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Synthesis of new 3,5-diarylisoxazolidines by cycloaddition of oxaziridines and alkenes

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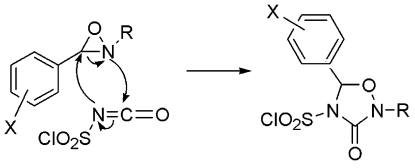
Abstract—This article reports a novel process of cycloaddition of *C*-aryloxaziridines with a variety of alkenes to afford stable, five-membered heterocycles **13**–**24**. The steric hindrance of the *tert*-butyl group on the nitrogen atom of the oxaziridine is responsible for the high stereoselectivity of the cycloaddition reaction.

1. Introduction

3,5-Diarylisoxazolidines represent a class of biologically active heterocycles.[1] However, only a few synthetic methods for these compounds have been reported, in which hydroxylamines[2] are often employed as starting material in a metal-induced intramolecular cyclization and a Cope elimination/intramolecular nitrone cycloaddition.[3]

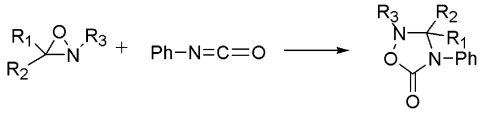
Herein, we describe a facile and highly efficient [3+2] cycloaddition reaction of a variety of aryl alkenes with 2-*tert*-butyl-3-aryloxaziridines, leading to 3,5-diarylisoxazolidines.

Davis and Sheppard have already reported in 1989 that oxaziridines undergo a cycloaddition reaction with a variety of heterocumulenes to afford a diverse set of five-membered heterocycles,[4] which do not include the isoxazolidines. Recently, Hassine et al.[5] have shown that cycloaddition of the 2-alkyl-3-aryloxaziridines with chlorosulfonylisocyanate occurs with cleavage of the C–N bond of the oxaziridine ring and gives the corresponding 1,2,4-oxadiazolidin-3-ones (Scheme 1).



Scheme 1.

Indeed, Agawa et al.[6] have previously reported cycloaddition of 2-alkyl-3-aryloxaziridines with phenylisocyanate, which proceeds with cleavage of the C–O bond of the oxaziridine ring to give the 1,2,4-oxadiazolidin-5-ones (Scheme 2).



Scheme 2.

However, any [3+2] cycloaddition reaction of oxaziridines with alkenes by selective cleavage of the C–O bond of the oxaziridine ring has never been reported, so the results of our experiments seem to be very interesting.

2. Results and discussions

Known oxaziridines **7**–**10**[7] and novel **11** and **12** have been prepared from the respective imines **1**–**6** according to a method known in literature[9] (Scheme 3), which concerns the addition of a *m*-CPBA solution to an imine in CH_2Cl_2 at 0 °C.

The structure of novel oxaziridines **11** and **12** has been assigned by comparison of the C_3–H chemical shifts with the data of known oxaziridines **7**–**10** already reported in the literature.[8]

Isoxazolidines **13**–**24** were obtained in high yield (Table 1) by refluxing oxaziridines **7**–**12** and aryl alkenes in toluene. The reaction was complete, in most cases, after 16 h. Only a small amount of by-product, such as styrenoxide, arylaldehyde, and aryliden-*tert*-butylimine, were observed and identified only by GC–MS. The isoxazolidines were very stable compounds, which were isolated as solids at room temperature.

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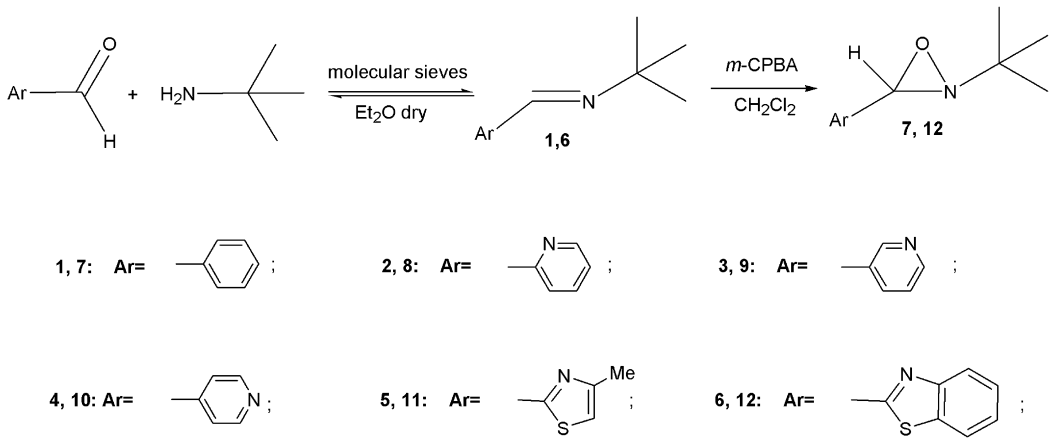
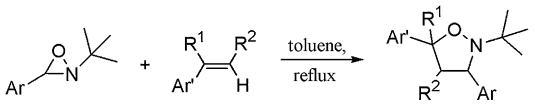
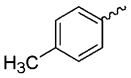
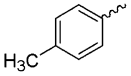
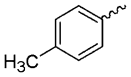
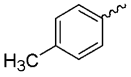
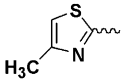
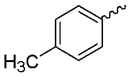
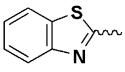
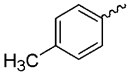
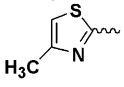
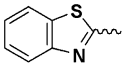


Scheme 3.

