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Synthesis of stable isoxazolines by [3+2] cycloaddition of oxaziridines with alkynes

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ABSTRACT

N-Alkyl substituted oxaziridines undergo a [3+2] cycloaddition reaction with a variety of terminal alkynes to give the product isoxazolines, whose stability appears to depend on the electronic properties of the groups on the C-3 and C-5 positions. The presence of an electron withdrawing group on C-5 and/or an electron donating group on C-3 causes isomerization of the isoxazolines to β-amino enones.

1. Introduction

The biological properties of oxaziridines have not been investigated very much; only recently, their potential as antifungal[1] and antitumor agents[2] has been reported. In contrast, their reactivity, stereochemistry, and usefulness in organic chemistry have been the object of several studies.[3–20] A number of methods of preparation have been reported including oxidation of imines with a peracid,[3] with cobalt-mediated molecular oxygen[4] or with urea–hydrogen peroxide,[5] amination of ketenes,[6] addition of hydroxamic acid to propiolates,[7] and photolysis of nitrones.[8]

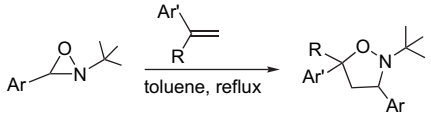
The strained oxaziridine ring promises an unusually high reactivity due to an inherently weak N–O bond and has received considerable attention mainly due to the chirality of the nitrogen atom showing an inversion barrier of 25–32 kcal/mol in *N*-alkyl substituted oxaziridines.[9]

The oxaziridines can be used as both oxygenating and aminating agents in reactions with a wide variety of nucleophiles. The general mechanism, as oxygenating agent, involves nucleophilic attack on the oxaziridine oxygen with simultaneous C–O bond cleavage. Oxaziridines have been used in the direct oxygenation of enolates,[10] epoxidation of alkenes,[11] oxidation of nitrogen nucleophiles,[12] and oxidation of C–H bonds.[13] Thioethers,[14] enamines,[15] organometallic reagents,[16] and tertiary Si–H bonds[17] can be oxygenated as well.

Oxaziridines can also be used as a source of electrophilic nitrogen in many transformations. Alcohols can be converted into *O*-alkyl oximes,[18] thioethers into sulfimides,[19] enolates into α-amino carbonyl compounds,[20] and C–H into amines.[6,20b] The general mechanism involves, in this case, nucleophilic attack on the oxaziridine nitrogen with simultaneous N–O bond cleavage.

The reactivity involving the oxaziridine C–O bond cleavage has been studied much less. In fact, only reactions of oxaziridines with heterocumulenes to afford five-membered heterocycles have been reported.[16]

Indeed, our previous results about the synthesis of isoxazolidines by a [3+2] cycloaddition of oxaziridines and alkenes via cleavage of the C–O bond, were considered as novel and interesting aspects (Scheme 1).[21]



Ar = Ph, 2-Pyridinyl, 3-Pyridinyl, 4-Pyridinyl, 2-Thiazolyl, 2-Benzothiazolyl
Ar' = *P*-MeC_6H_4, 2-Pyridinyl
R = H, Me

Scheme 1.

The possibility that Δ^4-isoxazolines could be obtained via a [3+2] cycloaddition reaction between alkynes and oxaziridines has been evaluated by us and the results of our study in this context are reported here.

Although the potential of Δ^4-isoxazolines as synthons for cyclic or acyclic nitrogen compounds[22] and their biological activity,[23] only a few synthetic methods of these compounds have been reported. More often than not, isoxazolines have not been isolated and characterized because of their instability under the conditions at which they are formed, due to their bias to undergo rearrangement reactions.[22] There are only two significant routes to Δ^4-isoxazolines. The most general and widely used one is due to Huisgen and co-workers and is based on the cycloaddition of nitrones with alkynes.[24] However, investigators are urged to be wary of early reports of isoxazolines formed by cycloadditions that are not supported by spectral characterization.

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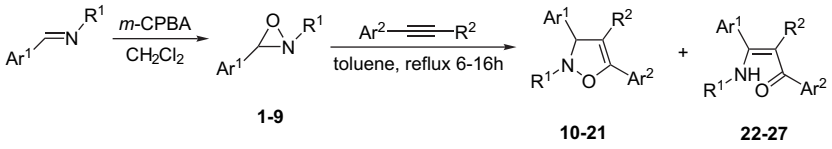


Scheme 2.

Another route to Δ^4-isoxazolines is based on the addition of Grignard reagents to isoxazolium salts[25] or their reduction with sodium borohydride.[26]

It seems to be also noteworthy the [3+2] cycloaddition reaction between unsaturated ketones and hydroxylamines (RNHOH) followed by dehydration.[27]

Herein, we describe a new and highly efficient methodology of synthesis of 3,5-di-aryl-4-isoxazolines based on the cycloaddition of a variety of aryl alkynes with 2-alkyl-3-aryloxaziridines.

