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Selectfluor mediated one pot synthesis of cyclohexanone ring fused isoxazole derivatives

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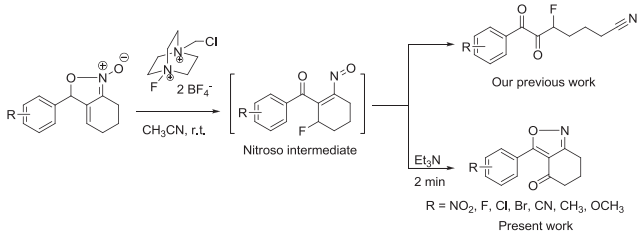
ABSTRACT

A Selectfluor and base mediated protocol for the synthesis of cyclohexanone ring fused isoxazole derivatives from isoxazoline *N*-oxides has been successfully developed. This rapid, one-pot, two-step transformation is achieved in acetonitrile, through nitroso intermediate followed by hydration, defluorination and N–O coupling in the presence of triethylamine. The scope and mechanism of the protocol have been demonstrated.

1. Introduction

Isoxazoles are valuable heterocyclic compounds of natural and synthetic origin with varied applications in industrial and medicinal agents and they have been demonstrated to be very versatile building blocks in organic synthesis.[1] Structurally, isoxazole rings are the core component in different drug categories and natural products.[2] The construction of the isoxazole ring can be achieved by several synthetic approaches,[3,4] including the two major routes such as 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides and the reaction of hydroxylamine with a three-carbon atom component, such as 1,3-diketone or an α,β-unsaturated ketone. Since, isoxazole derivatives has been a much attentive focus in recent agricultural and medicinal industries, synthesis of these compounds by alternative and optimized routes are required.

The carbon–fluorine bond is the strongest covalent bond in organic chemistry. Selective C–F bond activation and transformation have become an interesting challenge in organic synthesis.[5] In this context, base mediated C–F bond cleavage is a useful tool for the synthesis of heterocycles, which are difficult to obtain through classical methodologies. Recently, we reported the selective fluorination of isoxazoline *N*-oxides by C–C bond cleavage by using Selectfluor.[6] This reaction proceeds through nitroso intermediate and produced the corresponding ring-cleaved products in the absence of base. But in the presence of base, the above nitroso intermediate undergoes a simultaneous hydration, defluorination and N–O coupling to form cyclohexanone ring fused isoxazoles (Scheme 1). This rapid, multifaceted reaction without ring cleavage of isoxazoline *N*-oxides has not been reported till now. Thus, we intended to develop this reaction using different fluorinating agents.



Scheme 1. Selectfluor and base mediated formation of cyclohexanone ring fused isoxazoles.

Selectfluor (**A**), Selectfluor II (**B**), *N*-fluorobenzenesulfonimide (**C**) and 1-fluoropyridinium tetrafluoroborate (**D**) are among the important *N*-fluorinated compounds used in electrophilic fluorination (Fig. 1). Of these, Selectfluor (**A**) is a stable, nonvolatile, user-friendly reagent, widely used in one-step fluorination reaction.[7] Earlier, we have reported the synthesis of long-chain halo dioxo nitriles from isoxazoline *N*-oxides via nitroso intermediates by

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0040-4020/

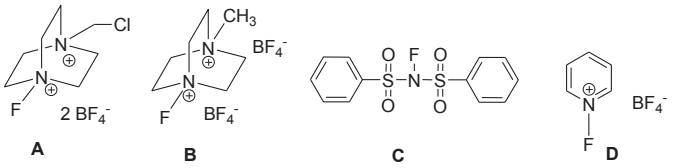


Fig. 1. Reagents used in this study.

