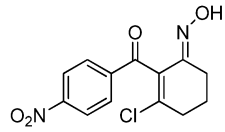
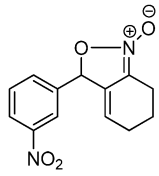
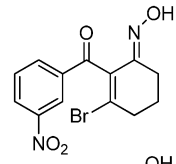
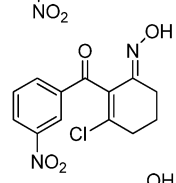
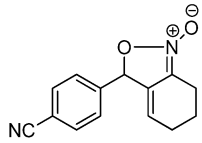
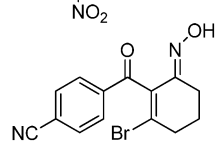
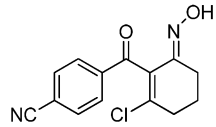
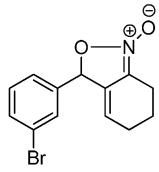
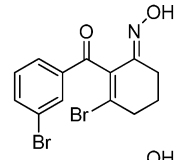
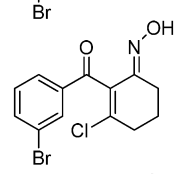
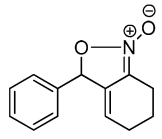
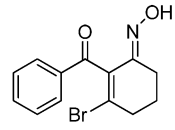
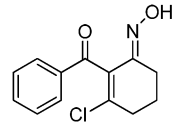

| Entry | Substrate | Reagent | Product | | Yield (%)[a, b] |
|---|---|---|---|---|---|
| 1[c] |  | NBS |  | **1a** | 89 |
| 2[c] | | TCCA |  | **1b** | 83 |
| 3[c] |  | NBS |  | **2a** | 88 |
| 4[c] | | TCCA |  | **2b** | 74 |
| 5[c] |  | NBS |  | **3a** | 91 |
| 6[c] | | TCCA |  | **3b** | 75 |
| 7[c] |  | NBS |  | **4a** | 65 |
| 8[c] | | TCCA |  | **4b** | 67 |
| 9[c] |  | NBS |  | **5a** | 73 |
| 10[c] | | TCCA |  | **5b** | 74 |


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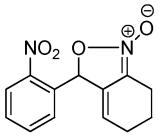
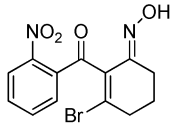
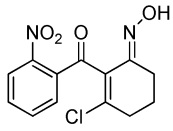
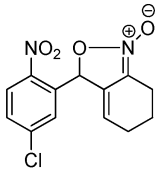
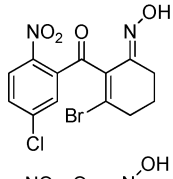
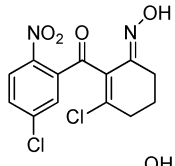
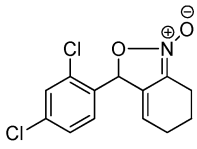
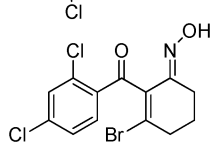
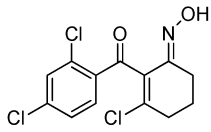
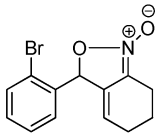
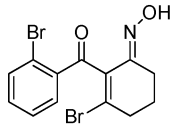
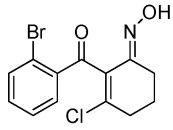
**Table 2. continued**

| Entry | Substrate | Reagent | Product | | Yield (%)[a, b] |
|---|---|---|---|---|---|
| 11[d] |  | NBS |  | **6a** | 76 |
| 12[d] | | TCCA |  | **6b** | 83 |
| 13[d] |  | NBS |  | **7a** | 57 |
| 14[d] | | TCCA |  | **7b** | 63 |
| 15[d] |  | NBS |  | **8a** | 70 |
| 16[d] | | TCCA |  | **8b** | 61 |
| 17[d] |  | NBS |  | **9a** | 67 |
| 18[d] | | TCCA |  | **9b** | 70 |

[a]Yields refer to isolated and purified compounds. [b]Unless otherwise stated, standard reaction conditions: *N*-oxide (0.5 mmol), NBS (1.1 equiv) or TCCA (0.37 equiv), solvent (3 mL), rt for 1 or 3 min then base was added. [c]Base was added after 3 min of NBS/TCCA treatment. [d]Base was added after 1 min of NBS/TCCA treatment.

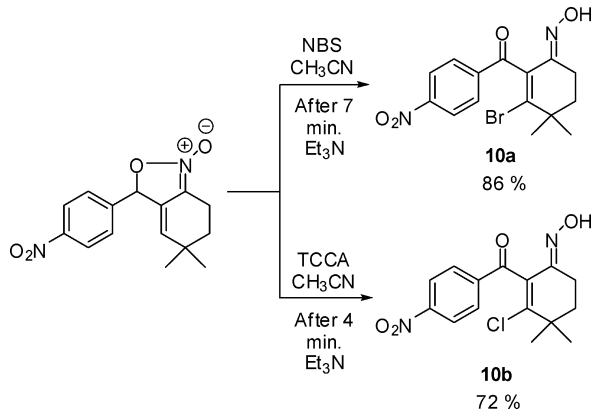
products were achieved in moderate yields (entries 8, 14, 16, and 18), and the results are comparable with the outcome of NBS treatment (entries 7, 13, 15, and 17). For the unsubstituted phenyl ring, the yield of the desired 3-oxoketoxime was similar to the results attained from the NBS treatment of the same isoxazoline *N*-oxide derivative.

