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Diastereoselective syntheses of pyrazolyl isoxazolidines via 1,3-dipolar cycloaddition

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Abstract—Synthesis of novel 2,3,4,5-tetrasubstituted isoxazolidine and 2,3,5-trisubstituted isoxazolidine by 1,3-dipolar cycloaddition of nitrones with electron-deficient and electron-rich olefins is described. 1,3-Dipolar cycloaddition of nitrones with β-nitrostyrene, gives exclusively *endo*-diastereoisomer of isoxazolidine and with ethyl vinyl ether, gives *exo*-diastereoisomer of isoxazolidine with de >95%. The stereochemistry of the products were assigned using extensive NMR studies.

1. Introduction

1,3-Dipolar cycloaddition is a fundamental tool for the synthesis of a number of five-membered heterocyclic compounds and has been employed in numerous syntheses using 1,3-dipoles such as nitrones, nitrile oxides, azomethine ylides, and nitronates.[1] The 1,3-dipolar cycloaddition of nitrones to alkenes provides a straight forward route to isoxazolidines,[2–6] which can be considered as masked forms of several functional group combinations. Thus, nitrone cycloadducts are attractive intermediates for the synthesis of several class of natural products and biologically active compounds such as β-aminoacids and alkaloids.[7]

The pyrazole unit is the core structure in a number of natural products.[8] Many pyrazole derivatives are known to exhibit a wide range of biological properties such as anti-hyperglycemic, analgesic, anti-inflammatory, antipyretic, anti-bacterial, hypoglycemic, sedative-hypnotic activity,[9,10] and anticoagulant activity.[11] Particularly, arylpyrazoles are widely used in medicinal and pesticide chemistry.[12] Recently some arylpyrazoles were reported to display non-nucleoside HIV-1 reverse transcriptase inhibitory activity.[13]

2. Results and discussion

We have investigated the complete regio- and stereoselectivity in the 1,3-dipolar cycloaddition of pyrazole derived nitrones with both electron-rich and electron-deficient olefinic systems. Pyrazole nitrones were prepared from pyrazole-4-carbaldehyde and phenylhydroxylamine in ethanol at room temperature.

2.1. Reaction of pyrazolyl nitrone with β-nitrostyrene

An equimolar mixture of a substituted pyrazolyl nitrone **1** and β-nitrostyrene **2** was refluxed in toluene to obtain a single *endo*-diastereoisomer **3** (Scheme 1) in moderate to good yield. The results are summarized in Table 1.

The *endo* stereochemistry of the cycloadducts was assigned based on the coupling constants and H–H COSY experiments. In ^{1}H NMR spectrum of compound **3c**, the doublet of doublet at δ 5.27 ($J_{4,5}$=5.3, $J_{4,3}$=3.0 Hz) was attributed to proton H_b. The two doublets at δ 5.80 ($J_{5,4}$=5.3 Hz) and δ 5.91 ($J_{3,4}$=3.0 Hz) were attributed to protons H_c and H_a, respectively. Literature survey reveals that cis vicinal ^{1}H couplings are always higher (5–9 Hz) than the trans (0–6 Hz) in isoxazolidines.[14,15] In compound **3c**, the coupling constants of H_b,H_a=3.0 and H_b,H_c=5.3 Hz and hence protons at C3 and C5 are trans with proton at C4. The coupling between H_a, H_b, and H_c protons were also confirmed by H–H COSY spectrum of compound **3c**. One proton singlet at 7.99 ppm corresponds to pyrazole ring proton. The X-ray crystallographic

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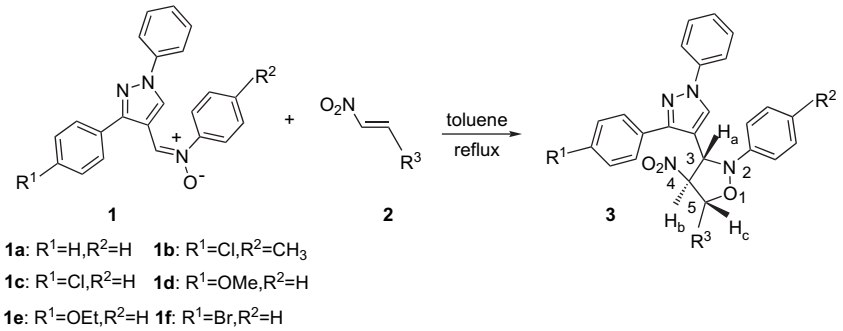


Scheme 1.