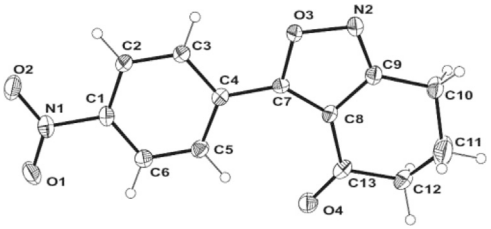


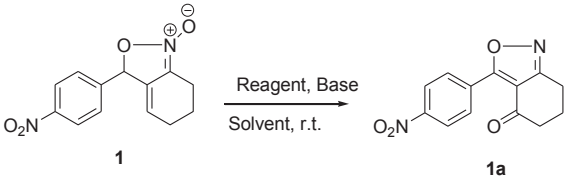
Fig. 2. Crystal structure of compound **1a**.[10]

using Selectfluor,[6] *N*-bromosuccinimide (NBS) and trichloroisocyanuric acid (TCCA).[8] In continuation of our research work on isoxazoline *N*-oxides and in order to utilize the nitroso intermediate for its wide application in various fields, we have developed a new route for the synthesis of cyclohexanone ring fused isoxazoles.

2. Results and discussion

To achieve this objective, we used cyclohexene-fused isoxazoline *N*-oxide **1** as a model substrate. When Selectfluor (**A**) was used, the starting material was completely consumed after 8 min, and the nitroso intermediate was formed, which on treatment with $NaHCO_3$, a cyclohexanone ring fused isoxazole was formed after 12 h, but the yield of the product was only 22% (Table 1, entry 1). Aiming to increase the yield of the product and also to decrease the reaction time, we tested the reaction with various other inorganic and organic bases, such as K_2CO_3, pyridine, diethylamine, triethylamine etc. (Table 1, entries 2–4). The reaction with K_2CO_3 provided 26% of the desired product, while pyridine and diethylamine gave a mixture of products. Interestingly, when triethylamine was used as base, the nitroso intermediate was completely converted into the desired product (i.e., **1a**) in good yield (84%) at room temperature (Table 1, entry 5). The structure of the product was confirmed by ^1H, ^{13}C NMR spectroscopy, MS, HRMS, and single-crystal X-ray analysis (Fig. 2).

Table 1
Optimization of the reaction conditions with various solvents, bases and reagents

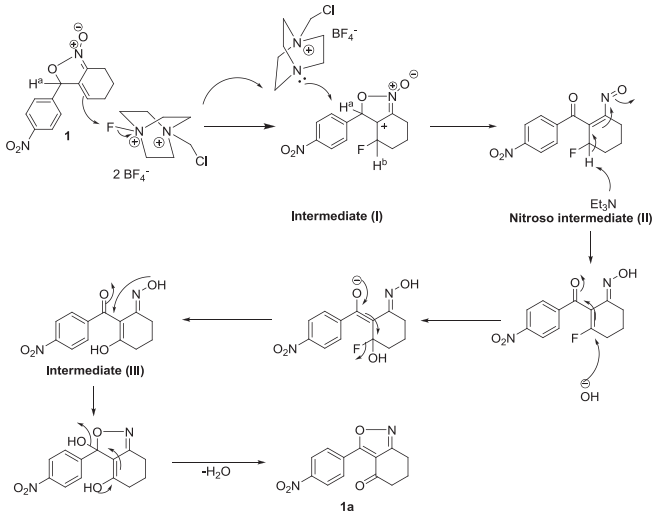


Entry[a]	Reagent	Solvent	Base	Time	Yield (%)[b]
1	Selectfluor (**A**)	CH_3CN	$NaHCO_3$	12 h	22
2	Selectfluor (**A**)	CH_3CN	K_2CO_3	4 h	26
3	Selectfluor (**A**)	CH_3CN	Pyridine	15 min	—[c]
4	Selectfluor (**A**)	CH_3CN	Et_2NH	20 min	—[c]
5	Selectfluor (**A**)	CH_3CN	Et_3N	10 min	84
6	Selectfluor (**A**)	$CHCl_3$	Et_3N	12 h	15
7	Selectfluor (**A**)	THF	Et_3N	2 h	28
8	Selectfluor (**A**)	CH_2Cl_2	Et_3N	12 h	18
9	Selectfluor (**A**)	MeOH	Et_3N	12 h	12
10	Selectfluor (**A**)	H_2O	Et_3N	12 h	10
11	Selectfluor (**B**)	CH_3CN	Et_3N	30 min	56
12	*N*-Fluorobenzenesulfonimide (**C**)	CH_3CN	Et_3N	10 h	38
13	1-Fluoropyridinium tetrafluoroborate (**D**)	CH_3CN	Et_3N	12 h	No reaction

[a] All the reactions were performed on 0.5 mmol scale by using 1.1 equiv of reagent.
[b] NMR yields (CH_2Br_2 as an internal standard).
[c] Mixture of products.