Table 1. Synthesis of 3,5-diaryl-isoxazolidines **13–24**



7-12 **13-24**

Entry	Ar	Ar′	R^1	R^2	*t* (h)	Product	Yield[a] (%)	trans/cis[b]
1			H	H	16	**13**	95	0/100
2			H	H	16	**14**	85	0/100
3			H	H	16	**15**	90	0/100
4			H	H	16	**16**	84	0/100
5			H	H	16	**17**	70	0/100
6			H	H	16	**18**	75	0/100
7			CH_3	H	16	**19**	50	40/60
8			CH_3	H	16	**20**	70	100/0
9			CH_3	H	16	**21**	50	40/60
10			H	H	8	**22**	95	25/75
11			H	H	8	**23**	90	40/60
12			H	H	8	**24**	90	40/60
13			H	CH_3	16	—	—	—

[a] Yields were calculated with pure, chromatographically isolated products.
[b] Diastereomeric ratios were calculated by ^{1}H NMR spectroscopy.

The reaction of oxaziridines **7–12** with *p*-Me-styrene produced isoxazolidines **13–18** in good yield (70–95%) and high stereoselectivity (Table 1, entries 1–6). As a result, only the cis isomers were obtained and identified by ^{1}H NMR spectroscopy. The structure of isoxazolidine **13** was assigned by NOESY analysis. The significant NOESY interaction observed between C_3–H and C_5–H shows that they are on the same side of the ring plane, and confirms their cis arrangement. These observations are in accordance with the X-ray crystal structure[10] analysis of **14** (Fig. 1).

The structures of isoxazolidines **15–24** were assigned by comparison of the C_4–H chemical shifts with the corresponding relative chemical shifts of compounds **13** and **14**.

In this case, the stereoselectivity observed seems to be due to steric interaction between the *p*-Me-phenyl ring of the arylalkene and the *tert*-butyl group of the oxaziridine, in a possible one-step cycloaddition mechanism (Scheme 4).

In Scheme 4, we have depicted two different approaches of oxaziridine **7** and *p*-Me-styrene: the favored situation with less steric interaction is **b**, which yields only *cis* isoxazolidine **13**.

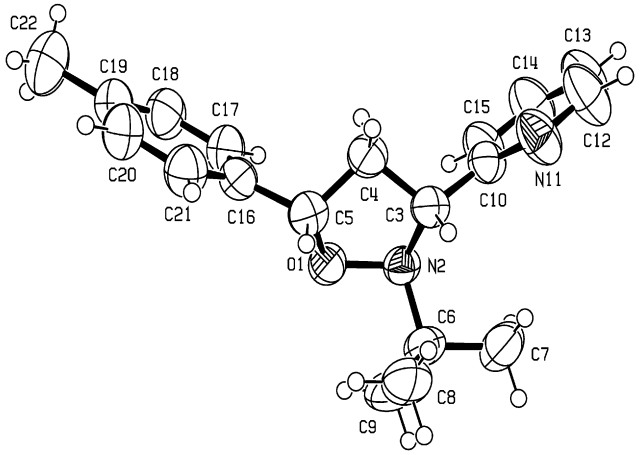
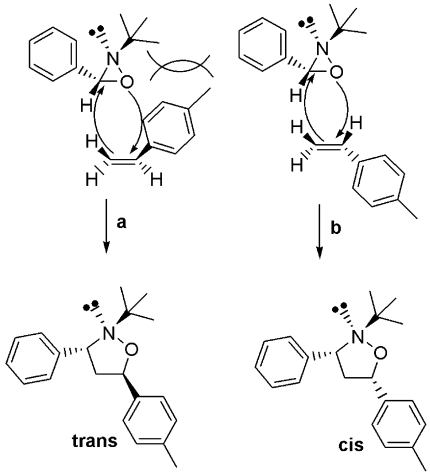


Figure 1. ORTEP projection of compound **14**. Atomic displacement parameters at 50% probability level. H atoms not to scale.[10]



Scheme 4.

When α-methyl-styrene was used with oxaziridines **7–9** under the same conditions, we isolated isoxazolidines **19–21**, and in addition to a lower yield (50–70%), an inversion (Table 1, entry 8) or reduction of stereoselectivity was also observed (Table 1, entries 7, 9). The same cycloaddition reaction, conducted on 2-vinyl-pyridine, with the oxaziridines **10–12** produced isoxazolidines with lower stereoselectivity but excellent yield (Table 1, entries 10–12).

We can explain the lower stereoselectivity observed in using α-methyl-styrene, as the result of a possible double steric interaction of the *tert*-butyl group with both the methyl and phenyl group of the alkene.

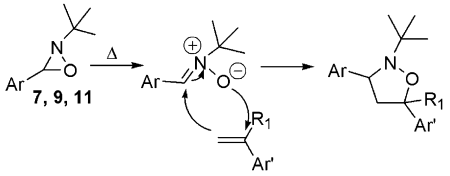
It was also observed that the presence of the 2-pyridinyl substituent as an electron withdrawing group on the carbon site of the alkene increases the rate of the cycloaddition reaction under the same conditions. Presumably, the higher rate of the cycloaddition reaction conducted on activated alkenes (with EWG) is responsible for the lessening of the stereoselectivity (Table 1) in comparison with alkenes having no EWG.