In order to extend the scope of our protocol, we treated 4,4-dimethyl-substituted cyclohexene fused isoxazoline *N*-oxide derivative with NBS and TCCA (Scheme 2). In both cases, the product was obtained in good yields; however, NBS was found to be more productive than TCCA.

After studying various cyclohexene fused isoxazoline *N*-oxide derivatives, we treated 4-methyleneisoxazoline *N*-oxide derivative with NBS and TCCA (Scheme 3), and the corresponding halomethylene derivatives were obtained in good yields.

After evaluating the scope of our protocol, we focused our attention toward exploring the synthetic application of our 3-

**Scheme 2. NBS and TCCA Treatment of 4,4-Dimethylcyclohexene-Fused Isoxazoline *N*-Oxide Derivative**





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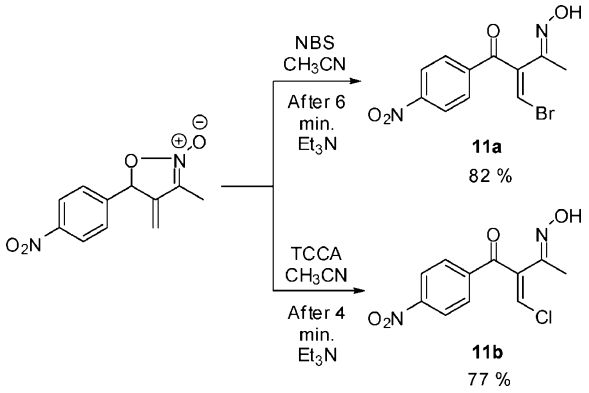
**Scheme 3. NBS and TCCA Treatment of 3-Methyl-4-methyleneisoxazoline *N*-Oxide Derivative**




oxoketoxime. In the literature, we found that both keto and oxime functionalities are prone to undergo reduction with suitable reducing agent.[6] In our case, to reduce the keto group selectively, we treated the compound **1a** with lithium aluminum hydride, and we were pleased to find that 3-hydroxyketoxime (**1c**) was formed (Scheme 4 and Figure 2). This result is very important and interesting as it produces a special type of Baylis–Hillman oxime, which contains a 3-bromo functionality. There is no reported method in the literature that describes the synthesis of such compound.[7] On treating compound **1c** with HTIB in MeOH, the corresponding isoxazoline *N*-oxide was formed. This isoxazoline *N*-oxide is new in the literature as it contains halo functionality at cyclohexene ring.[2,3]

Next, we protected the OH functionality of compound **1a** with acetate to obtain the Baylis–Hillman oxime acetate (Scheme 5). However, on treatment with LAH, compound **1e** underwent acetate deprotection and reduction to produce compound **1c** in poor yield.

In conclusion, here we have demonstrated an unprecedented halonium ion and base-mediated transformation of isoxazoline *N*-oxide derivatives into 3-oxoketoximes. The reaction occurs via the nitric oxide intermediate. The base-mediated removal of a proton from the nitric oxide intermediate produces the ketoxime derivatives. Selective reduction of the keto functionality of the 3-oxoketoxime produces a novel type of Baylis–Hillman oxime derivative.

## EXPERIMENTAL SECTION

**General Information.** Reagents and solvents were purchased from various commercial sources and were used directly without any further purification unless otherwise stated. Column chromatography was performed with 63–200 mesh silica gel. $^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million ($\delta$) using TMS and chloroform as internal standards, and coupling constants are expressed in hertz. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet), coupling constants (Hz), and integration. IR spectra were recorded on an FT-IR spectrometer and are reported in cm$^{-1}$. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. HRMS spectra were recorded using ESI-TOF or EI$^+$ mode. Isoxazoline *N*-oxides were synthesized by following the procedure depicted in our previous publication.[3b]

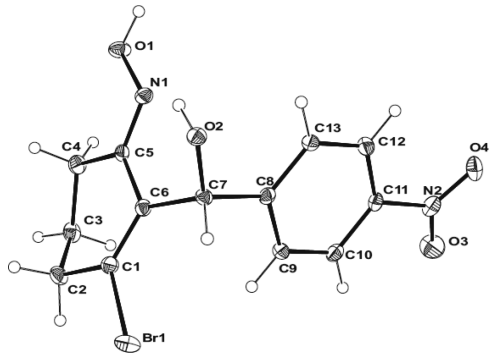



**Figure 2.** Crystal structure of compound **1c**.

**Representative Procedure for Preparation of 3-Oxoketoxime Derivatives.** To a stirred solution of isoxazoline *N*-oxide derivative (0.5 mmol) in $CH_3CN$ (4 mL) in a 50 mL round-bottom flask was added NBS (1.1 equiv) or TCCA (0.37 equiv) at ambient temperature. The reaction was monitored by TLC. After complete conversion of the starting material into the intermediate (3 min for **1a/b** to **5a/b** and 1 min for **6a/b** to **9a/b**), triethylamine (30 mol %) was added to the reaction mixture and the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was added to 15 mL of brine solution and the organic layer was extracted with ethyl acetate (15 mL × 3). The combined organic layer was dried over magnesium sulfate, and the solvent was evaporated at reduced pressure. The resulting residue was further purified by column chromatography.