2. Results and discussion

Known oxaziridines **1**, **2**, **4**–**6**, and **8**[28,21] and novel oxaziridines **3**, **7**, and **9** were prepared via oxidation of the corresponding imines with *m*-chloroperbenzoic acid (*m*-CPBA). The oxaziridines **1**–**5** were isolated exclusively in the *trans* isomeric form, while the oxaziridines **6**–**9** were obtained in a diastereomeric mixture (Scheme 2).[28]

A solution of oxaziridine (1.0 mmol) and alkyne (1.5 mmol) was refluxed in toluene for 6–16 h, until TLC showed that the reaction was complete. After solvent evaporation, the yellow crude material was flash chromatographed on a silica gel column.

The main reaction products were the isoxazolidines **10**–**21**. Only a small amount of by-products, such as arylaldehydes and aryl-imines, were observed and identified by GC–MS.

Many isoxazolidines proved to be unstable under the experimental conditions: at 110 °C they converted into the rearranged β-amino enones **22**–**27** following the N–O bond cleavage. The analysis of the data in Table 1 suggests that the N–O bond cleavage is facilitated when an electron withdrawing group (EWG), such as an α-aza-heterocycle, is on the C-3 (entries 4, 6, 9, 11, and 14, Table 1) or an electron donating group (ERG), as a *p*-MeO-C_6H_4, is on C-5 (entry 12, Table 1) of the isoxazoline moiety.

The isoxazolines and the corresponding opened compounds were isolated pure and identified by ^{1}H and ^{13}C NMR spectroscopy. Chemical shifts of the C-3 and C-4 protons are consistent with those reported for similar compounds.[25,26]

The rate of the cycloaddition reaction seems to depend on the electronic properties of groups on the carbon atom of the oxaziridine. An EWG, such as an α-aza-heterocycle, increases the cyclization rate, so that the reaction was complete within 6 h (entries 5 and 7, Table 1). For reaction times longer than 6 h, isoxazolines **13** and **14** isomerize to the opened compounds **22** and **23**, respectively (entries 4 and 6, Table 1). Accordingly, refluxing of isoxazoline **14** overnight in toluene gave **23** as the sole product, while compounds **24**, **26**, and **27** were formed even at lower temperature and using shorter reaction times. Spectroscopic data of products **22**–**27** showed in the ^{1}H NMR spectrum a chemical shift of the N–H proton at ≅11.6 ppm and a value of infrared absorbance of the C=O at ≅1590 cm^{-1}, in accordance with a hydrogen-bridged cyclic structure (Scheme 2).

The high regioselectivity observed in the cycloaddition reaction could be the result of steric interactions: approach A should be favored (Scheme 3).

Accordingly, there was no [3+2] cycloaddition reaction when an internal alkyne such as 1-phenyl-propyne was refluxed with oxaziridine **1**.

An EWG such as an α-aza-heterocycle (2-pyridine, 2-benzothiazole) on the carbon atom of the oxaziridine makes the oxygen atom more electrophilic and increases the cyclization rate (entries 5 and 7, Table 1) according the approach A.

However, an alternative mechanism via a nitrone can also be considered. A two-step mechanism could be proposed: the oxaziridine rearranges to the isomeric nitrone, which then reacts with the alkyne to give the isoxazoline. This hypothesis is not in accordance with the electrophilic trend of the oxygen atom in the cycloaddition reaction; moreover, the reaction of *N*-alkyl-nitrones with alkynes was reported not to be regioselective giving mixtures of 5- and 4-substituted isoxazolines.[29]

3. Conclusion

In conclusion, we have reported a new reaction of oxaziridines, which is useful in organic synthesis: the [3+2] cycloaddition reaction with alkynes. By this reaction, it is possible to synthesize isoxazolines, which are not easy to obtain by other methods.

4. Experimental

4.1. General

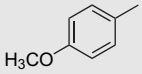
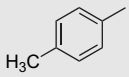
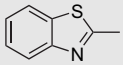
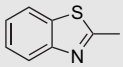
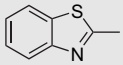
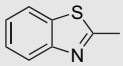
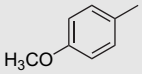
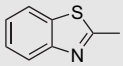
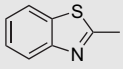
All reactions were performed under N_2 using oven-dried glassware. Et_2O and THF were distilled from sodium/benzophenone ketyl before use. CH_2Cl_2 was distilled from calcium hydride before use. Column chromatography was performed using 100–200 times excess 32–64 μm grade silica gel. TLC analysis was performed on glass TLC plates (0.25 mm 60 F-254 silica gel). Gas chromatography (GC) was conducted on an Rt_x-5 30-m fused silica capillary column (split ratio ~ 100:1). The following program was used: method A=initial temperature of 100 °C for 0.0 min, ramp 10 °C/min to 280 °C, and hold for 15 min; the standard operating conditions were 300 °C injector temperature and 290 °C detector temperature. GC–MS was conducted using method A temperature program.