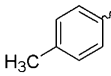
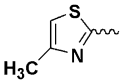
From a mechanistic point of view, oxaziridines **7–12** undergo cycloaddition with aryl alkenes, involving selective cleavage of the C–O bond of the oxaziridine ring (Scheme 4), and appears to be similar to the cycloaddition reaction presented by Agawa et al.[6]

However, an alternative mechanism via the nitrone can also be assumed (Table 2), where the oxaziridines rearrange to the isomeric nitrones upon heating followed by the nitrone reacting with the alkene to give the isoxazolidine.

To explain this, we refluxed oxaziridine **9** in toluene over night, and subsequently isolated the isomeric nitrone **9a** in quantitative yield. We refluxed **9a** with *p*-Me-styrene in toluene over night. The ^{1}H NMR spectrum of the crude reaction mixture indicated that there was starting material present again, and only 20–30% of the nitrone **9a** had reacted to give isoxazolidine **15** (Table 2, entry 2). When the isomeric nitrones **7a**, **11a**, obtained in the same conditions, were refluxed with 2-vinyl-pyridine, no trace

Table 2. Two-step mechanism of the cycloaddition reaction via nitrone



Entry	Ar	Ar′	R[1]	Oxaziridine	Nitrone	Product	Yield[a] (%)
1			H	**7**		**7a**	—	—
2			H	**9**		**9a**	**15**	30
3			H	**11**		**11a**	—	—

[a] Yields were calculated with pure, chromatographically isolated products.

of isoxazolidines were observed (Table 2, entries 2, 3). The results obtained in the reaction of nitrones **9a** and **11a** with alkenes seem to be not in accordance with the results of oxaziridine cycloaddition reaction so it is more probable that it is a one-step mechanism (Scheme 4).

Finally, when we used *trans* β-methyl-styrene in cycloaddition reactions under the same conditions, no cyclic product was observed. Only by-products such as β-methyl-styrenoxide, benzaldehyde, and aryliden-*tert*-butylimine, were identified only by GC–MS (Table 1, entry 13). Oxaziridine probably only reacts with terminal alkenes to give cycloaddition products.

In future, the study of cycloaddition reactions of diverse functionalized oxaziridines with different alkenes might elucidate the stereoselectivity of these reactions.

3. Conclusion

In conclusion, the chemistry reported could potentially offer a convenient entry to 3,5-disubstituted isoxazolidines, which serve as valuable synthetic building blocks for the construction of bioactive natural products.[11]

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-530-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^{-1} 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 spectral data were collected at 400 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.

4.2. General procedure for the preparation of imines 1–6

The appropriate amine (1 mmol) and the corresponding aldehyde (1 mmol) were dissolved in anhydrous Et_2O (20 ml) in presence of 7 g of molecular sieves (4 Å, 1.6 mm pellets), according to Taguchi's method.[12] The formation of the imine was monitored by GC. After 1 h, the molecular sieves were filtered and the solvent evaporated to obtain the pure imine.

4.2.1. *tert*-Butyl-(4-methyl-thiazol-2-ylmethylene)-amine (5). Yield 182 mg, 99%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 2.47 (s, 3H), 6.92 (s, 1H), 8.37 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 17.0, 29.4, 58.2, 115.7, 149.8, 153.7, 157.8; GC–MS (70 eV) *m*/*z* 182 (35) [M$^+$], 167 (75), 126 (100), 99 (60), 57 (27); FTIR ($CHCl_3$) cm^{-1} 3035, 2974, 1638, 1517, 1457, 1364, 1227. Anal. Calcd for $C_9H_{14}N_2S$: C, 59.30; H, 7.74; N, 15.37. Found: C, 59.20; H, 7.71; N, 15.33.

4.2.2. *tert*-Butyl-benzothiazol-2-ylmethylene-amine (6). Yield 218 mg, 99%; yellow solid; mp 54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 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 29.3, 58.8, 121.9, 123.8, 126.2, 126.3, 135.0, 150.5, 153.6, 169.0; GC–MS (70 eV) *m*/*z* 218 (24) [M$^+$], 203 (45), 162 (82), 135 (100), 109 (15), 57 (62); FTIR ($CHCl_3$) cm^{-1} 3068, 2976, 1638, 1501, 1458, 1434, 1365, 1317, 1220. Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.89; H, 6.40; N, 12.75.

4.3. General procedure for the preparation of oxaziridines 7–12

A small excess of *m*-chloroperbenzoic acid (1.1 mmol) in methylene chloride (3 ml) was added with stirring and cooling (0–5 °C) to a solution of imine (1 mmol) in of methylene chloride (5 ml). 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 $MgSO_4$ (anhydrous), the solvent was evaporated and the residue was purified by a column chromatography (silica gel partly deactivated with TEA, petroleum ether/ethyl ether=95:5 for **7**; petroleum ether/ethyl ether=8:2 for **8**–**12**).

4.3.1. 2-*tert*-Butyl-3-(4-methyl-thiazol-2-yl)-oxaziridine (11). Yield 168 mg, 85%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 2.46 (s, 3H), 5.09 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.8, 25.0, 59.1, 71.1, 116.2, 153.1, 166.2; GC–MS (70 eV) *m*/*z* 198 (67) [M$^+$], 142 (100), 126 (5), 112 (35), 99 (4), 71 (15), 57 (86); FTIR ($CHCl_3$) cm^{-1} 3106, 2974, 1528, 1484, 1444, 1365, 1331, 1262, 1207. Anal. Calcd for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found: C, 54.22; H, 7.09; N, 14.03.