Having achieved this result, we conducted the same reaction in different solvents, as shown in Table 1. Whilst acetonitrile was used as solvent at room temperature, the nitroso intermediate was formed quickly, and the desired product (i.e., **1a**) was formed in good yields by the addition of triethylamine. With other solvents, the reaction times were longer, and the yields were lower. The reason might be explained by the assumption that the solubility of selectfluor is higher in acetonitrile than other solvents. Thus, we selected acetonitrile as a suitable solvent for this reaction (Table 1, entry 5). As shown in Table 1, we tested the reaction with various other fluorinating reagents, such as Selectfluor II (**B**), *N*-fluorobenzenesulfonimide (**C**) and 1-fluoropyridinium tetrafluoroborate (**D**) (Table 1, entries 11–13). The desired product was formed in moderate yield for Selectfluor II (**B**), and poor yield for *N*-fluorobenzenesulfonimide (**C**), however, no reaction was progressed for the latter.

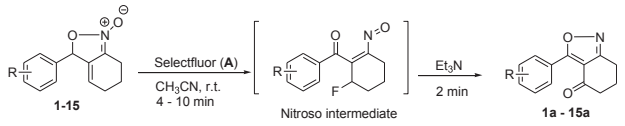
We assume that, in this reaction a fluorocarbocationic intermediate (**I**) was generated upon the electrophilic addition of Selectfluor to the cyclohexene ring.[6,9] It leads to the loss of a proton (H^a) to produce the nitroso intermediate (**II**) in the presence of base that was formed from the Selectfluor. This intermediate (**II**) was isolated and confirmed by ^1H NMR and ^{13}C NMR spectra (see Supplementary data). When triethylamine was added, intermediate (**II**) might undergo a rapid multifaceted set of reactions, starting with a base-induced ketoxime formation, followed by a sequential nucleophilic addition of hydroxide (^-OH)/elimination of floride (F^-), which afforded intermediate (**III**), and a subsequent N–O coupling, which produced the final product (**1a**) (Scheme 2).



Scheme 2. Plausible mechanism for the formation of cyclohexanone ring fused isoxazoles.

Having obtained the optimized conditions, we turned our attention to examine the substrate scope of this method. As shown in Table 2, various *p*-substituted isoxazoles were successfully synthesized from isoxazoline *N*-oxides. For the substrates bearing

Table 2
Selectfluor and base mediated synthesis of cyclohexanone ring fused isoxazoles from *o*- or *m*- or *p*- and unsubstituted isoxazoline *N*-oxides