NMR spectroscopy data were collected at 400 MHz or 500 MHz. The following solvent and reference values (ppm) were used: $CDCl_3$ (^{1}H: 7.26, ^{13}C: 77.0). The purity of all products was determined to be >95% by NMR and/or GC analyses unless specified otherwise. Samples for IR analysis were prepared as dilute solutions in $CHCl_3$, and data are reported as wave numbers (cm^{-1}). Melting points were determined in open capillary tubes. Low-resolution and high-resolution electron impact (EI) mass spectra were obtained with a typical ionization voltage of 70 eV. The electrospray ionization (HR-ESI-MS) experiments were carried out on a hybrid QqTOF mass spectrometer (PE SCIEX-QSTAR) fitted with an ion spray ionization source.

4.2. General procedure for the preparation of imines

The appropriate amine (1 mmol) and the corresponding aldehyde (1 mmol) were dissolved in anhydrous Et_2O (20 mL) in the presence of 7 g of molecular sieves (4 Å, 1.6 mm pellets), according to Tagushi's method.[30] The formation of imine was monitored by GC. After 1 h the molecular sieves were filtered and the solvent evaporated to obtain the pure imine.

Table 1
Synthesis of 3,5-diaryl-isoxazolines **10**–**21**

Entry	Oxaziridine	Ar^1	R^1	Ar^2	R^2	*t* (h)	Total yield[a] (%)	Product distribution[b]
1	**1**		*t*-Bu		H	16	90	**10**(100)
2	**2**		*t*-Bu		H	16	93	**11**(100)
3	**3**		*t*-Bu		H	16	91	**12**(100)
4	**4**		*t*-Bu		H	16	81	**13**(45), **22**(55)
5	**4**		*t*-Bu		H	6	92	**13**(100), **22**(0)
6	**5**		*t*-Bu		H	16	98	**14**(2), **23**(98)
7	**5**		*t*-Bu		H	6	82	**14**(95), **23**(5)
8	**6**		Et		H	16	50	**15**(100)
9	**7**		Et		H	8	80	**16**(0), **24**(100)
10	**1**		*t*-Bu		H	10	90	**17**(100)
11	**5**		*t*-Bu		H	6	90	**18**(90), **25**(10)
12	**1**		*t*-Bu		H	16	60	**19**(0), **26**(100)
13	**8**		*i*-Pr		H	16	60	**20**(100)
14	**9**		*i*-Pr		H	8	70	**21**(0), **27**(100)
15	**1**		*t*-Bu		Me	48	—	—
16	**5**		*t*-Bu		Me	48	—	—

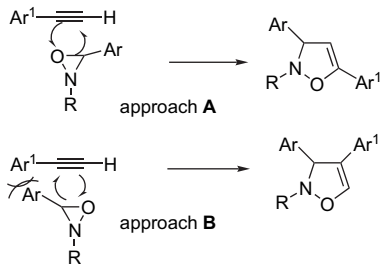
[a] Yields based on chromatographically isolated, pure products.
[b] Product distributions evaluated by GC and ^{1}H NMR spectroscopy.

4.2.1. tert-Butyl-(4-methyl-benzilidene)-amine

Yield 173 mg; 99%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.36 (s, 3H), 7.19 (d, 2H, *J*=7.9 Hz), 7.63 (d, 2H, *J*=7.9 Hz), 8.23 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.4, 29.7, 57.0, 127.8, 129.2, 134.5, 140.2, 155.0; GC–MS (70 eV) *m*/*z* 175 (9) [M^+], 160 (100), 135 (13), 118 (54), 91 (33), 57 (26); FTIR ($CHCl_3$) cm^{-1} 3024, 2968, 1641, 1575, 1458, 1370, 1202, 1106. HRMS: calcd for $C_{12}H_{17}N$: 175.1362; found: 175.1365.

4.2.2. tert-Butyl-(4-methoxy-benzilidene)-amine

Yield 189 mg; 99%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 3.81 (s, 3H), 6.90 (d, 2H, *J*=8.7 Hz), 7.68 (d, 2H, *J*=8.7 Hz), 8.20 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 29.7, 55.2, 56.8, 113.8, 129.3, 130.1, 154.4, 162.2; GC–MS (70 eV) *m*/*z* 191 (12) [M^+], 176 (100), 134 (45), 77 (23), 57 (24); FTIR ($CHCl_3$) cm^{-1} 3024, 2967, 1641, 1579, 1512, 1308, 1251, 1165. HRMS: calcd for $C_{12}H_{17}NO$: 191.1311; found: 191.1308.