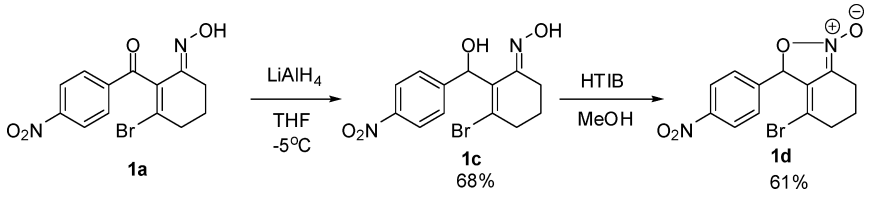
**Procedure for the Reduction of 1a.** To a stirred solution of compound **1a** (0.5 mmol) in dry THF (3 mL) under $N_2$ at 0 to −5 °C in a two-necked round-bottom flask was added LAH (0.75 mmol) in small pinches. The reaction mixture was stirred for 10 min, and then it was quenched with water. Ten milliliters of brine water was added to the reaction mixture, and then the reaction mixture was extracted with ethyl acetate. The solvent was evaporated, and the crude reaction mixture was purified with column chromatography.

Compound **1e** was prepared by the acetylation of compound **1a**, following our previous report.[3b]

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(4-nitrophenyl)-methanone (**1a**):* light yellow solid (151.1 mg, 89%); mp 144–146 °C; IR (KBr, cm$^{-1}$) 1685, 1606, 1527, 1344; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.31 (d, $J$ = 8.8 Hz, 2H), 8.05 (d, $J$ = 8.8 Hz, 2H), 7.32 (s, 1H), 2.85 (t, $J$ = 6.2 Hz, 2H), 2.76 (t, $J$ = 6.8 Hz, 2H), 2.03 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 192.9, 155.9, 150.9, 139.9, 135.8, 130.5, 130.3, 124.3, 36.1, 21.9, 21.1; MS (FAB) $m/z$ (relative intensity): 339 ($M^+$+1, 87), 337 (78), 257 (11), 241 (5); HRMS (ESI) calcd for $C_{13}H_{12}N_2O_4{}^{79}Br$ ([M + H]$^+$): 338.9980, found 338.9986.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(3-nitrophenyl)-methanone (**2a**):* colorless solid (149.0 mg, 88%); mp 156–158 °C; IR (KBr, cm$^{-1}$) 1637, 1535, 1344; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$

**Scheme 4. Preparation of 4-Bromomethyleneisoxazoline *N*-Oxide**





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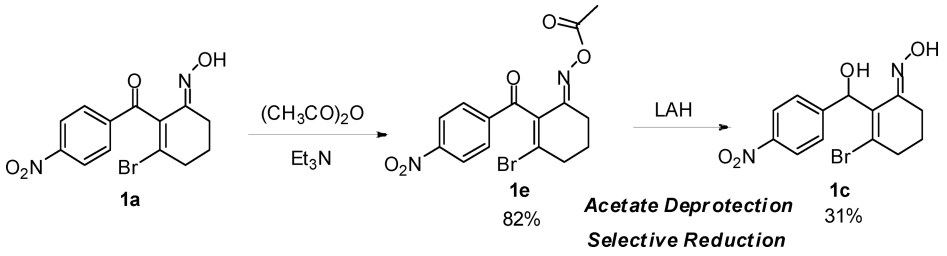
**Scheme 5. Reduction of OH-Protected 3-Oxoketoxime**




8.67 (t, $J$ = 1.7 Hz, 1H), 8.42 (ddd, $J$ = 8.2, 2.2, 1.0 Hz, 1H), 8.23−8.21 (m, 1H), 7.71−7.67 (m, 1H), 7.35 (s, 1H), 2.85 (t, $J$ = 6.1 Hz, 2H), 2.75 (t, $J$ = 6.6 Hz, 2H), 2.03 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 192.5, 155.7, 148.9, 136.9, 135.4, 134.9, 130.5, 130.3, 128.1, 124.3, 36.1, 21.8, 21.1; MS (EI) $m/z$ (relative intensity) 338 ($M^+$, 24), 321 (100), 293 (43), 249 (51), 231 (76), 215 (56); HRMS (ESI) calcd for $C_{13}H_{11}N_2O_4{}^{79}Br$ ($M^+$) 337.9902, found 337.9907.