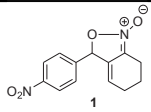
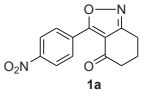
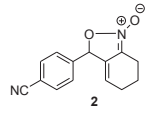
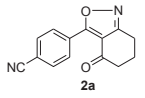
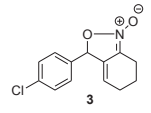
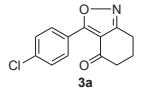
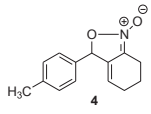
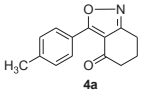
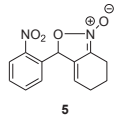
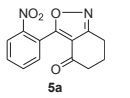
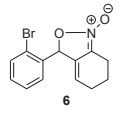
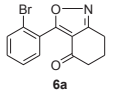
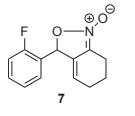
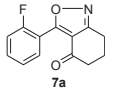
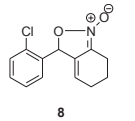
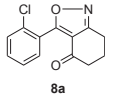
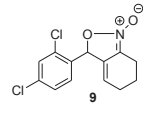
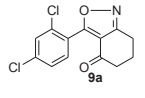
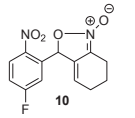
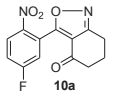
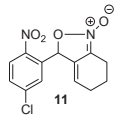
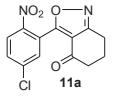
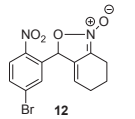
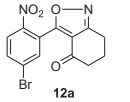
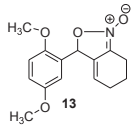
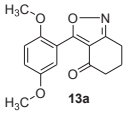
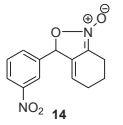
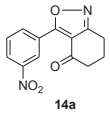
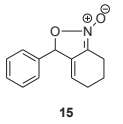
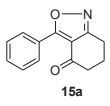
Entry[a]	Substrate	Product	Time (min)	Yield (%)[b]
1			(8)10	79
2			(8)10	75
3			(8)10	81
4			(10)12	84
5			(4)6	63
6			(4)6	68
7			(4)6	78
8			(4)6	70
9			(8)10	72
10			(5)7	51
11			(5)7	56
12			(5)7	61

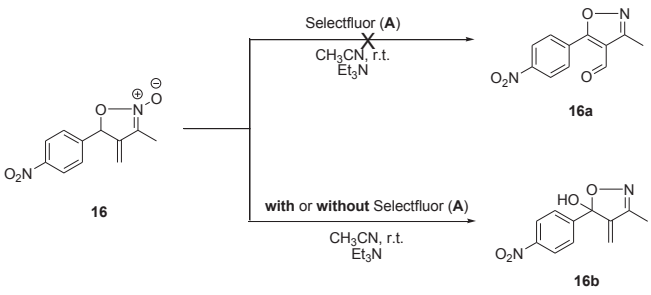
Table 2 (*continued*)

Entry[a]	Substrate	Product	Time (min)	Yield (%)[b]
13			(8)10	58
14			(8)10	65
15			(8)10	80

[a] All the reactions were performed on 0.5 mmol scale by using 1.1 equiv of reagent.
[b] Isolated yields. The time mentioned in the parentheses corresponds the time for addition of triethylamine.

either an electron withdrawing group (nitro, cyano and chloro) or an electron donating group (methyl) on the aromatic ring, the reaction proceeded smoothly and furnished the corresponding isoxazoles in good yields (Table 2, entries 1–4). Subsequently, we tested a number of *o*- or *m*-substituted and unsubstituted phenyl derivatives, with the optimized conditions. *o*-substituted derivatives such as 2-nitro, 2-bromo, 2-fluoro, and 2-chloro produced the desired products in moderate to good yields (Table 2, entries 5–8). Similarly, the disubstituted derivatives such as 2,4-dichloro, 2-nitro-5-fluoro, 2-nitro-5-chloro, 2-nitro-5-bromo, 2,5-dimethoxy also gave moderate to good yields of desired products (Table 2, entries 9–13). Finally, the *m*-substituted derivative (3-nitro) and unsubstituted derivatives were tested and the yield was moderate for the former (entry 14) and good for the latter (entry 15).

Finally, in order to enhance the substrate scope, we tested the reaction of isoxazoline *N*-oxide (**16**) generated from acyclic Baylis–Hillman oxime, in the present reaction conditions. Under these conditions, the reaction provided a different product **16b** rather than **16a**. On the other hand, the treatment of triethylamine with compound **16** in acetonitrile also produced the same product (Scheme 3). The structure of this new product was confirmed by ^{1}H, ^{13}C NMR spectroscopy, MS, HRMS, and single-crystal X-ray analysis (Fig. 3). The plausible base mediated reaction pathway for the formation of **16b** is described in Scheme 4. From these two experiments, it is quite clear that the formation of nitroso intermediate did not occur with Selectfluor in the case of acyclic isoxazoline *N*-oxide.