Scheme 3.

4.2.3. Ethyl-benzothiazol-2-ylmethylene-amine

Yield 188 mg; 99%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.3 Hz), 3.62–3.68 (m, 2H), 7.42 (t, 1H, J=7.9 Hz), 7.48 (t, 1H, J=8.1 Hz), 7.90 (d, 1H, J=7.9 Hz), 8.05 (d, 1H, J=8.1 Hz), 8.62 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.3, 55.8, 121.9, 123.8, 126.2, 126.3, 135.0, 150.5, 153.6, 169.0; GC–MS (70 eV) m/z 190 (22) [M^+], 175 (100), 148 (50), 135 (18); FTIR ($CHCl_3$) cm^{-1} 3069, 3030, 2982, 1630, 1511, 1459, 1434, 1367, 1316, 1221. HRMS: calcd for $C_{10}H_{10}N_2S$: 190.0566; found: 190.0567.

4.2.4. iso-Propyl-benzothiazol-2-ylmethylene-amine

Yield 202 mg; 99%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (d, 6H, J=6.3 Hz), 3.72–3.75 (heptet, 1H, J=6.3 Hz), 7.42 (t, 1H, J=7.9 Hz), 7.48 (t, 1H, J=8.1 Hz), 7.91 (d, 1H, J=7.8 Hz), 8.07 (d, 1H, J=7.7 Hz), 8.55 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 23.6, 61.3, 121.9, 123.9, 126.3, 126.4, 135.0, 153.1, 153.6, 167.7; GC–MS (70 eV) m/z 204 (20) [M^+], 189 (100), 148 (45), 135 (16); FTIR ($CHCl_3$) cm^{-1} 3065, 3030, 2987, 1630, 1509, 1456, 1433, 1364, 1321, 1218. HRMS: calcd for $C_{11}H_{12}N_2S$: 204.0723; found: 204.0726.

4.3. General procedure for the preparation of oxaziridines 1–9

A small excess of *m*-chloroperbenzoic acid (1.1 mmol) in 3 mL of methylene chloride was added with stirring and cooling (0–5 °C) to a solution of imine (1 mmol) in 5 mL of methylene chloride. When the reaction was complete, the formed *m*-chlorobenzoic acid was removed by filtration. The filtrate was washed two times with a dilute solution of Na_2SO_3 (5%), then with a solution of Na_2CO_3, and finally with water. After drying over $MgSO_4$, the solvent was evaporated and the residue purified by a column chromatography (silica gel partly deactivated with triethylamine, petroleum ether/ethyl ether=95:5 for **1**, **2**, **3**, **6**, and **8**; petroleum ether/ethyl ether=8:2 for **4**, **5**, **7**, and **9**).

*4.3.1. 2-tert-Butyl-3-(4-methyl-phenyl)-oxaziridine (**3**)*

Yield 172 mg; 90%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 2.34 (s, 3H), 4.65 (s, 1H), 7.17 (d, 2H, J=7.9 Hz), 7.33 (d, 2H, J=7.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.3, 25.2, 58.3, 73.6, 127.5, 129.1, 132.6, 139.7; GC–MS (70 eV) m/z 191 (19) [M^+], 160 (75), 135 (33), 119 (40), 91 (29), 57 (100); FTIR ($CHCl_3$) cm^{-1} 2974, 1617, 1529, 1475, 1388, 1363, 1309, 1260. HRMS: calcd for $C_{12}H_{17}NO$: 191.1311; found: 191.1314.

*4.3.2. 2-Ethyl-3-benzothiazol-2yl-oxaziridine (**7**)*

Yield 165 mg; 80%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.3 Hz), 2.79–2.88 (m, 1H), 3.07–3.15 (m, 1H), 5.05 (s, 1H), 7.40 (t, 1H, J=7.9 Hz), 7.48 (t, 1H, J=7.9 Hz), 7.88 (d, 1H, J=8.2 Hz), 8.06 (d, 1H, J=8.2 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 12.3, 56.7, 77.4, 122.0, 123.4, 126.0, 126.2, 135.3, 153.7, 166.8; GC–MS (70 eV) m/z 206 (34) [M^+], 162 (64), 135 (100), 108 (28); FTIR ($CHCl_3$) cm^{-1} 3064, 3031, 2987, 2939, 2878, 1601, 1523, 1458, 1317, 1241, 1158, 1084. HRMS: calcd for $C_{10}H_{10}N_2SO$: 206.0515; found: 206.0512.