*(E)-4-(2-Bromo-6-(hydroxyimino)cyclohex-1-enecarbonyl)-benzonitrile (**3a**):* colorless solid (145.5 mg, 91%); mp 149−151 °C; IR (KBr, $cm^{-1}$) 1638, 1404, 1299; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96 (d, $J$ = 8.4 Hz, 2H), 7.75 (d, $J$ = 8.4 Hz, 2H), 7.39 (s, 1H), 2.82 (t, $J$ = 6.1 Hz, 2H), 2.71 (t, $J$ = 6.7 Hz, 2H), 2.03−1.97 (m, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 193.2, 155.7, 138.5, 135.7, 132.9, 130.2, 129.8, 118.1, 117.0, 36.1, 21.8, 21.1; MS (ESI) $m/z$ (relative intensity) 319 ($M^+$ + 1, 100), 280 (20), 262 (13); HRMS (ESI) calcd for $C_{14}H_{12}N_2O_2{}^{79}Br$ ([M + H]$^+$) 319.0082, found 319.0089.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(3-bromophenyl)-methanone (**4a**):* colorless solid (121.1 mg, 65%); mp 144−146 °C; IR (KBr, $cm^{-1}$) 1670, 1636, 1421, 1343; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02 (t, $J$ = 1.8 Hz, 1H), 7.78 (dt, $J$ = 7.8, 1.3 Hz, 1H), 7.76 (s, 1H), 7.69 (ddd, $J$ = 8.0, 1.9, 1.0 Hz, 1H), 7.34 (t, $J$ = 7.9 Hz, 1H), 2.81 (t, $J$ = 6.2 Hz, 2H), 2.70 (t, $J$ = 6.7 Hz, 2H) 1.98 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 193.2, 155.6, 137.3, 136.8, 135.9, 132.2, 130.6, 129.8, 128.3, 123.3, 36.1, 21.9, 21.1; HRMS (ESI) calcd for $C_{13}H_{12}NO_2{}^{79}Br_2$ ([M + H]$^+$) 371.9235, found 371.9245, calcd for $C_{13}H_{12}NO_2{}^{79}Br^{81}Br$ ([M + H]$^+$) 373.9214, found 373.9212, calcd for $C_{13}H_{12}NO_2{}^{81}Br_2$ ([M + H]$^+$) 375.9193, found 375.9193.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(phenyl)-methanone (**5a**):* colorless solid (107.0 mg, 73%); mp 132−134 °C; IR (KBr, $cm^{-1}$) 1672, 1638, 1448, 1346, 1309, 1241; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 7.4 Hz, 2H), 7.79 (s, 1H), 7.57 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.6 Hz, 2H), 2.79 (t, $J$ = 6.1 Hz, 2H), 2.69 (t, $J$ = 6.6 Hz, 2H), 1.97 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 194.6, 155.5, 136.4, 135.4, 133.9, 129.6, 129.3, 128.9, 36.1, 21.9, 21.1; HRMS (ESI) calcd for $C_{13}H_{13}NO_2{}^{79}Br$ ([M + H]$^+$) 294.0129, found 294.0134, calcd for $C_{13}H_{13}NO_2{}^{81}Br$ ([M + H]$^+$) 296.0108, found 296.0121.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(2-nitrophenyl)-methanone (**6a**):* light brown solid (128.6 mg, 76%); mp 110−112 °C; IR (KBr, $cm^{-1}$) 1640, 1533, 1348; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.78−7.76 (m, 1H), 7.67−7.59 (m, 3H), 7.33 (br, 1H), 2.81 (t, $J$ = 6.1 Hz, 2H), 2.71 (t, $J$ = 6.7 Hz, 2H), 1.96 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (400 MHz, DMSO) $\delta$ 190.7, 154.3, 149.0, 135.3, 134.9, 132.6, 131.9, 128.9, 126.3, 123.6, 35.4, 21.2, 20.5; MS (ESI) $m/z$ (relative intensity) 341 [($M^+$ + 2) + 1, 100], 339 ($M^+$+1, 97), 305 (40), 300 (27), 259 (83), 231 (37); HRMS (ESI) calcd for $C_{13}H_{12}N_2O_4{}^{79}Br$ ([M + H]$^+$) 338.9980, found 338.9988, calcd for $C_{13}H_{12}N_2O_4{}^{81}Br$ ([M + H]$^+$) 340.9959, found 340.9975.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(5-chloro-2-nitrophenyl)methanone (**7a**):* colorless solid (106.5 mg, 57%); mp 128−130 °C; IR (KBr, $cm^{-1}$) 1637, 1539, 1377; $^1$H NMR (400 MHz, DMSO) $\delta$ 11.43 (s, 1H), 7.98 (m, 2H), 7.96 (m 1H), 2.81 (t, $J$ = 5.9 Hz, 2H), 2.63 (t, $J$ = 6.5 Hz, 2H), 1.89 (pentet, $J$ = 6.1 Hz, 2H); $^{13}$C NMR (400 MHz, DMSO) $\delta$ 189.7, 154.5, 147.5, 136.4, 134.8, 134.6, 131.3, 130.2, 128.6, 125.7, 35.5, 21.1, 20.5; MS (ESI) $m/z$ (relative intensity) 375 [($M^+$ + 2) + 1, 23], 373 ($M^+$ + 1, 17), 322 (3); HRMS (ESI) calcd for $C_{13}H_{11}N_2O_4{}^{35}Cl^{79}Br$ ([M + H]$^+$) 372.9591, found 372.9587, calcd for $C_{13}H_{11}N_2O_4{}^{35}Cl^{81}Br$ ([M + H]$^+$): 374.9570, found 374.9550.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(2,4-dichlorophenyl)methanone (**8a**):* colorless solid (127.7 mg, 70%); mp 138−140 °C; IR (KBr, $cm^{-1}$) 1638, 1462, 1343; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.80 (d, $J$ = 8.5 Hz, 1H), 7.65 (s, 1H), 7.46 (d, $J$ = 2.0 Hz, 1H), 7.31 (dd, $J$ = 8.5, 2.0 Hz, 1H), 2.77 (t, $J$ = 6.2 Hz, 2H), 2.71−2.67 (m, 2H), 1.94 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 191.4, 155.6, 139.4, 137.3, 135.1, 133.5, 133.2, 131.6, 129.9, 127.6, 36.4, 21.6, 21.2; HRMS (ESI) calcd for $C_{13}H_{11}NO_2{}^{79}Br^{35}Cl_2$ ([M + H]$^+$) 361.9350, found 361.9359, calcd for $C_{13}H_{11}NO_2{}^{81}Br^{35}Cl_2$ ([M + H]$^+$) 363.9329, found 363.9337, calcd for $C_{13}H_{11}NO_2{}^{81}Br^{37}Cl^{35}Cl$ ([M + H]$^+$) 365.9299, found 365.9310, calcd for $C_{13}H_{11}NO_2{}^{81}Br^{37}Cl_2$ ([M + H]$^+$) 367.9269, found 367.9288.