Table 1. Synthesis of 2,3,4,5-tetrasubstituted isoxazolidine

Entry	Nitrones	R^3	Product	*t* (h)	Yield[a] (%)
1	**1a**	Ph	**3a**	6	75
2	**1b**	Ph	**3b**	9	65
3	**1c**	Ph	**3c**	7	71
4	**1d**	Ph	**3d**	7	67
5	**1e**	Ph	**3e**	7.5	68
6	**1a**	4-OMeC_6H_4	**3f**	9.5	61
7	**1c**	4-OMeC_6H_4	**3g**	9	63
8	**1f**	Ph	**3h**	7	70

[a] Isolated yield of *endo*-diastereoisomer.

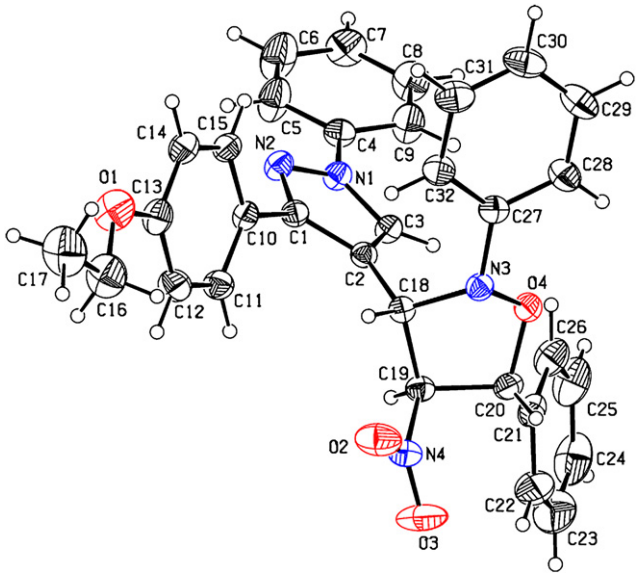


Figure 1. ORTEP diagram of compound **3e**.

structure (ORTEP projection) of one such *para*-ethoxy substituted cycloadduct **3e** is depicted in Figure 1.[16]

2.2. Reaction of pyrazolyl nitrone with ethyl vinyl ether

The reaction of nitrone **1** with ethyl vinyl ether **4** in toluene at 60 °C gave exclusively the 2,3,5-trisubstituted isoxazolidine **5** in moderate to good yield (Scheme 2).

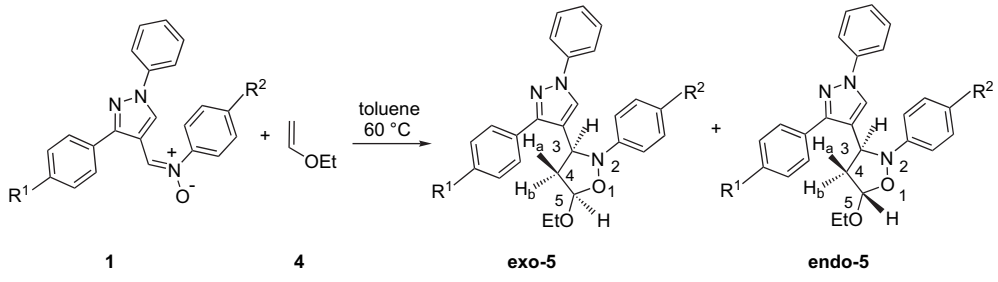
In all the reactions *exo*-diastereoisomer was the major product with de is >95%. The cycloadducts were characterized by spectral and elemental analysis. The results are summarized in Table 2.