Scheme 3. Base mediated synthesis of 3-methyl-4-methylene-5-(4-nitrophenyl)-4,5-dihydroisoxazol-5-ol.

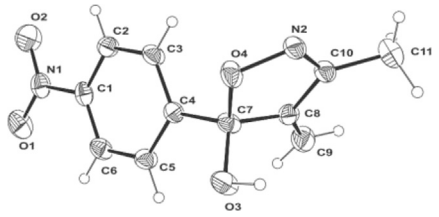
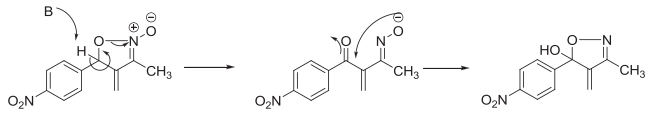


Fig. 3. Crystal structure of compound **16b**.[10]



Scheme 4. Plausible reaction pathway for the formation of **16b**.

3. Conclusion

In conclusion, we have demonstrated a Selectfluor and base mediated protocol for the synthesis of cyclohexanone ring fused isoxazole derivatives from isoxazoline *N*-oxides via nitroso intermediates. The scope of this transformation is broad, and we have reported the synthesis of a series of isoxazole derivatives from substrates bearing electron-donating or electron-withdrawing groups on the phenyl ring.

4. Experimental section

4.1. General

General remarks: Reagents and solvents were purchased from commercial suppliers and were used directly without any further purification unless otherwise stated. Column chromatography was performed on 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 (ppm) on the δ scale by using $CDCl_3$ and DMSO-d_6 as an internal standard, and coupling constants are expressed in Hertz (Hz). IR spectra were recorded with an FTIR spectrometer, and data are reported in cm^{-1}. Melting points were recorded by using an Electro Thermal capillary melting point apparatus.

*4.1.1. Procedure for the Selectfluor and base mediated synthesis of cyclohexanone ring fused isoxazole derivatives from Isoxazoline N-oxides (**1a**–**15a**).* Selectfluor (0.55 mmol) was added to a stirred solution of isoxazoline *N*-oxide derivative (0.5 mmol) in acetonitrile (2 mL) at room temperature. The reaction was monitored by TLC. After the formation of the intermediate (for details, refer Table 2), add 0.2 mL of triethylamine. After 2 min, the reaction mixture was added to brine (15 mL) and the organic phase was extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried with magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography.

*4.1.2. Procedure for the preparation of 3-methyl-4-methylene-5-(4-nitrophenyl)-4,5-dihydro isoxazol-5-ol (**16b**).* Triethylamine (0.2 ml) was added to a stirred solution of isoxazoline *N*-oxide derivative **16** (0.5 mmol) in acetonitrile (2 mL) at room temperature. The reaction was monitored by TLC. After the completion of the reaction (30 min) the reaction mixture was added to brine (15 mL) and the organic phase was extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried with magnesium sulfate and filtered. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography.

4.2. Spectral data

*4.2.1. 3-(4-Nitrophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**1a**).* White solid; mp 226–228 °C, IR [NaCl, cm^{-1}] 3429, 1692, 1682, 1565, 1533, 1347; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J=8.8 Hz, 2H), 8.35 (d, J=8.9 Hz, 2H), 3.02 (t, J=6.4 Hz, 2H), 2.67 (t, J=6.3 Hz, 2H), 2.24–2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.7, 168.1, 165.4, 149.8, 131.8, 129.9, 124.1, 114.2, 40.3, 22.4, 21.9; MS *m*/*z* (relative intensity): 257 (100), 255 (10); HRMS (ESI$^-$) calcd for $C_{13}H_9N_2O_4$ ([M−H]$^-$): 257.0562, found 257.0562.