*(E)-(2-Bromo-6-(hydroxyimino)cyclohex-1-enyl)(2-bromophenyl)-methanone (**9a**):* colorless solid (124.3 mg, 67%); mp 119−121 °C; IR (KBr, $cm^{-1}$) 1639, 1428, 1226; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.79 (dd, $J$ = 7.6, 2.0 Hz, 1H), 7.67 (dd, $J$ = 7.8, 1.4 Hz, 1H), 7.49 (s, 1H), 7.38 (dt, $J$ = 7.6, 1.6 Hz, 1H), 7.33 (dt, $J$ = 7.6, 1.9 Hz, 1H), 2.77 (t, $J$ = 6.2 Hz, 2H), 2.71 (t, $J$ = 7.0 Hz, 2H), 1.96 (pentet, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 192.7, 155.5, 136.9, 136.1, 135.1, 133.2, 132.6, 129.9, 127.3, 122.1, 36.3, 21.5, 21.1; HRMS (ESI) calcd for $C_{13}H_{12}NO_2{}^{79}Br_2$ ([M + H]$^+$) 371.9235, found 371.9241, calcd for $C_{13}H_{12}NO_2{}^{79}Br^{81}Br$ ([M + H]$^+$) 373.9214, found 373.9218, calcd for $C_{13}H_{12}NO_2{}^{81}Br_2$ ([M + H]$^+$) 375.9193, found 375.9204.

*(E)-(2-Bromo-6-(hydroxyimino)-3,3-dimethylcyclohex-1-enyl)(4-nitrophenyl)methanone (**10a**):* colorless solid (157.5 mg (inseparable mixture of $E$ and $Z$ (6:1), 86%); mp 181−183 °C; IR (KBr, $cm^{-1}$) 3431, 1639; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.31 (d, $J$ = 8.6 Hz, 2H), 8.02 (d, $J$ = 8.6 Hz, 2H), 2.81−2.78 (m, 2H), 1.95 (t, $J$ = 6.8 Hz, 2H), 1.31 (s, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 192.5, 154.3, 150.3, 139.2, 139.1, 135.3, 130.2, 124.3, 38.3, 34.7, 18.6; HRMS (EI) calcd for $C_{15}H_{15}N_2O_4{}^{79}Br$ ([M]$^+$) 366.0215, found 366.0213, calcd for $C_{15}H_{15}N_2O_4{}^{81}Br$ ([M]$^+$) 368.0195, found 368.0189.

*2-(Bromomethylene)-3-(hydroxyimino)-1-(4-nitrophenyl)butan-1-one (**11a**):* colorless solid (127.7 mg, 82%); mp 149−151 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.65 (s, 1H), 8.38−8.35 (m, 2H), 8.11−8.08 (m, 2H), 7.49 (s, 1H), 2.09 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 193.1, 154.1, 150.3, 143.4, 139.1, 130.1, 124.3, 111.3, 9.7; HRMS (EI) calcd for $C_{11}H_9N_2O_4{}^{79}Br$ ([M]$^+$) 311.9746, found 311.9743, calcd for $C_{11}H_9N_2O_4{}^{81}Br$ ([M]$^+$) 313.9725, found 313.9769.