The stereochemistry of the *exo*-diastereoisomer was confirmed by coupling constants and NOE measurements. In the ^{1}H NMR spectrum of **5e**, two doublet of doublet of doublets at δ 2.42 ($J_{4a,4b}$=13.0, $J_{4a,3}$=6.1, $J_{4a,5}$=2.3 Hz) and δ 2.96 ($J_{4b,4a}$=13.0, $J_{4b,3}$=9.2, $J_{4b,5}$=6.1 Hz) were assigned to protons C4–Ha and C4–Hb, respectively. The two doublet of doublets at δ 4.56 ($J_{3,4b}$=9.2 Hz, $J_{3,4a}$ =6.1 Hz) and δ 5.43 ($J_{5,4b}$=6.1 Hz, $J_{5,4a}$=2.3 Hz) were attributed to C3–H and C5–H. From the coupling constants, the protons at C3 and C5 were found to be cis to C4–Hb and trans to C4–Ha.

Table 2. Synthesis of 2,3,5-trisubstituted isoxazolidine

Entry	Nitrones	Product	*t* (h)	Yield[a] (%)	*exo*:*endo*[b]
1	**1a**	**5a**	4.0	72	98:2
2	**1c**	**5b**	4.5	69	96:4
3	**1d**	**5c**	4.5	63	97:3
4	**1e**	**5d**	5.0	62	97:3
5	**1f**	**5e**	4.5	68	95:5

[a] Isolated yield of *exo*-diastereoisomer.
[b] Determined by ^{1}H NMR spectroscopy of the crude product.



Scheme 2.

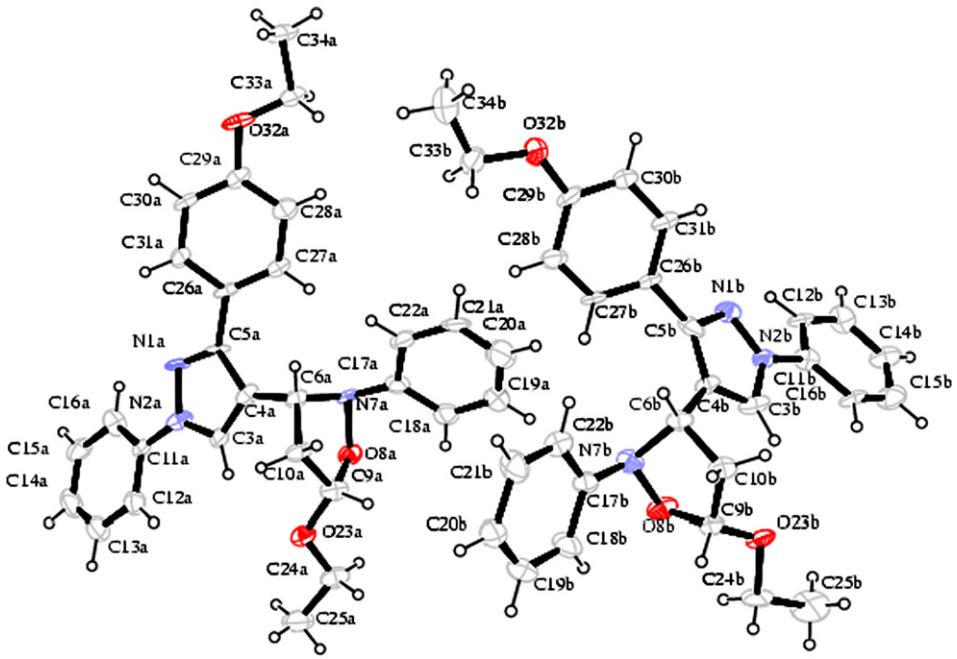


Figure 2. ORTEP diagram of compound **5d**.

In one-dimensional NOE measurements (Fig. 3) selective irradiation of C5–H proton induced enhancements of the vicinal proton C4–Hb (δ 2.96) and selective irradiation of C3–H proton enhanced the signal of C4–Hb (δ 2.96) proton. These observations clearly indicated that the C3–H and C5–H protons are cis to each other (Fig. 3).

The structure of **5d** was confirmed through single crystal X-ray diffraction studies (Fig. 2).[17]

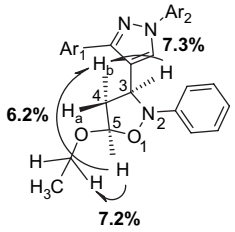


Figure 3. Characteristic NOE of compound **5e**.