*4.2.2. 4-(4-Oxo-4,5,6,7-tetrahydrobenzo[c]isoxazol-3-yl) benzonitrile (**2a**).* White solid; mp 208–210 °C, IR [NaCl, cm^{-1}] 3499, 2870, 1680, 1573, 1542, 1049; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J=8.5 Hz, 2H), 7.81 (d, J=8.5 Hz, 2H), 3.01 (t, J=6.3 Hz, 2H), 2.66 (t, J=6.4 Hz, 2H), 2.23–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.7, 168.4, 165.4, 132.7, 130.2, 129.2, 118.3, 115.6, 113.9, 40.3, 22.3, 21.9; MS *m*/*z* (relative intensity): 239 (100), 247 (20); HRMS (EI$^+$) calcd for $C_{14}H_{10}N_2O_2$ ([M$^+$H]$^+$): 239.0743, found 239.0744.

*4.2.3. 3-(4-Chlorophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**3a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3422, 2958, 1678, 1583, 1466; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.38 (d, J=8.6 Hz, 2H), 7.69 (d, J=8.6 Hz, 2H), 2.94 (t, J=6.3 Hz, 2H), 2.60 (t, J=6.3 Hz, 2H), 2.12–2.06 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6); δ 192.8, 167.9, 165.3, 137.2, 129.9, 129.1, 124.6, 112.6, 21.6, 20.9; MS *m*/*z* (relative intensity): 247 (100), 246 (10), 220 (10); HRMS (EI$^+$) calcd for $C_{13}H_{10}O_2NCl$ ([M$^+$]): 247.0400, found 247.0401.

*4.2.4. 3-p-Tolyl-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**4a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3414, 2927, 1678, 1580, 1481; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J=8.0 Hz, 2H), 7.24 (d, J=8.0 Hz, 2H), 2.66 (t, J=6.6 Hz, 2H), 2.54–2.50 (m, 2H), 2.40 (s, 3H), 2.01–1.94 (m, 2H), ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.7, 171.1, 165.1, 143.3, 129.6, 128.9, 123.9, 112.2, 40.3, 22.5, 22.1, 21.9; MS *m*/*z* (relative intensity): 228 (100), 227 (20), 212 (10); HRMS (FAB$^+$) calcd for $C_{14}H_{14}O_2N$ ([M$^+$H]$^+$): 228.1025, found 228.1021.

*4.2.5. 3-(2-Nitrophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**5a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3399, 2950, 1689, 1530, 1349, 1061; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, J=7.6 Hz, 1H), 7.76–7.69 (m, 3H), 3.02 (t, J=6.3 Hz, 2H), 2.54 (t, J=6.4 Hz, 2H), 2.22–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.7, 167.3, 164.4, 148.6, 133.3, 132.3, 132.0, 125.4, 122.0, 113.9, 39.3, 22.6, 21.7; MS *m*/*z* (relative intensity): 259 (100), 257 (10), 233 (20); HRMS (EI$^+$) calcd for $C_{13}H_{11}O_4N_2$ ([M$^+$H]$^+$): 259.0719, found 259.0721.

*4.2.6. 3-(2-Bromophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**6a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3414, 2950, 1689, 1614, 1421, 1322; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72–7.70 (m, 1H), 7.56–7.54 (m, 1H), 7.45–7.36 (m, 2H), 3.02 (t, J=6.3 Hz, 2H), 2.57 (t, J=6.4 Hz, 2H), 2.23–2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.1, 170.0, 164.3, 133.8, 132.6, 132.1, 128.4, 127.4, 122.9, 114.5, 39.7, 22.7, 21.7; MS *m*/*z* (relative intensity): 292 (100), 278 (15), 275 (5); HRMS (EI$^+$) calcd for $C_{13}H_{11}O_2N$ Br ([M$^+$H]$^+$): 291.9973, found 291.9969.

*4.2.7. 3-(2-Fluorophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**7a**).* Yellow liquid; IR [NaCl, cm^{-1}] 3422, 2950, 1689, 1625, 1591, 1464; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.29 (m, 1H), 7.57–7.51 (m, 1H), 7.31–7.20 (m, 2H), 3.01 (t, J=6.3 Hz, 2H), 2.59 (t, J=6.4 Hz, 2H), 2.22–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.1, 166.7,

164.5, 161.6, 159.0, 133.9 (d, J=9.0 Hz), 131.4, 124.4 (d, J=4.0 Hz), 116.7 (d, J=21.0 Hz), 115.2 (d, J=13.0 Hz), 39.9, 22.6, 21.9; MS m/z (relative intensity): 231 (100), 230 (20); HRMS (EI^+) calcd for $C_{13}H_{10}O_2N$ F ($[M^+]$): 231.0696, found 231.0698.