4.3.2. 2-*tert*-Butyl-3-(benzothiazolyl)-oxaziridine (12). Yield 210 mg, 90%; yellow solid; mp 48–49 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 5.23 (s, 1H), 7.42 (t, 1H, *J*=7.9 Hz), 7.50 (t, 1H, *J*=8.1 Hz), 7.90 (d, 1H, *J*=7.9 Hz), 8.05 (d, 1H, *J*=8.1 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.0, 59.4, 71.5, 122.1, 123.4, 125.8, 125.9, 135.6, 152.9, 168.1; GC–MS (70 eV) *m*/*z* 234 (76) [M$^+$], 219 (96), 191 (58), 162 (100), 135 (50), 134 (44), 57 (10); FTIR ($CHCl_3$) cm^{-1} 3068, 3035, 2980, 1523, 1477, 1459, 1358, 1318, 1240, 1205. Anal. Calcd for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96. Found: C, 61.41; H, 6.07; N, 12.05.

4.4. General procedure for the cycloaddition reaction

A solution of alkene (1.5 mmol) and oxaziridine **7**–**12** (1.0 mmol) in toluene (10 ml) was refluxed under magnetic stirring over night (Table 1). After this time, TLC showed the reaction to be complete. The solution was cooled to rt, and evaporated to dryness to give a yellow crude material. Isoxazolines **13**–**24** were isolated by flash chromatography (silica gel, petroleum ether/ethyl ether=8:2 for **13**, **14** and **17**, **19**; petroleum ether/ethyl ether=7:3 for **15**, **16**, **18**, **20**, **21**, **23**; ethyl acetate for **22**, **24**).

4.4.1. 2-*tert*-Butyl-3-phenyl-5-*p*-tolyl-isoxazolidine (13). Yield 224 mg, 95%; white solid; mp 62–63 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 2.31 (s, 3H), 2.29–2.37 (m, 1H), 2.85–2.91 (m, 1H), 4.45 (dd, 1H, *J*=6.8, 10.0 Hz), 5.08 (dd, 1H, *J*=10.2, 5.0 Hz), 7.12 (d, 2H, *J*=7.9 Hz), 7.16–7.19 (m, 1H), 7.25–7.34 (m, 4H), 7.48 (d, 2H, *J*=7.2 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 26.2, 51.2, 60.3, 64.4, 80.2, 126.5, 126.8, 126.9, 128.3, 129.0, 137.1, 137.3, 144.0; GC–MS (70 eV) *m*/*z* 295 (9) [M$^+$], 207 (66), 146 (25), 121 (50), 91 (44), 57 (100); FTIR ($CHCl_3$) cm^{-1} 3030, 2978, 1602, 1515, 1455, 1364, 1224, 1037. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.25; H, 8.49; N, 4.69.

4.4.2. 2-*tert*-Butyl-3-(pyridine-2-yl)-5-*p*-tolyl-isoxazolidine (14). Yield 156 mg, 85%; white solid; mp 68–69 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 2.23 (s, 3H), 2.24–2.33 (m, 1H), 2.94–3.0 (m, 1H), 4.59 (dd, 1H, *J*=7.5, 9.1 Hz), 5.05 (dd, 1H, *J*=5.2, 9.8 Hz), 7.03–7.12 (m, 3H), 7.20 (d, 2H, *J*=7.8 Hz), 7.55 (t, 1H, *J*=7.8 Hz), 7.70 (d, 1H, *J*=7.8 Hz), 8.37 (d, 1H, *J*=4.5 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 26.1, 49.2, 60.4, 66.2, 80.7, 121.4, 121.8, 126.5, 129.0, 136.7, 137.4, 148.5, 163.9; GC–MS (70 eV) *m*/*z* 296 (1) [M$^+$], 209 (100), 147 (10), 119 (30), 91 (40), 57 (27); FTIR ($CHCl_3$) cm^{-1} 3057, 2976, 1593, 1516, 1474, 1435, 1364, 1228, 1048. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.05; H, 8.16; N, 9.45. Found: C, 77.12; H, 8.09; N, 9.39.

4.4.3. 2-*tert*-Butyl-3-(pyridin-3-yl)-5-*p*-tolyl-isoxazolidine (15). Yield 253 mg, 90%; white solid; mp 74–75 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 2.33 (s, 3H), 2.27–2.34 (m, 1H), 2.92–2.98 (m, 1H), 4.50 (dd, 1H, *J*=7.0 Hz, *J*=9.6 Hz), 5.12 (dd, 1H, *J*=4.9, 10.0 Hz), 7.15 (d, 2H, *J*=7.9 Hz), 7.22–7.26 (m, 1H), 7.30 (d, 2H, *J*=8.0 Hz), 7.90 (dt, 1H, *J*=1.8, 7.8 Hz), 8.45 (dd, 1H, *J*=1.8, 4.8 Hz), 8.61 (d, 1H, *J*=1.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 26.2, 50.8, 60.5, 61.8, 80.4, 123.5, 126.4, 129.1, 134.7, 136.6, 137.6, 139.7, 148.4, 149.6; GC–MS (70 eV) *m/z* 296 (5) [M$^+$], 208 (60), 147 (65), 118 (100), 91 (90), 57 (90); FTIR ($CHCl_3$) cm^{-1} 3034, 2983, 1578, 1515, 1478, 1427, 1364, 1228, 1027. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.06; H, 8.23; N, 9.35. HRMS calcd for $C_{19}H_{24}N_2O$: 297.1968, found 297.1974.