*4.3.3. 2-iso-Propyl-3-benzothiazol-2yl-oxaziridine (**9**)*

Yield 187 mg; 85%; oil. *Major diastereomer* (trans): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, 3H, J=6.6 Hz), 1.35 (d, 3H, J=6.4 Hz), 2.40–2.50 (m, 1H), 5.05 (s, 1H), 7.40 (t, 1H, J=7.9 Hz), 7.48 (t, 1H, J=7.9 Hz), 7.88 (d, 1H, J=8.2 Hz), 8.06 (d, 1H, J=8.2 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.6, 21.2, 62.8, 77.0, 122.0, 123.5, 126.0, 126.2, 135.5, 153.0, 167.1; GC–MS (70 eV) m/z 220 (31) [M^+], 205 (58), 162 (100), 135 (80), 108 (28), 58 (75); FTIR ($CHCl_3$) cm^{-1} 3067, 3029, 2986, 2941, 2876, 1605, 1524, 1455, 1319, 1241, 1158. HRMS: calcd for $C_{11}H_{12}N_2SO$: 220.0671; found: 220.0671.

Minor diastereomer (cis): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, 3H, J=6.5 Hz), 1.32 (d, 3H, J=6.2 Hz), 2.79–2.82 (m, 1H), 5.30 (s, 1H), 7.40 (t, 1H, J=7.9 Hz), 7.48 (t, 1H, J=7.9 Hz), 7.88 (d, 1H, J=8.2 Hz), 8.06 (d, 1H, J=8.2 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.0, 21.8, 54.1, 76.8, 121.6, 125.4, 123.4, 126.6, 135.3, 153.8, 163.4; GC–MS (70 eV) m/z 220 (41) [M^+], 205 (60), 162 (100), 135 (75), 108 (32), 58 (70); FTIR ($CHCl_3$) cm^{-1} 3067, 3030, 2986, 2939, 2877, 1601, 1524, 1458, 1316, 1243, 1158. HRMS: calcd for $C_{11}H_{12}N_2SO$: 220.0671; found: 220.0671.

4.4. General procedure for the cycloaddition reaction

A solution of the alkyne (1.5 mmol) and oxaziridines **1**–**9** (1.0 mmol) in toluene (10 mL) was refluxed under magnetic stirring for 6–16 h (Table 1). After this time, TLC was used to monitor reaction progress. The solution was cooled to rt and evaporated to dryness to give a yellow crude material. The reaction mixture was purified by flash chromatography (silica gel, petroleum ether/ethyl ether=95:5 for entries 1, 2, 3, 8, 12, and 13 of Table 1; petroleum ether/ethyl ether=85:15 for entries 4, 5, 6, 7, 9, 10, 11, and 14 of Table 1).

*4.4.1. 2-tert-Butyl-3,5-diphenyl-isoxazoline (**10**)*

Yield 251 mg; 90%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 5.27 (d, 1H, J=2.8 Hz), 5.28 (d, 1H, J=2.8 Hz), 7.24 (t, 1H, J=7.7 Hz), 7.30–7.38 (m, 5H), 7.43 (d, 2H, J=7.3 Hz), 7.57 (dd, 2H, J=1.3 Hz, J=8.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.1, 60.9, 68.6, 97.1, 125.6, 127.2, 128.3, 128.5, 128.6, 128.8, 144.5, 152.8; GC–MS (70 eV) m/z 279 (42) [M^+], 222 (51), 206 (62), 105 (100), 77 (40), 57 (12); FTIR ($CHCl_3$) cm^{-1} 3065, 3031, 2977, 2937, 2874, 1658, 1600, 1493, 1365, 1051, 1025. HRMS: calcd for $C_{19}H_{21}NO$: 279.1624; found: 279.1620.

*4.4.2. 2-tert-Butyl-3-(4-methoxy-phenyl)-5-phenyl-isoxazoline (**11**)*

Yield 287 mg; 93%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 3.80 (s, 3H), 5.24 (s, 2H), 6.87 (d, 2H, J=7.1 Hz), 7.30–7.38 (m, 5H), 7.57 (d, 2H, J=7.1 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.1, 55.3, 60.8, 68.1, 97.2, 113.9, 125.5, 128.4, 128.7, 136.8, 152.7, 158.8; GC–MS (70 eV) m/z 309 (30) [M^+], 252 (68), 251 (100), 236 (40), 105 (80), 77 (66), 57 (15); FTIR ($CHCl_3$) cm^{-1} 3063, 3030, 2975, 2935, 2840, 1660, 1607, 1510, 1248, 1173, 1034. HRMS: calcd for $C_{20}H_{23}NO_2$: 309.1730; found: 309.1733.