*4.2.8. 3-(2-Chlorophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**8a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3414, 2950, 1692, 1533, 1347; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62–7.60 (m, 1H), 7.54–7.45 (m, 2H), 7.40–7.36 (m, 1H), 3.02 (t, J=6.3 Hz, 2H), 2.57 (t, J=6.4 Hz, 2H), 2.23–2.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.1, 168.9, 164.3, 134.0, 132.6, 131.9, 130.5, 126.8, 126.3, 114.7, 39.8, 22.7, 21.9; MS m/z (relative intensity): 249 (100), 212 (20), 201 (20); HRMS (EI^+) calcd for $C_{13}H_{10}O_2NCl$ ($[M^+H]^+$): 247.0400, found 247.0402.

*4.2.9. 3-(2,4-Dichlorophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**9a**).* White solid; mp 108–110 °C, IR [NaCl, cm^{-1}] 3422, 2950, 1689, 1610, 1459; ^1H NMR (400 MHz, $CDCl_3$): δ 7.59–7.54 (m, 2H), 7.37 (dd, J=2.0, 8.4 Hz, 1H), 3.02 (t, J=6.3 Hz, 2H), 2.57 (t, J=6.3 Hz, 2H), 2.23–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.1, 167.8, 164.4, 138.4, 134.9, 132.8, 130.6, 127.3, 124.7, 114.8, 39.7, 22.7, 21.8; MS m/z (relative intensity): 281 (100), 273 (55); HRMS (EI^+) calcd for $C_{13}H_9O_2N$ Cl_2 ($[M^+]$): 281.0010, found 281.0014.

*4.2.10. 3-(5-Fluoro-2-nitrophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**10a**).* Yellow liquid; IR [NaCl, cm^{-1}] 3422, 1692, 1636, 1533, 1347; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J=4.8, 9.1 Hz, 1H), 7.44–7.36 (m, 2H), 3.02 (t, J=6.4 Hz, 2H), 2.55 (t, J=6.4 Hz, 2H), 2.23–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.6, 165.7, 164.5, 163.2, 128.2 (d, J=9.0 Hz), 124.7 (d, J=10.0 Hz), 119.5, 119.2 (d, J=5.0 Hz), 118.9, 114.3, 39.3, 23.6, 21.7; MS m/z (relative intensity): 277 (30), 273 (100), 272 (10); HRMS (EI^+) calcd for $C_{13}H_{10}N_2O_4$ F ($[M^+H]^+$): 277.0625, found 277.0624.

*4.2.11. 3-(5-Chloro-2-nitrophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**11a**).* Yellow liquid; IR [NaCl, cm^{-1}] 2950, 1692, 1621, 1533, 1347; ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J=8.7 Hz, 1H), 7.70–7.65 (m, 2H), 3.02 (t, J=6.3 Hz, 2H), 2.54 (t, J=6.4 Hz, 2H), 2.22–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.6, 165.7, 164.5, 146.8, 140.0, 132.2, 131.9, 126.8, 123.6, 114.3, 39.2, 22.6, 21.7; MS m/z (relative intensity): 293 (100), 277 (10), 273 (5); HRMS (FAB^+) calcd for $C_{13}H_{10}O_4N_2Cl$ ($[M^+H]^+$): 293.0329, found 293.0332.