4.4.4. 2-*tert*-Butyl-3-(pyridine-4-yl)-5-*p*-tolyl-isoxazolidine (16). Yield 239 mg, 85%; yellow solid; mp 59–60 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.19–2.25 (m, 1H), 2.26 (s, 3H), 2.85–2.91 (m, 1H), 4.37 (dd, 1H, *J*=7.4, 9.4 Hz), 5.04 (dd, 1H, *J*=5.2, 9.9 Hz), 7.06 (d, 2H, *J*=7.9 Hz), 7.20 (d, 2H, *J*=7.9 Hz), 7.34 (d, 2H, *J*=5.8 Hz), 8.44 (d, 2H, *J*=5.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 26.1, 50.3, 60.4, 63.1, 80.5, 122.0, 126.4, 129.1, 136.3, 137.7, 149.9, 153.5; GC–MS (70 eV) *m/z* 296 (9) [M$^+$], 208 (90), 147 (70), 119 (98), 118 (100), 91 (95), 57 (99); FTIR ($CHCl_3$) cm^{-1} 3032, 2977, 1600, 1562, 1515, 1416, 1365, 1250, 1228. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.05; H, 8.16; N, 9.45. Found: C, 76.89; H, 8.20; N, 9.41.

4.4.5. 2-*tert*-Butyl-3-(4-methyl-thiazol-2-yl)-5-*p*-tolyl-isoxazolidine (17). Yield 118 mg, 70%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.23 (s, 3H), 2.31 (s, 3H), 2.38–2.47 (m, 1H), 2.98–3.05 (m, 1H), 4.80 (t, 1H, *J*=7.9 Hz), 5.08 (dd, 1H, *J*=5.7, 9.3 Hz), 6.67 (s, 1H), 7.03 (d, 2H, *J*=8.0 Hz), 7.15 (d, 2H, *J*=8.0 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 17.1, 21.1, 26.3, 48.4, 60.7, 62.2, 81.4, 113.5, 126.6, 129.0, 136.2, 137.6, 152.2, 175.8; GC–MS (70 eV) *m/z* 316 (0) [M$^+$], 229 (100), 142 (40), 119 (41), 91 (55), 57 (75); FTIR ($CHCl_3$) cm^{-1} 3031, 2977, 1605, 1533, 1515, 1446, 1363, 1248, 1201. Anal. Calcd for $C_{18}H_{24}N_2OS$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.51; H, 7.58; N, 8.79.

4.4.6. 2-*tert*-Butyl-3-(benzothiazolyl)-5-*p*-tolyl-isoxazolidine (18). Yield 158 mg, 75%; yellow solid; mp 117–118 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.22 (s, 3H), 2.48–2.55 (m, 1H), 3.04–3.13 (m, 1H), 4.91 (t, 1H, *J*=8.0 Hz), 5.11 (dd, 1H, *J*=5.7, 9.3 Hz), 7.02 (d, 2H, *J*=8.0 Hz), 7.17 (d, 2H, *J*=8.0 Hz), 7.25 (t, 1H, *J*=7.9 Hz), 7.36 (t, 1H, *J*=8.1 Hz), 7.77 (d, 1H, *J*=7.9 Hz), 7.82 (d, 1H, *J*=8.1 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 21.1, 26.2, 48.1, 60.8, 62.5, 81.4, 121.8, 122.5, 124.7, 125.7, 126.6, 129.1, 135.2, 135.9, 137.7, 153.5, 178.1; GC–MS (70 eV) *m/z* 352 (1) [M$^+$], 337 (100), 202 (78), 162 (55), 134 (52), 117 (56), 91 (44), 57 (37); FTIR ($CHCl_3$) cm^{-1} 3030, 3010, 2974, 1605, 1515, 1456, 1364, 1324, 1240, 1198. Anal. Calcd for $C_{21}H_{24}N_2OS$: C, 71.56; H, 6.86; N, 7.95. Found: C, 72.00; H, 7.01; N, 7.69.

4.4.7. 2-*tert*-Butyl-5-methyl-3,5-diphenyl-isoxazolidine (19). Inseparable diastereomeric mixture of two *cis*- and *trans*-configurated isoxazolidine (dr=8:2 from the ^{1}H NMR spectrum of the crude reaction mixture). Overall yield 118 mg, 50%; oil. *Major diastereomer (cis)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.70 (s, 3H), 2.45 (dd, 1H, *J*=7.6, 12.3 Hz), 2.85 (dd, 1H, *J*=8.9, 12.3 Hz), 4.20 (dd, 1H, *J*=7.6, 8.9 Hz), 7.05–7.12 (m, 2H), 7.19–7.25 (m, 2H), 7.29–7.35 (m, 3H), 7.42–7.49 (m, 3H); GC–MS (70 eV) *m/z* 295 (25) [M$^+$], 280 (27), 207 (98), 177 (23), 121 (100), 57 (55). *Minor diastereomer (trans)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 9H); 1.52 (s, 3H); 2.58 (dd, 1H, *J*=7.0, 9.2 Hz); 2.75 (dd, 1H, *J*=9.2, 12.3 Hz), 4.21 (dd, 1H, *J*=7.0, 9.2 Hz), 7.05–7.12 (m, 2H), 7.19–7.25 (m, 2H), 7.29–7.35 (m, 3H), 7.42–7.49 (m, 3H); GC–MS (70 eV) *m/z* 295 (15) [M$^+$], 280 (12), 207 (75), 121 (100), 57 (75); ^{13}C NMR (100.62 MHz, $CDCl_3$) on the inseparable mixture: δ 26.2, 26.6, 29.6, 30.0, 55.2, 55.4, 58.2, 58.3, 63.6, 64.1, 80.1, 80.2, 124.8, 125.2, 126.0, 126.4, 126.8, 127.3, 127.5, 127.8, 128.0, 128.3, 144.9, 147.6; FTIR ($CHCl_3$) cm^{-1} 3065, 2975, 2931, 1602, 1494, 1447, 1364, 1220. Anal. Calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.40; H, 8.48; N, 4.89.