*4.4.3. 2-tert-Butyl-5-phenyl-3-p-tolyl-isoxazoline (**12**)*

Yield 266 mg; 91%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.33 (s, 3H), 5.24 (s, 2H), 7.14 (d, 2H, J=7.9 Hz), 7.30–7.38 (m, 5H), 7.56 (d, 2H, J=7.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 25.1, 60.8, 68.4, 97.2, 125.5, 127.1, 128.3, 128.7, 129.2, 136.8, 141.6, 152.7; GC–MS (70 eV) m/z 293 (29) [M^+], 236 (43), 235 (28), 105 (100), 77 (35), 57 (10); FTIR ($CHCl_3$) cm^{-1} 3060, 3030, 2977, 2932, 2872, 1660, 1599, 1230, 1178, 1024. HRMS: calcd for $C_{20}H_{23}NO_2$: 293.1781; found: 293.1782.

*4.4.4. 2-tert-Butyl-5-phenyl-3-(pyridin-2-yl)-isoxazoline (**13**)*

Yield 257 mg; 92% (entry 5); oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 5.40 (d, 1H, J=2.9 Hz), 5.46 (d, 1H, J=2.9 Hz), 7.16 (t, 1H, J=6.5 Hz), 7.31–7.37 (m, 3H), 7.56 (dd, 2H, J=1.3 Hz, J=7.4 Hz), 7.68–7.75 (m, 2H), 8.51 (d, 1H, J=5.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 24.9, 60.8, 70.5, 96.3, 122.06, 122.12, 125.5, 128.3, 128.4, 128.9, 137.2, 148.2, 152.9, 163.6; GC–MS (70 eV) m/z 280 (8) [M^+],

236 (43), 235 (28), 105 (100), 77 (35), 57 (10); FTIR ($CHCl_3$) cm^{-1} 3060, 3030, 2977, 2932, 2872, 1660, 1599, 1230, 1178, 1024. HRMS: calcd for $C_{18}H_{20}N_2O$: 280.1577; found: 280.1572.

*4.4.5. 3-tert-Butyl-amino-1-phenyl-3-pyridin-2-yl-propenone (**22**)*

Yield 125 mg; 44% (entry 4); oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 5.64 (s, 1H), 7.30–7.46 (m, 5H), 7.77 (t, 1H, J=7.6 Hz), 7.86 (d, 2H, J=6.6 Hz), 6.68 (d, 1H, J=5.0 Hz), 11.72 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 31.4, 54.2, 94.3, 123.7, 127.0, 128.1, 128.2, 130.7, 136.4, 140.3, 148.8, 156.0, 164.2, 188.4; GC–MS (70 eV) m/z 280 (15) [M^+], 237 (46), 147 (22), 105 (100), 77 (45), 57 (18); FTIR ($CHCl_3$) cm^{-1} 3064, 3035, 2998, 2929, 2855, 1678, 1583, 1464, 1341, 1230, 1200. HRMS: calcd for $C_{18}H_{20}N_2O$: 280.1577; found: 280.1575.

*4.4.6. 2-tert-Butyl-5-phenyl-3-benzothiazolyl-isoxazoline (**14**)*

Yield 262 mg; 78% (entry 7); oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 5.49 (d, 1H, J=2.9 Hz), 5.79 (d, 1H, J=2.9 Hz), 7.33–7.37 (m, 5H), 7.45 (t, 1H, J=8.0 Hz), 7.54 (t, 1H, J=1.3 Hz, J=7.9 Hz), 7.87 (d, 1H, J=7.9 Hz), 7.97 (d, 1H, J=8.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.0, 61.2, 67.5, 94.4, 121.9, 122.7, 124.5, 125.7, 128.4, 128.7, 128.9, 129.5, 135.5, 153.9, 154.1, 179.3; GC–MS (70 eV) m/z 336 (0) [M^+], 278 (100), 250 (22), 223 (19), 105 (20), 77 (49); FTIR ($CHCl_3$) cm^{-1} 3068, 3034, 2957, 2927, 1673, 1599, 1367, 1218. HRMS: calcd for $C_{20}H_{20}N_2OS$: 336.1298; found: 336.1293.

*4.4.7. 3-tert-Butyl-amino-1-phenyl-3-benzothiazolyl-propenone (**23**)*

Yield 323 mg; 96% (entry 6); oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 6.00 (s, 1H), 7.38–7.57 (m, 5H), 7.90 (d, 2H, J=8.2 Hz), 7.95 (d, 1H, J=8.0 Hz), 8.14 (d, 1H, J=8.1 Hz), 11.62 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 31.1, 54.6, 95.9, 121.6, 122.3, 124.1, 126.3, 126.7, 127.1, 128.2, 131.1, 135.0, 139.5, 152.8, 156.3, 188.7; GC–MS (70 eV) m/z 336 (35) [M^+], 279 (100), 251 (38), 105 (88), 77 (58), 57 (20); FTIR ($CHCl_3$) cm^{-1} 3392, 3068, 3030, 3006, 2968, 2933, 2872, 1675, 1588, 1531, 1329, 1231, 1192. HRMS: calcd for $C_{20}H_{20}N_2OS$: 336.1298; found: 336.1295.