3. Conclusion

In summary, the synthesis of some novel pyrazolyl isoxazolidine is reported for the first time. The adducts were obtained using highly regio and diastereoselective 1,3-dipolar cycloaddition strategy. Based on the inherent biological activity of the pyrazole unit, we anticipate that these novel pyrazolyl containing isoxazolidine will display enhanced activity.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were recorded on a Perkin–Elmer FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz, respectively. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX 6000 ESI spectrometer. Elemental analyses were recorded using a Thermo Finnigan FLASH EA 1112 CHN analyzer. Column chromatography was performed on silica gel (100–200 mesh, SRL, India). Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Merck, Germany).

4.2. Experimental procedure for compound 3

A mixture of pyrazolyl nitrone (0.5 mmol) and β-nitrostyrene (0.5 mmol) was refluxed in dry toluene (10 mL) until completion of the reaction as evidenced by TLC analysis. The solvent was evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethylacetate–petroleum ether (4:96) to afford pure isoxazolidine.

4.2.1. 3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-4-nitro-2,5-diphenyl-isoxazolidine (*endo* 3a). Yellow solid; 0.183 g; mp 170 °C; R_f 0.49 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3047, 1597, 1554, 1500, 1351 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.28 (dd, 1H, J=5.3, 3.0 Hz, C4–H), 5.76 (d, 1H, J=5.3 Hz, C5–H), 6.03 (d, 1H, J=3.0 Hz, C3–H), 7.05 (t, 1H, J=6.8 Hz, Ar–H), 7.13 (d, 2H, J=7.6 Hz, Ar–H), 7.29–7.33 (m, 3H, Ar–H), 7.39–7.47 (m, 10H, Ar–H), 7.65 (dd, 2H, J=6.8, 1.5 Hz, Ar–H), 7.69 (d, 2H, J=7.6 Hz, Ar–H), 8.02 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.5, 83.9, 99.9, 115.4, 118.4, 119.1, 123.4, 126.7, 126.9, 128.1, 128.3, 128.8, 129.0, 129.1, 129.3, 129.4, 129.6, 132.2, 135.5, 139.7, 148.3, 151.1; MS m/z=488 M$^+$. Anal. Calcd for $C_{30}H_{24}N_4O_3$ (488.54): C, 73.76; H, 4.95; N, 11.47. Found: C, 73.81; H, 4.87; N, 11.54.

4.2.2. 3-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-4-nitro-5-phenyl-2-*p*-tolyl-isoxazolidine (*endo* 3b). Colorless solid; 0.174 g; mp 128 °C; R_f 0.51 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3051, 1598, 1564, 1501, 1347 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 5.25 (dd, 1H, J=4.5, 3.8 Hz, C4–H), 5.78 (d, 1H, J=5.3 Hz, C5–H), 5.82 (d, 1H, J=3.8 Hz, C3–H), 7.02 (d, 2H, J=8.4 Hz, Ar–H), 7.10 (t, 1H, J=8.4 Hz, Ar–H), 7.28–7.33 (m, 3H, Ar–H), 7.39–7.46 (m, 7H, Ar–H), 7.57 (d, 2H, J=8.4 Hz, Ar–H), 7.65 (d, 2H, J=7.6 Hz, Ar–H), 7.96 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.8, 66.9, 83.2, 99.7, 116.4, 117.7, 119.1, 126.5, 127.1, 128.4, 129.1, 129.5, 129.6, 129.9, 130.1, 133.7, 134.8, 136.1, 139.6, 145.5, 150.1, 162.8; MS m/z=537 M^+. Anal. Calcd for $C_{31}H_{25}ClN_4O_3$ (537.02): C, 69.34; H, 4.69; N, 10.43. Found: C, 69.22; H, 4.75; N, 10.52.