4.4.8. 2-*tert*-Butyl-5-methyl-3-(pyridin-2-yl)-5-phenyl-isoxazolidine (20). Yield 128 mg, 70%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.55 (s, 3H), 2.71 (dd, 1H, *J*=12.3, 5.5 Hz), 2.94 (dd, 1H, *J*=9.6, 12.3 Hz), 4.48 (dd, 1H, *J*=5.5, 9.6 Hz), 7.13–7.16 (m, 1H), 7.21–7.26 (m, 1H), 7.33 (t, 2H, *J*=7.9 Hz), 7.42 (d, 2H, *J*=7.9 Hz), 7.69 (t, 1H, *J*=7.7 Hz), 7.88 (d, 1H, *J*=7.9 Hz), 8.52 (d, 1H, *J*=4.6 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 26.4, 30.1, 51.8, 64.9, 58.0, 82.0, 121.8, 124.8, 126.5, 128.1, 136.0, 136.5, 147.0, 148.8, 163.1; GC–MS (70 eV.) *m/z* 296 (6) [M$^+$], 281 (10), 209 (100), 106 (28), 77 (15), 57 (18); FTIR ($CHCl_3$) cm^{-1} 3062, 2974, 2932, 1592, 1494, 1469, 1435, 1364, 1229. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.05; H, 8.16; N, 9.45. Found: C, 77.12; H, 8.21; N, 9.50.

4.4.9. 2-*tert*-Butyl-5-methyl-3-(pyridin-3-yl)-5-phenyl-isoxazolidine (21). Inseparable diastereomeric mixture of two *cis*- and *trans*-configurated isoxazolidine (dr=8:2 from the ^{1}H NMR spectrum of the crude reaction mixture). Overall yield 141 mg, 50%; oil. *Major diastereomer (cis)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.70 (s, 3H), 2.41 (dd, 1H, *J*=7.2, 12.3 Hz), 2.89 (dd, 1H, *J*=9.1, 12.3 Hz), 4.24 (dd, 1H, *J*=7.2, 9.1 Hz), 7.21–7.44 (m, 6H), 7.89 (d, 1H, *J*=7.9 Hz), 8.48 (d, 1H, *J*=3.8 Hz), 8.64 (s, 1H); GC–MS (70 eV) *m/z* 296 (15) [M$^+$], 240 (8), 208 (100), 122 (43), 118 (60), 77 (25), 57 (40). *Minor diastereomer (trans)*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.52 (s, 3H), 2.56 (dd, 1H, *J*=5.6, 12.3 Hz), 2.76 (dd, 1H, *J*=10.0, 12.3 Hz), 4.24 (dd, 1H, *J*=5.6, 10.0 Hz), 6.96 (dd, 1H, *J*=4.8, 7.8 Hz), 7.21–7.44 (m, 6H), 8.21–8.23 (m, 2H); GC–MS (70 eV) *m/z* 296 (15) [M$^+$], 240 (10), 208 (100), 122 (57), 118 (56), 77 (23), 57 (41). ^{13}C NMR (100.62 MHz, $CDCl_3$) on the inseparable mixture: δ 26.1, 26.7, 29.2, 29.9, 54.2, 55.2, 58.3, 58.5, 61.1, 80.4, 80.9, 123.1, 123.4, 124.8, 125.2, 126.3, 127.1, 127.2, 127.9, 128.2, 128.6, 134.9, 135.2, 139.7, 140.4, 148.8, 150.9, 152.3, 153.3; FTIR ($CHCl_3$) cm^{-1} 3061, 2976, 2932, 1594, 1494, 1447, 1427, 1364, 1280, 1224. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.17; H, 8.19; N, 9.40.