*4.4.8. 2-Ethyl-3,5-diphenyl-isoxazoline (**15**)*

Yield 125 mg; 50%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.1 Hz), 2.96–3.05 (m, 1H), 3.25–3.32 (m, 1H), 4.95 (d, 1H, J= 2.6 Hz), 5.38 (d, 1H, J=2.6 Hz), 7.25–7.38 (m, 8H), 7.59 (dd, 2H, J=1.7 Hz, J=7.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 12.5, 54.4, 75.1, 96.1, 125.7, 127.1, 127.6, 128.4, 128.6, 128.9, 129.1, 142.4, 152.5; GC–MS (70 eV) m/z 251 (50) [M^+], 234 (100), 174 (20), 105 (26), 77 (28); FTIR ($CHCl_3$) cm^{-1} 3063, 3030, 2928, 2854, 1656, 1601, 1494, 1449, 1274. HRMS: calcd for $C_{17}H_{17}NO$: 251.1311; found: 251.1310.

*4.4.9. 3-Ethyl-amino-1-phenyl-3-benzothiazolyl-propenone (**24**)*

Yield 246 mg; 80%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, 3H, J=7.3 Hz), 3.69–3.76 (m, 2H), 6.23 (s, 1H), 7.38–7.59 (m, 5H), 7.92 (dd, 2H, J=1.3 Hz, J=7.9 Hz), 7.97 (d, 1H, J=7.8 Hz), 8.14 (d, 1H, J=7.8 Hz), 11.24 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.0, 39.9, 94.4, 121.6, 124.2, 126.5, 126.8, 127.1, 128.3, 131.2, 134.9, 139.8, 153.3, 155.7, 161.8, 189.2; GC–MS (70 eV) m/z 308 (100) [M^+], 293 (74), 236 (26), 203 (66), 160 (52), 136 (15), 105 (30), 77 (35); FTIR ($CHCl_3$) cm^{-1} 3395, 3069, 3031, 3008, 2973, 2936, 2872, 1685, 1589, 1531, 1329, 1231, 1192. HRMS: calcd for $C_{18}H_{16}N_2OS$: 308.0985; found: 308.0981.

*4.4.10. 2-tert-Butyl-5-(pyridin-2-yl)-3-phenyl-isoxazoline (**17**)*

Yield 252 mg; 90%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 5.27 (d, 1H, J=2.7 Hz), 5.70 (d, 1H, J=2.7 Hz), 7.14–7.18 (m, 2H), 7.25 (t, 2H, J=7.4 Hz), 7.37 (d, 2H, J=7.8 Hz), 7.48 (d, 1H, J=7.8 Hz), 7.65 (t, 1H, J=7.8 Hz), 8.51 (d, 1H, J=4.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.2, 60.9, 68.6, 101.1, 120.2, 123.3, 127.2, 127.3, 128.5, 136.6, 143.9, 147.9, 149.6, 152.5; GC–MS (70 eV) m/z 280 (73) [M^+], 223 (100), 207 (40), 195 (10), 169 (45), 147 (16), 120 (90), 106 (35), 78 (60), 57 (13); FTIR ($CHCl_3$) cm^{-1} 3060, 3030, 2986, 2929, 2856, 1675, 1585, 1365, 1211. HRMS: calcd for $C_{18}H_{20}N_2O$: 280.1577; found: 280.1579.

*4.4.11. 2-tert-Butyl-5-(pyridin-2-yl)-3-benzothiazolyl-isoxazoline (**18**)*

Yield 273 mg; 81%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 5.86 (d, 1H, J=3.0 Hz), 5.94 (d, 1H, J=3.0 Hz), 7.24 (dd, 1H, J=4.6 Hz, J=7.4 Hz), 7.34 (t, 1H, J=7.5 Hz), 7.45 (t, 1H, J=7.5 Hz), 7.55 (d, 1H, J=8.0 Hz), 7.71 (t, 1H, J=7.8 Hz), 7.87 (d, 1H, J=7.8 Hz), 7.97 (d, 1H, J=8.0 Hz), 8.59 (d, 1H, J=4.6 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.1, 61.2, 67.6, 98.5, 120.5, 121.6, 122.9, 123.7, 124.7, 125.8, 135.6, 136.6, 147.2, 149.7, 153.6, 153.9, 175.5; GC–MS (70 eV) m/z 337 (7) [M^+], 279 (18), 231 (55), 175 (100), 148 (12), 78 (20), 57 (6); FTIR ($CHCl_3$) cm^{-1} 3030, 2975, 1585, 1475, 1431, 1363, 1197. HRMS: calcd for $C_{19}H_{19}N_3OS$: 337.1251; found: 337.1247.