4.2.3. 3-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-4-nitro-2,5-diphenyl-isoxazolidine (*endo* 3c). Yellow solid; 0.185 g; mp 134 °C; R_f 0.48 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3061, 1599, 1555, 1497, 1358 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.27 (dd, 1H, J=4.6, 3.0 Hz, C4–H), 5.80 (d, 1H, J=4.6 Hz, C5–H), 5.91 (d, 1H, J=3.0 Hz, C3–H), 7.07 (t, 1H, J=7.6 Hz, Ar–H), 7.13 (d, 2H, J=7.6 Hz, Ar–H), 7.30–7.47 (m, 12H, Ar–H), 7.60 (d, 2H, J=8.4 Hz, Ar–H), 7.66 (d, 2H, J=8.4 Hz, Ar–H), 7.99 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.7, 83.5, 99.7, 115.8, 118.0, 119.1, 123.8, 126.6, 127.1, 128.4, 129.1, 129.2, 129.3, 129.4, 129.6, 130.7, 134.9, 135.7, 139.6, 148.2, 150.0; MS m/z=523 M^+. Anal. Calcd for $C_{30}H_{23}ClN_4O_3$ (522.99): C, 68.90; H, 4.43; N, 10.71. Found: C, 68.83; H, 4.49; N, 10.75.

4.2.4. 3-[3-(4-Methoxy-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-4-nitro-2,5-diphenyl-isoxazolidine (*endo* 3d). Yellow solid; 0.173 g; mp 148 °C; R_f 0.41 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3062, 1601, 1554, 1497, 1351 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H, OCH_3), 5.29 (dd, 1H, J=5.3, 3.0 Hz, C4–H), 5.77 (d, 1H, J=5.3 Hz, C5–H), 5.97 (d, 1H, J=3.0 Hz, C3–H), 6.92 (d, 2H, J=9.2 Hz, Ar–H), 7.05 (t, 1H, J=7.6 Hz, Ar–H), 7.13 (d, 2H, J=7.6 Hz, Ar–H), 7.27–7.32 (m, 3H, Ar–H), 7.39–7.45 (m, 7H, Ar–H), 7.57 (d, 2H, J=8.4 Hz, Ar–H), 7.66 (d, 2H, J=7.6 Hz, Ar–H), 7.98 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.4, 66.7, 83.8, 99.8, 114.5, 115.5, 117.9, 119.0, 123.5, 124.7, 126.7, 126.8, 128.0, 129.1, 129.3, 129.3, 129.5, 129.6, 135.7, 139.8, 148.3, 150.9, 160.0; MS m/z=519 M^+. Anal. Calcd for $C_{31}H_{26}N_4O_4$ (518.57): C, 71.80; H, 5.05; N, 10.80. Found: C, 71.75; H, 5.01; N, 10.92.

4.2.5. 3-[3-(4-Ethoxy-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-4-nitro-2,5-diphenyl-isoxazolidine (*endo* 3e). Yellow solid; 0.181 g; mp 156 °C; R_f 0.47 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3047, 1600, 1553, 1497, 1375 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.42 (t, 3H, J=6.9 Hz, OCH_2CH_3), 4.05 (q, 2H, J=6.9 Hz, OCH_2CH_3), 5.29 (dd, 1H, J=4.6, 2.3 Hz, C4–H), 5.76 (d, 1H, J=4.6 Hz, C5–H), 5.98 (d, 1H, J=2.3 Hz, C3–H), 6.92 (d, 2H, J=8.4 Hz, Ar–H), 7.04 (t, 1H, J=7.6 Hz, Ar–H), 7.13 (d, 2H, J=7.6 Hz, Ar–H), 7.27–7.32 (m, 3H, Ar–H), 7.39–7.45 (m, 7H, Ar–H), 7.55 (d, 2H, J=8.4 Hz, Ar–H), 7.66 (d, 2H, J=7.6 Hz, Ar–H), 7.98 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 63.6, 66.6, 83.9, 99.8, 114.9, 115.5, 117.9, 119.0, 123.4, 124.5, 126.7, 126.8, 127.9, 129.1, 129.2, 129.3, 129.5, 129.6, 135.6, 139.8, 148.4, 150.9, 159.5; MS m/z=533 M^+. Anal. Calcd for $C_{32}H_{28}N_4O_4$ (532.60): C, 72.17; H, 5.30; N, 10.52. Found: C, 72.19; H, 5.26; N, 10.56.