4.4.10. 2-*tert*-Butyl-3-pyridin-4-yl-5-pyridin-2-yl-isoxazolidine (22). Overall yield 267 mg, 95%; oil. *Major diastereomer (cis)*: yield 200 mg, 71%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 2.51–2.58 (m, 1H), 2.64–2.70 (m, 1H), 4.35 (dd, 1H, J=3.6, 9.2 Hz), 5.17 (dd, 1H, J=9.7 Hz), 7.16–7.24 (m, 1H), 7.49–7.51 (m, 3H), 7.72 (d, 1H, J=6.0 Hz), 8.53 (d, 1H, J=4.5 Hz), 8.56 (d, 2H, J=4.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 15.0, 46.6, 60.0, 61.7, 78.1, 120.2, 121.9, 122.3, 136.4, 148.7, 150.1, 153.8, 160.7; GC–MS (70 eV) *m/z* 283 (5) [M$^+$], 268 (10), 197 (60), 147 (100), 122 (25), 106 (55), 79 (90), 57 (95); FTIR ($CHCl_3$) cm^{-1} 3061, 2975, 1599, 1475, 1436, 1416, 1365, 1234. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 72.12; H, 7.38; N, 14.90. *Minor diastereomer (trans)*: yield 67 mg, 24%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 2.47 (dt, 1H, J=7.4, 12.3 Hz), 3.14–3.21 (m, 1H), 4.36 (t, 1H, J=8.1 Hz), 5.26 (t, 1H, J=6.9 Hz), 7.15–7.19 (m, 1H), 7.25 (d, 2H, J=5.9 Hz), 7.58–7.73 (m, 2H), 8.43 (d, 2H, J=5.9 Hz), 8.47 (d, 1H, J=4.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 25.9, 47.9, 59.6, 62.1, 79.6, 120.2, 121.9, 122.1, 136.4, 148.6, 149.5, 153.2, 160.8; GC–MS (70 eV) *m/z* 283 (2) [M$^+$], 268 (8), 197 (58), 147 (100), 122 (26), 106 (52), 79 (90), 57 (95); FTIR ($CHCl_3$) cm^{-1} 3061, 2975, 1599, 1475, 1436, 1416, 1365, 1234. Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.05; H, 7.47; N, 14.83. Found: C, 72.17; H, 7.39; N, 14.80.

4.4.11. 2-*tert*-Butyl-3-(4-methyl-thiazol-2-yl)-5-pyridin-2-yl-isoxazolidine (23). Overall yield 245 mg, 90%. *Major diastereomer (cis)*: yield 147 mg, 54%; white solid; mp 64–65 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.33 (s, 3H), 2.72–2.78 (m, 1H), 3.20–3.25 (m, 1H), 4.78 (dd, 1H, J=5.8, 8.9 Hz), 5.31 (t, 1H, J=6.5 Hz), 6.66 (s, 1H), 7.11–7.14 (m, 1H), 7.61–7.66 (m, 2H), 8.45 (d, 1H, J=4.5 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 16.9, 26.1, 46.1, 60.0, 61.2, 80.7, 113.6, 120.6, 122.2, 130.4, 148.6, 152.0, 160.7, 175.5; GC–MS (70 eV) *m/z* 303 (0) [M$^+$], 246 (13), 217 (10), 126 (50), 99 (40), 79 (55), 57 (100); FTIR ($CHCl_3$) cm^{-1} 3067, 2973, 2873, 1594, 1531, 1477, 1437, 1364, 1309, 1230. Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85. Found: C, 63.25; H, 6.88; N, 13.80. *Minor diastereomer (trans)*: yield 98 mg, 36%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 2.42 (s, 3H), 2.54–2.60 (m, 1H), 2.82 (ddd, 1H, J=1.3, 5.1, 12.3 Hz), 4.78 (dd, 1H, J=1.3, 9.6 Hz), 5.12 (dd, J=5.1, 11.1 Hz), 6.8 (s, 1H), 7.20 (dd, 1H, J=5.0, 6.7 Hz), 7.47 (d, 1H, J=7.8 Hz), 7.69 (t, 1H, J=7.8 Hz), 8.52 (d, 1H, J=4.5 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 17.1, 26.0, 45.2, 59.2, 61.1, 78.5, 114.0, 120.5, 122.7, 136.6, 149.0, 153.0, 158.2, 176.2; GC–MS (70 eV) *m/z* 303 (0) [M$^+$], 246 (15), 217 (12), 126 (50), 99 (43), 79 (55), 57 (100); FTIR ($CHCl_3$) cm^{-1} 3067, 2973, 2873, 1594, 1531, 1477, 1437, 1364, 1309, 1230. Anal. Calcd for $C_{16}H_{21}N_3OS$: C, 63.33; H, 6.98; N, 13.85. Found: C, 63.37; H, 7.01; N, 13.89.