*(E)-(2-Chloro-6-(hydroxyimino)cyclohex-1-enyl)(4-nitrophenyl)-methanone (**1b**):* colorless solid (122.0 mg, 83%); mp 172−174 °C; IR (KBr, $cm^{-1}$) 1683, 1626, 1527, 1346; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.28 (d, $J$ = 8.6 Hz, 2H), 8.01 (d, $J$ = 8.6 Hz, 2H), 7.87 (s, 1H), 2.69 (t, $J$ = 6.4 Hz, 4H), 2.01 (pentet, $J$ = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 192.5, 155.5, 150.9, 140.2, 139.6, 132.7, 130.4, 124.2, 33.7, 21.1, 21.0; MS (FAB) $m/z$ (relative intensity) 295 ($M^+$+1, 100), 262 (7), 227 (15), 184 (13); HRMS (FAB) calcd for $C_{13}H_{12}N_2O_4{}^{35}Cl$ ([M + H]$^+$) 295.0486, found 295.0489.

*(E)-(2-Chloro-6-(hydroxyimino)cyclohex-1-enyl)(3-nitrophenyl)-methanone (**2b**):* colorless solid (109.6 mg, 74%); mp 165−167 °C; IR (KBr, $cm^{-1}$) 1634, 1534, 1344; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.65 (t, $J$ = 1.8 Hz, 1H), 8.42 (ddd, $J$ = 8.1, 2.1, 1.0 Hz, 1H), 8.20 (dd, $J$ = 6.7, 1.1 Hz, 1H), 7.68 (t, $J$ = 7.9 Hz, 1H), 7.52 (s, 1H), 2.71 (m, 4H), 2.03 (pentet, $J$ = 6.5 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 191.9, 155.5, 148.9, 139.7, 137.2, 134.8, 132.5, 130.3, 128.1, 124.2, 33.7, 21.1, 21.0; MS (FAB) $m/z$ (relative intensity) 294 ($M^+$, 13), 277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(61), 231 (51), 203 (48); HRMS (FAB) calcd for $C_{13}H_{11}N_2O_4{}^{35}Cl$ ($M^+$) 294.0407, found 294.0414.

*(E)-4-((2-Chloro-6-(hydroxyimino)cyclohex-1-enyl)(hydroxy)methyl)benzonitrile (**3b**):* light yellow solid (102.5 mg, 75%); mp 172−174 °C; IR (KBr, $cm^{-1}$) 1635, 1406, 1350; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 8.3 Hz, 2H), 7.75 (d, $J$ = 8.3 Hz, 2H), 7.54 (s, 1H), 2.71−2.66 (m, 4H), 2.01 (pentet, $J$ = 6.4 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.5, 155.4, 139.2, 138.7, 132.7, 132.6, 129.6, 117.9, 116.9, 33.5, 20.9, 20.8; MS (FAB) $m/z$ (relative intensity): 275 ($M^+$ + 1, 63), 185 (50), 154 (100), 136 (81); HRMS (FAB) calcd for $C_{14}H_{12}N_2O_2{}^{35}Cl$ ([M + H]$^+$) 275.0587, found 275.0585.

*(E)-(3-Bromophenyl)(2-chloro-6-(hydroxyimino)cyclohex-1-enyl)methanone (**4b**):* colorless solid (110.1 mg, 67%); mp 162−164 °C; IR (KBr, $cm^{-1}$) 1636, 1421, 1350; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.01 (t, $J$ = 1.7 Hz, 1H), 7.77 (dt, $J$ = 7.8, 1.3 Hz, 1H), 7.71 (s, 1H), 7.70−7.68 (m, 1H), 7.34 (t, $J$ = 7.8 Hz, 1H), 2.71−2.65 (m, 4H), 2.02−1.96 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.7, 155.5, 138.9, 137.7, 136.8, 132.9, 132.2, 130.6, 128.2, 123.3, 33.7, 21.2, 21.0; MS (FAB) $m/z$ (relative intensity): 332 [($M^+$ + 4) + 1, 24], 330 [($M^+$ + 2) + 1, 75], 328 [($M^+$ + 1, 62], 314 (100), 312 (89); HRMS (FAB) calcd for $C_{13}H_{11}NO_2{}^{35}Cl^{79}Br$ ([M + H]$^+$) 327.9740, found 327.9748, calcd for $C_{13}H_{11}NO_2{}^{35}Cl^{81}Br$ ([M + H]$^+$) 329.9719, found 329.9734, calcd for $C_{13}H_{11}NO_2{}^{37}Cl^{81}Br$ ([M + H]$^+$) 331.9689, found 331.9698.

*(E)-(2-Chloro-6-(hydroxyimino)cyclohex-1-enyl)(phenyl)methanone (**5b**):* colorless solid (92.4 mg, 74%); mp 147−149 °C; IR (KBr, $cm^{-1}$) 1668, 1637, 1352, 1240; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.89 (s, 1H), 7.87 (s, 2H), 7.57 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.8 Hz, 2H), 2.68−2.66 (m, 2H), 2.65−2.63 (m, 2H), 1.98 (pentet, $J$ = 6.4 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.0, 155.4, 138.4, 135.8, 134.0, 133.5, 129.5, 128.9, 33.7, 21.2, 21.1; MS (FAB) $m/z$ (relative intensity) 250 ($M^+$ + 1, 100), 154 (88), 136 (58); HRMS (FAB) calcd for $C_{13}H_{13}NO_2{}^{35}Cl$ ([M + H]$^+$) 250.0635, found 250.0639.