*4.2.12. 3-(5-Bromo-2-nitrophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**12a**).* Yellow liquid; IR [NaCl, cm^{-1}] 3422, 2942, 1686, 1625, 1530, 1345; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J=8.6 Hz, 1H), 7.87–7.82 (m, 2H), 3.02 (t, J=6.3 Hz, 2H), 2.54 (t, J=6.4 Hz, 2H), 2.22–2.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.6, 165.6, 164.5, 147.3, 135.3, 134.7, 128.2, 126.8, 123.6, 114.3, 39.2, 22.6, 21.7; MS m/z (relative intensity): 335 (70), 291 (100), 289 (70); HRMS (EI^+) calcd for $C_{13}H_9N_2O_4Br$ ($[M]^-$): 335.9746, found 335.9751.

*4.2.13. 3-(2,5-Dimethoxyphenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**13a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3429, 2942, 1689, 1580, 1493; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.06 (dd, J=3.1, 9.1 Hz, 1H), 6.96 (d, J=9.1 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.98 (t, J=6.3 Hz, 2H), 2.56 (t, J=6.3 Hz, 2H), 2.20–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.0, 169.2, 164.3, 153.3, 152.5, 119.6, 116.3, 115.8, 113.9, 113.3, 56.6, 56.2, 39.9, 22.7, 21.9; MS m/z (relative intensity): 273 (100), 256 (15), 242 (50); HRMS (EI^+) calcd for $C_{15}H_{15}O_4N$ ($[M^+]$): 273.1001, found 273.0997.

*4.2.14. 3-(3-Nitrophenyl)-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**14a**).* White solid; mp 173–175 °C, IR [NaCl, cm^{-1}] 3422, 1667, 1527, 1341, 1092; ^1H NMR (400 MHz, $CDCl_3$): δ 9.39 (s, 1H), 8.81 (d, J=7.9 Hz, 1H), 8.39 (dd, J=1.1, 8.3 Hz, 1H), 7.73 (t, J=8.1 Hz, 1H), 3.03 (t, J=6.3 Hz, 2H), 2.68 (t, J=6.6 Hz, 2H), 2.24–2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.8, 168.1, 165.4,148.7, 134.3, 130.2, 127.9,126.7,123.9, 113.7, 40.2, 22.4, 21.9; MS m/z (relative intensity): 258 (100), 257 (15), 241 (25), 229 (10); HRMS (EI^+) calcd for $C_{13}H_{11}O_4N_2$ ($[M^+H]^+$): 258.0641, found 258.0635.

*4.2.15. 3-Phenyl-6,7-dihydrobenzo[c]isoxazol-4(5H)-one (**15a**).* Colorless liquid; IR [NaCl, cm^{-1}] 3414, 2935, 1644, 1455, 1258; ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J=7.0 Hz, 2H), 7.54–7.46 (m, 3H), 2.95 (t, J=6.3 Hz, 2H), 2.59 (t, J=6.3 Hz, 2H), 2.17–2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 192.7, 170.9, 165.1, 132.5, 128.9, 126.5, 112.5, 40.3, 22.4, 22.0; MS m/z (relative intensity): 214 (100), 197 (10), 190 (5), 173 (20); HRMS (ESI) calcd for $C_{13}H_{12}NO_2$ ($[M^+H]^+$): 214.0868, found 214.0865.

*4.2.16. 3-Methyl-4-methylene-5-(4-nitrophenyl)-4,5-dihydro isoxazol-5-ol (**16b**).* White solid, mp 184–186 °C, IR [NaCl, cm^{-1}] 1604, 1521, 1414, 1343, 1220, 1179; ^1H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, J=8.8 Hz, 2H), 7.98 (s, 1H), 7.65 (d, J=8.8 Hz, 2H) 5.72 (s, 1H); 5.32 (s, 1H), 2.08 (s, 3H), ^{13}C NMR (100 MHz, DMSO-d_6); δ 153.4, 150.9, 148.3, 147.4, 126.9, 123.5, 116.2, 104.1, 9.7, MS m/z (relative intensity): 234 (100), 217 (20), 205 (15), 150 (70); HRMS (EI^+) calcd for $C_{11}H_{10}O_4N_2$ ($[M^+]$): 234.0641, found 234.0647.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.08.024.

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10. CCDC-955136 (**1a**) and CCDC-989222 (**16a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via*www.ccdc.cam.ac.uk/data_request/cif