4.4.12. 2-*tert*-Butyl-3-benzothiazolyl-5-pyridin-2-yl-isoxazolidine (24). Overall yield 275 mg, 90%. *Major diastereomer (cis)*: yield 165 mg, 54%; oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 2.84–3.00 (m, 1H), 3.30–3.37 (m, 1H), 4.90 (dd, 1H, J=5.9, 9.3 Hz), 5.35 (t, 1H, J=7.1 Hz), 7.11–7.15 (m, 1H), 7.31 (t, 1H, J=8.2 Hz), 7.41 (t, 1H, J=7.5 Hz), 7.65–7.68 (m, 2H), 7.68 (d, 1H, J=7.6 Hz), 7.87 (d, 1H, J=8.2 Hz), 8.44 (d, 1H, J=4.8 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 26.2, 45.9, 61.8, 65.8, 80.7, 120.6, 121.7, 122.3, 122.6, 124.6, 125.7, 126.0, 136.0, 136.5, 148.8, 160.6, 177.8; GC–MS (70 eV) *m/z* 339 (0) [M$^+$], 282 (33), 266 (85), 162 (85), 135 (100), 79 (17), 57 (78); FTIR ($CHCl_3$) cm^{-1} 3069, 2975, 2875, 1594, 1514, 1477, 1437, 1365, 1311, 1229. Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.23; N, 12.38. Found: C, 67.19; H, 6.19; N, 12.41. *Minor diastereomer (trans)*: 110 mg, 36%; yellow solid; mp 141–142 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 2.67–2.75 (m, 1H), 2.89–2.94 (m, 1H), 4.90 (dd, J=1.3, 9.9 Hz), 5.21 (dd, 1H, J=5.2, 11.0 Hz), 7.21 (dd, 1H, J=5.0, 6.3 Hz), 7.37 (t, 1H, J=7.5 Hz), 7.45–7.50 (m, 2H), 7.70 (t, 1H, J=7.7 Hz), 7.90 (d, 1H, J=8.1 Hz), 7.95 (d, 1H, J=8.1 Hz), 8.53 (d, 1H, J=4.5 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 26.0, 45.1, 59.4, 61.5, 78.7, 120.8, 121.7, 122.7, 122.8, 124.6, 125.8, 127.0, 136.4, 136.7, 149.1, 157.9, 178.5; GC–MS (70 eV) *m/z* 339 (0), 282 (35), 266 (85), 162 (85), 135 (100), 79 (20), 57 (80); FTIR ($CHCl_3$) cm^{-1} 3069, 2975, 2875, 1594, 1514, 1477, 1437, 1365, 1311, 1229. Anal. Calcd for $C_{19}H_{21}N_3OS$: C, 67.23; H, 6.23; N, 12.38. Found: C, 67.17; H, 6.20; N, 12.45.

4.5. General procedure for the preparation of nitrones 7a, 9a, 11a

A solution of oxaziridine **7**, **9**, **11** (1.0 mmol) in toluene (10 ml) was refluxed under magnetic stirring over night. After this time, TLC showed the reaction to be complete. The solution was cooled to rt and evaporated to dryness to give nitrones **7a**, **9a**, **11a** in high yield (99%).

4.5.1. (*Z*)-*N*-*tert*-Butyl-α-(phenyl)-nitrone (7a). Yield 175 mg, 99%; white solid; mp 73–74 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 9H), 7.38–7.42 (m, 3H), 7.54 (s, 1H), 8.29 (d, 2H, J=6.9 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.2, 70.6, 128.3, 128.6, 129.7, 129.9, 130.9; GC–MS (70 eV) *m/z* 177 (46) [M$^+$], 121 (33), 120 (11), 57 (100); FTIR ($CHCl_3$) cm^{-1} 3063, 3030, 2982, 1562, 1445, 1407, 1363, 1244, 1192, 1121. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.49; H, 8.54; N, 7.88.

4.5.2. (*Z*)-*N*-*tert*-Butyl-α-(pyridin-3-yl)-nitrone (9a). Yield 176 mg, 99%; yellow solid; mp 80–81 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 7.35 (dd, 1H, J=5.0, 8.1 Hz), 7.61 (s, 1H), 8.58 (d, 1H, J=5.0 Hz), 8.98 (s, 1H), 9.12 (d, 1H, J=8.1 Hz); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 28.3, 71.5, 123.4, 126.9, 127.5, 134.6, 150.1, 150.2; GC–MS (70 eV) *m/z* 178 (15) [M$^+$], 122 (63), 121 (33), 57 (100); FTIR ($CHCl_3$) cm^{-1} 3060, 3030, 2983, 1561, 1416, 1364, 1240, 1196, 1133. Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.35; H, 7.94; N, 15.70.

4.5.3. (*Z*)-*N*-*tert*-Butyl-α-(4-methyl-thiazol-2-yl)-nitrone (11a). Yield 196 mg, 99%; white solid; mp 90–91 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9H), 2.53 (s, 3H), 7.03 (s, 1H), 8.34 (s, 1H); ^{13}C NMR (100.62 MHz, $CDCl_3$) δ 17.1, 28.0, 70.4, 115.8, 126.6, 153.9, 156.7; GC–MS (70 eV) *m/z* 198 (31) [M$^+$], 142 (100), 112 (20), 57 (72); FTIR ($CHCl_3$) cm^{-1} 3030, 2984, 1561, 1508, 1342, 1240, 1194, 1116. Anal. Calcd

for $C_9H_{14}N_2OS$: C, 54.52; H, 7.12; N, 14.13. Found: C, 54.49; H, 7.13; N, 14.11.

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References and notes

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10. Crystallographic data for compound **14**. $C_{19}H_{24}N_2O$, M_r=296.40, T=295 K, 0.46×0.38×0.16 mm^3, colorless crystal, triclinic, space group P-1, a=8.0826(8), b=10.3580(11), c=11.3458(11) Å, α=70.0120(10), β=85.903(2), γ=82.743(2)°, V=885.09(15) Å^3, Z=4, D_c=1.112 g cm^{-3}, λ (Mo Kα)=0.71073 Å, μ (Mo Kα)=0.069 mm^{-1}. Data collection: Bruker SMART APEX diffractometer, data collection $2\theta<55.75°$, 10057 data collected, 4194 independent, 2736 observed [$I>2\sigma(I)$]. The structure was solved by SIR2002 (Burla, M. C.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **2003**, *36*, 1103), and refined on F^2 by SHELX97 (Sheldrick, G. M. *Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997). Final R=0.0480, wR=0.1371, on observed data, goodness-of-fit=1.044, $-0.17<\Delta\rho<0.15$ e Å^{-3}. Bond distances and angles are in the normal range. Crystallographic data, excluding structure factors, have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publicaton Number CCDC 640786. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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