*(E)-(2-Chloro-6-(hydroxyimino)cyclohex-1-enyl)(2-nitrophenyl)methanone (**6b**):* brown solid (121.8 mg, 83%); mp 112−114 °C; IR (KBr, $cm^{-1}$) 1724, 1683, 1637, 1535; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.4 (s, 1H), 7.97−7.95 (m, 1H), 7.87−7.86 (m, 2H), 7.81−7.76 (m, 1H), 2.66 (t, $J$ = 6.1 Hz, 2H), 2.60 (t, $J$ = 6.6 Hz, 2H), 1.91 (pentet, $J$ = 6.3 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 190.1, 154.1, 148.9, 137.9, 134.9, 132.6, 132.5, 131.9, 127.1, 123.6, 33.0, 20.5, 20.4; HRMS (ESI) calcd for $C_{13}H_{10}N_2O_4{}^{35}Cl$ ([M − H]$^-$) 293.0329, found 293.0324.

*(E)-(5-Chloro-2-nitrophenyl)(2-chloro-6-(hydroxyimino)cyclohex-1-enyl)methanone (**7b**):* colorless solid (104.2 mg, 63%); mp 139−141 °C; IR (KBr, $cm^{-1}$) 1636, 1540, 1377; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.42 (s, 1H), 7.98−7.97 (m, 2H), 7.95−7.94 (m, 1H), 2.68 (t, $J$ = 6.0 Hz, 2H), 2.60 (t, $J$ = 6.5 Hz, 2H), 1.89 (pentet, $J$ = 6.3 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 189.0, 154.1, 147.3, 139.1, 136.5, 134.5, 131.9, 131.0, 129.6, 125.7, 33.1, 20.4, 20.3; MS (FAB) $m/z$ (relative intensity) 329 ($M^+$ + 1, 20), 210 (3), 174 (13); HRMS (FAB) calcd for $C_{13}H_{11}N_2O_4{}^{35}Cl_2$ ([M + H]$^+$) 329.0096, found 329.0092.

*(E)-(2-Chloro-6-(hydroxyimino)cyclohex-1-enyl)(2,4-dichlorophenyl)methanone (**8b**):* colorless solid (97.2 mg, 61%); mp 152−154 °C; IR (KBr, $cm^{-1}$) 1638, 1465, 1351, 1225; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.78 (d, $J$ = 8.5 Hz, 1H), 7.45 (d, $J$ = 1.9 Hz, 1H), 7.39 (s, 1H), 7.32 (dd, $J$ = 8.4, 21.9 Hz, 1H), 2.68 (t, $J$ = 6.7 Hz, 2H), 2.62 (t, $J$ = 6.2 Hz, 2H), 1.96 (pentet, $J$ = 6.5 Hz, 2H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 190.9, 155.4, 139.3, 139.2, 134.9, 134.5, 133.9, 133.3, 131.5, 127.6, 34.0, 21.2, 20.9; MS (FAB) $m/z$ (relative intensity) 320 [($M^+$ + 2) + 1, 100], 318 ($M^+$ + 1, 95), 282 (13), 173 (23); HRMS (FAB) calcd for $C_{13}H_{11}NO_2{}^{35}Cl_3$ ([M + H]$^+$) 317.9855, found 317.9861.

*(E)-(2-Bromophenyl)(2-chloro-6-(hydroxyimino)cyclohex-1-enyl)methanone (**9b**):* colorless solid (114.4 mg, 70%); mp 127−129 °C; IR (KBr, $cm^{-1}$) 1687, 1640, 1583, 1427, 1354; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.77 (dd, $J$ = 7.6, 1.9 Hz, 1H), 7.67 (dd, $J$ = 7.7, 1.3 Hz, 1H), 7.39 (dt, $J$ = 7.5, 1.0 Hz, 1H), 7.33 (dt, $J$ = 7.5, 1.9 Hz, 1H), 2.69 (t, $J$ = 6.7 Hz, 2H), 2.63 (t, $J$ = 6.2 Hz, 2H), 1.97 (pentet, $J$ = 6.5 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.6, 155.4, 139.4, 136.9, 135.2, 134.2, 133.4, 132.6, 127.6, 121.9, 34.0, 21.2, 10.9; MS (FAB) $m/z$ (relative intensity) 332 [($M^+$ + 4) + 1, 32], 330 [($M^+$ + 2) + 1, 92], 328 [($M^+$ + 1, 76], 314 (100), 312 (85); HRMS (FAB) calcd for $C_{13}H_{11}NO_2{}^{35}Cl^{79}Br$ ([M + H]$^+$) 327.9740, found 327.9748, calcd for $C_{13}H_{11}NO_2{}^{35}Cl^{81}Br$ ([M + H]$^+$) 329.9719, found 329.9734, calcd for $C_{13}H_{11}NO_2{}^{37}Cl^{81}Br$ ([M + H]$^+$) 331.9689, found 331.9707.