*4.4.12. 3-tert-Butyl-amino-1-(pyridin-2-yl)-3-benzothiazolyl-propenone (**25**)*

Yield 30 mg; 9%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 6.79 (s, 1H), 7.34 (dd, 1H, J=4.6 Hz, J=7.8 Hz), 7.49 (t, 1H, J=8.0 Hz), 7.56 (t, 1H, J=8.1 Hz), 7.81 (td, 1H, J=1.7 Hz, J=7.8 Hz), 7.95 (d, 1H, J=7.8 Hz), 8.13 (d, 2H, J=8.0 Hz), 8.60 (d, 1H, J=4.6 Hz), 11.66 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 31.2, 54.9, 95.5, 121.5, 121.6, 124.1, 125.4, 126.3, 126.6, 135.5, 136.8, 148.6, 153.1, 155.6, 157.3, 164.0, 186.7; GC–MS (70 eV) m/z 337 (80) [M^+], 322 (10), 305 (55), 294 (60), 203 (100), 161 (80), 78 (79), 57 (15); FTIR ($CHCl_3$) cm^{-1} 3068, 3030, 3011, 2968, 2931, 2870, 1677, 1593, 1531, 1327, 1230, 1192. HRMS: calcd for $C_{19}H_{19}N_3OS$: 337.1251; found: 337.1248.

*4.4.13. 3-tert-Butyl-amino-1-(4-methoxy-phenyl)-3-phenyl-propenone (**26**)*

Yield 185 mg; 60%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 3.83 (s, 3H), 6.87 (d, 2H, J=8.9 Hz), 7.26 (s, 1H), 7.38–7.42 (m, 5H), 7.84 (d, 2H, J=8.9 Hz), 11.73 (br s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 31.8, 53.9, 55.3, 94.8, 113.4, 127.8, 128.3, 128.8, 128.9, 133.0, 137.8, 161.7, 166.5, 186.9; GC–MS (70 eV) m/z 309 (45) [M^+], 294 (25), 252 (100), 135 (35), 77 (10), 57 (5); FTIR ($CHCl_3$) cm^{-1} 3063, 3030, 3012, 2975, 2935, 1680, 1597, 1310, 1238, 1193. HRMS: calcd for $C_{20}H_{23}NO_2$: 309.1730; found: 309.1727.

*4.4.14. 2-iso-Propyl-3,5-diphenyl-isoxazoline (**20**)*

Yield 159 mg; 60%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, 3H, J=6.5 Hz), 1.27 (d, 3H, J=6.4 Hz), 3.27–3.36 (m, 1H), 5.14 (d, 1H, J= 2.6 Hz), 5.33 (d, 1H, J=2.5 Hz), 7.32–7.40 (m, 8H), 7.58 (dd, 2H, J=1.7 Hz, J=7.3 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 18.7, 21.0, 62.3, 74.1, 96.3, 125.6, 127.1, 127.5, 128.3, 128.6, 129.0, 129.2, 142.4, 152.8; GC–MS (70 eV) m/z 265 (50) [M^+], 222 (25), 188 (18), 167 (25), 118 (23), 105 (100), 91 (30), 77 (40); FTIR ($CHCl_3$) cm^{-1} 3066, 3030, 2978, 2935, 2875, 1661, 1602, 1493, 1365, 1051, 1025. HRMS: calcd for $C_{18}H_{19}NO$: 265.1468; found: 265.1471.

*4.4.15. 3-iso-Propyl-amino-1-phenyl-3-benzothiazolyl-propenone (**27**)*

Yield 225 mg; 70%; oil; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, 6H, J=6.3 Hz), 4.29–4.48 (m, 1H), 6.19 (s, 1H), 7.40–7.69 (m, 5H), 7.88–8.07 (m, 3H), 8.14 (d, 1H, J=8.1 Hz), 11.19 (br d, 1H, J=6.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 24.2, 46.4, 94.4, 121.6, 124.3, 126.5, 126.8, 127.1, 128.3, 131.2, 135.0, 139.8, 153.4, 155.1, 162.0, 189.2; GC–MS (70 eV) m/z 322 (100) [M^+], 307 (95), 217 (80), 160 (56), 105 (70), 77 (45); FTIR ($CHCl_3$) cm^{-1} 3352, 3069, 3032, 3012, 2969, 2935, 2875, 1685, 1592, 1531, 1329, 1231, 1190. HRMS: calcd for $C_{22}H_{18}N_2OS$: 322.1141; found: 322.1144.

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