4.2.6. 3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-(4-methoxy-phenyl)-4-nitro-2-phenyl-isoxazolidine (*endo* 3f). Yellow solid; 0.157 g; mp 142 °C; R_f 0.44 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3065, 1598, 1557, 1491, 1351 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 5.22 (dd, 1H, J=5.3, 2.3 Hz, C4–H), 5.66 (d, 1H, J=5.3 Hz, C5–H), 6.06 (d, 1H, J=3.1 Hz, C3–H), 6.89 (d, 2H, J=8.4 Hz, Ar–H), 7.03 (t, 1H, J=7.6 Hz, Ar–H), 7.11 (d, 2H, J=8.4 Hz, Ar–H), 7.25–7.32 (m, 6H, Ar–H), 7.38–7.46 (m, 4H, Ar–H), 7.64 (d, 2H, J=6.9 Hz, Ar–H), 7.70 (d, 2H, J=7.6 Hz, Ar–H), 8.08 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5, 65.5, 84.2, 100.1, 114.5, 115.1, 118.8, 119.1, 119.9, 123.2, 126.9, 127.9, 128.2, 128.4, 128.9, 129.1, 129.4, 129.6, 129.8, 131.0, 139.7, 148.5, 151.0, 160.5; MS m/z=518 M^+. Anal. Calcd for $C_{31}H_{26}N_4O_4$ (518.57): C, 71.80; H, 5.05; N, 10.80. Found: C, 71.66; H, 5.09; N, 10.88.

4.2.7. 3-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-(4-methoxy-phenyl)-4-nitro-2-phenyl-isoxazolidine (*endo* 3g). Colorless solid; 0.174 g; mp 132 °C; R_f 0.42 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3062, 1690, 1561, 1508, 1351 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 3H, OCH_3), 5.21 (dd, 1H, J=3.0, 5.3 Hz, C4–H), 5.70 (d, 1H, J=4.6 Hz, C5–H), 5.95 (d, 1H, J=3.0 Hz, C3–H), 6.90 (d, 2H, J=8.4 Hz, Ar–H), 7.05 (t, 1H, J=7.6 Hz, Ar–H), 7.11 (d, 2H, J=8.4 Hz, Ar–H), 7.25–7.33 (m, 5H, Ar–H), 7.38 (d, 2H, J=8.4 Hz, Ar–H), 7.45 (t, 2H, J=7.6 Hz, Ar–H), 7.61 (d, 2H, J=8.4 Hz, Ar–H), 7.69 (d, 2H, J=8.4 Hz, Ar–H), 8.06 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5, 66.6, 83.9, 99.8, 114.5, 115.4, 118.5, 119.1, 123.50 127.0, 127.1, 128.2, 128.3, 129.2, 129.4, 129.5, 129.6, 130.8, 131.9, 139.6, 148.4, 149.9, 160.4; MS m/z=553 M^+. Anal. Calcd for $C_{31}H_{25}ClN_4O_4$ (553.01): C, 67.33; H, 4.56; N, 10.13. Found: C, 67.41; H, 4.52; N, 10.25.

4.2.8. 3-[3-(4-Bromo-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-4-nitro-2,5-diphenyl-isoxazolidine (*endo* 3h). Colorless solid; 0.198 g; mp 134 °C; R_f 0.48 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 3068, 1594, 1564, 1498, 1374 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.29 (dd, 1H, J=5.3, 3.0 Hz, C4–H), 5.84 (d, 1H, J=5.3 Hz, C5–H), 5.93 (d, 1H, J=3.0 Hz, C3–H), 7.09 (t, 1H, J=7.6 Hz, Ar–H), 7.18 (d, 2H, J=7.6 Hz, Ar–H), 7.32–7.47 (m, 12H, Ar–H), 7.59 (d, 2H, J=6.9 Hz, Ar–H), 7.68 (d, 2H, J=6.9 Hz, Ar–H), 7.97 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 66.8, 84.0, 99.8, 115.6, 118.4, 119.2, 124.1, 126.9, 127.3, 128.6, 129.2, 129.3, 129.4, 129.5, 130.8, 135.1, 135.9, 139.6, 148.7, 150.2; MS m/z=567 M^+. Anal. Calcd for $C_{30}H_{23}BrN_4O_3$ (566.44): C, 63.50; H, 4.09; N, 9.87. Found: C, 63.62; H, 4.26; N, 9.74.