*(E)-(2-Chloro-6-(hydroxyimino)-3,3-dimethylcyclohex-1-enyl)(4-nitrophenyl)methanone (**10b**):* colorless solid (115.8 mg, 72%); mp 146−148 °C; IR (KBr, $cm^{-1}$) 3345, 2963, 1686, 1527, 1347; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.30−8.27 (m, 2H), 7.99−7.97 (m, 2H), 7.74 (br, 1H), 2.75 (t, $J$ = 6.8 Hz, 2H), 1.89 (t, $J$ = 6.8 Hz, 2H), 1.30 (s, 6H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 192.2, 154.1, 150.4, 144.8, 139.6, 132.4, 130.2, 124.4, 37.6, 34.9, 26.2, 18.6; HRMS (EI) calcd for $C_{15}H_{15}N_2O_4{}^{35}Cl$ ($M^+$) 322.0720, found 322.0711.

*2-(Chloromethylene)-3-(hydroxyimino)-1-(4-nitrophenyl)butan-1-one (**11b**):* colorless solid (103.0 mg, 77%); mp 131−133 °C; IR (KBr, $cm^{-1}$) 3695, 1687, 1525; $^1H$ NMR (400 MHz, DMSO-$d_6$): 11.66 (s, 1H), 8.38−8.35 (m, 2H), 8.11−8.08 (m, 2H), 7.35 (s, 1H), 2.07 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.4, 153.3, 150.4, 140.9, 139.4, 130.1, 124.4, 121.6, 9.8; HRMS (EI) calcd for $C_{11}H_8N_2O_4{}^{35}Cl$ ([M − H]$^-$) 267.0173, found 267.0178, calcd for $C_{11}H_8N_2O_4{}^{37}Cl$ ([M − H]$^-$) 269.0142, found 269.0172.

*(E)-3-Bromo-2-(hydroxy(4-nitrophenyl)methyl)cyclohex-2-enone oxime (**1c**):* colorless solid (116.0 mg, 68%); mp 165−167 °C; IR (KBr, $cm^{-1}$) 3402, 1632, 1522, 1344; $^1H$ NMR (400 MHz, $CDCl_3$): 8.14 (d, $J$ = 8.7 Hz, 2H), 7.54 (d, $J$ = 8.5 Hz, 2H), 7.42 (s, 1H), 6.08 (d, $J$ = 11.7 Hz, 1H), 5.09 (d, $J$ = 11.6 Hz, 1H), 2.87 (t, $J$ = 6.2 Hz, 2H), 2.81 − 2.57 (m, 1H), 2.57 − 2.49 (m, 1H), 1.95 − 1.81 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 155.7, 150.7, 147.2, 134.7, 133.3, 126.3, 123.6, 75.4, 37.6, 22.3, 21.7; MS (ESI) $m/z$ (relative intensity) 343 [($M^+$ + 2) + 1, 100], 343 ($M^+$ + 1, 91), 325 (12), 321 (25), 298 (37); HRMS (ESI) calcd for $C_{13}H_{14}N_2O_4{}^{79}Br$ ([M + H]$^+$) 341.0137, found 341.0135, calcd for $C_{13}H_{14}N_2O_4{}^{81}Br$ ([M + H]$^+$) 343.0116, found 343.0118.

*4-Bromo-3-(4-nitrophenyl)-3,5,6,7-tetrahydrobenzo[c]isoxazole 1-oxide (**1d**):* yellow solid (103.4 mg, 61%); mp 156−158 °C; IR (KBr, $cm^{-1}$) 2949, 1630, 1523; $^1H$ NMR (400 MHz, $CDCl_3$): 8.24 (d, $J$ = 8.6 Hz, 2H), 7.58 (d, $J$ = 8.6 Hz, 2H), 6.06 (t, $J$ = 2.6 Hz, 1H), 2.73−2.64 (m, 4H), 2.03−1.97 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 148.6, 142.4, 134.9, 129.3, 124.2, 116.5, 115.8,80.0, 35.4, 22.4, 20.5; MS (ESI) $m/z$ (relative intensity) 337 ($M^-$ − 1, 100), 309 (8); HRMS (ESI) calcd for $C_{13}H_{10}{}^{79}BrN_2O_4$ ([M − H]$^-$) 336.9824, found 336.9817.

*(E)-1-(3-Bromo-2-(4-nitrobenzoyl)cyclohex-2-enylideneaminooxy)ethanone (**1e**):* white solid (156.0 mg, 82%); mp 136−138 °C; IR (KBr, $cm^{-1}$) 2942, 1772, 1689, 1527; $^1H$ NMR (400 MHz, DMSO-$d_6$): 8.35−8.33 (m, 2H), 8.16−8.14 (m, 2H), 2.89 (t, $J$ = 6.0 Hz, 2H), 2.80 (t, $J$ = 6.6 Hz, 2H), 1.97 (s, 3H); $^{13}C$ NMR (100 MHz, DMSO-$d_6$) $\delta$ 191.9, 167.6, 161.7, 150.5, 139.0, 136.1, 134.0, 130.4, 124.3, 35.4, 22.3, 21.0, 19.2; HRMS (ESI) calcd for $C_{15}H_{12}{}^{79}BrN_2O_5$ ([M − H]$^-$) 378.9930, found 378.9936, calcd for $C_{15}H_{12}{}^{81}BrN_2O_5$ ([M − H]$^-$) 380.9909, found 380.9896.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Crystallographic data and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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