4.3. Experimental procedure for compound 5

A mixture of pyrazole nitrone (0.5 mmol) and ethyl vinyl ether (5 mmol) was refluxed in dry toluene (10 mL) at 60 °C until the completion of the reaction as evidenced by

TLC analysis. The solvent was evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethylacetate–petroleum ether (3:97) to afford pure isoxazolidine.

4.3.1. 3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-5-ethoxy-2-phenyl-isoxazolidine (*exo* 5a). Yellow solid; 0.148 g; mp 54 °C; R_f 0.48 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 2963, 1588, 1492, 1236, 1191, 1052 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=6.9 Hz, OCH_2CH_3), 2.44 (ddd, 1H, J=13.0, 5.3, 1.5 Hz, C4–Ha), 2.99 (ddd, 1H, J=13.7, 9.2, 6.9 Hz, C4-Hb), 3.64 (dq, 1H, J=9.9, 6.8 Hz, OCH_2CH_3), 4.02 (dq, 1H, J=9.1, 6.8 Hz, OCH_2CH_3), 4.64 (dd, 1H, J=9.1, 5.3 Hz, C3–H), 5.43 (dd, 1H, J=6.1, 1.5 Hz, C5–H), 6.96 (t, 1H, J=7.6 Hz, Ar–H), 7.01 (d, 2H, J=7.6 Hz, Ar–H), 7.18 (t, 2H, J=6.8 Hz, Ar–H), 7.27 (t, 1H, J=7.6 Hz, Ar–H), 7.37–7.45 (m, 5H, Ar–H), 7.62 (d, 2H, J=6.8 Hz, Ar–H), 7.75 (d, 2H, J=7.6 Hz, Ar–H), 8.26 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4, 45.3, 60.9, 64.1, 101.5, 116.9, 118.9, 121.9, 123.0, 126.4, 127.6, 128.2, 128.5, 128.7, 128.8, 129.5, 133.2, 140.1, 150.1, 151.1; MS m/z=412 M^+. Anal. Calcd for $C_{26}H_{25}N_3O_2$ (411.50): C, 75.89; H, 6.12; N, 10.21. Found: C, 75.95; H, 6.19; N, 10.09.

4.3.2. 3-[3-(4-Chloro-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-ethoxy-2-phenyl-isoxazolidine (*exo* 5b). Yellow solid; 0.153 g; mp 42 °C; R_f 0.50 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 2959, 1599, 1500, 1249, 1181, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, 3H, J=6.9 Hz, OCH_2CH_3), 2.43 (ddd, 1H, J=13.0, 6.1, 2.3 Hz, C4–Ha), 2.96 (ddd, 1H, J=13.0, 9.2, 6.1 Hz, C4–Hb), 3.63 (dq, 1H, J=9.9, 7.6 Hz, OCH_2CH_3), 4.01 (dq, 1H, J=9.9, 7.6 Hz, OCH_2CH_3), 4.57 (dd, 1H, J=9.2, 6.1 Hz, C3–H), 5.44 (dd, 1H, J=6.1, 2.3 Hz, C5–H), 6.97–7.02 (m, 3H, Ar–H), 7.20 (t, 2H, J=8.4 Hz, Ar–H), 7.28 (t, 1H, J=6.8 Hz, Ar–H), 7.39 (d, 2H, J=8.4 Hz, Ar–H), 7.42 (t, 2H, J=7.6 Hz, Ar–H), 7.56 (d, 2H, J=8.4 Hz, Ar–H), 7.74 (d, 2H, J=7.6 Hz, Ar–H), 8.24 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4, 45.1, 61.2, 64.1, 101.4, 117.1, 118.9, 121.6, 123.3, 126.6, 127.9, 128.8, 128.9, 129.5, 129.7, 131.7, 134.2, 139.9, 149.9, 150.0; MS m/z=445 M^+. Anal. Calcd for $C_{26}H_{24}ClN_3O_2$ (445.95): C, 70.03; H, 5.42; N, 9.42. Found: C, 70.09; H, 5.38; N, 9.52.

4.3.3. 5-Ethoxy-3-[3-(4-methoxy-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-phenyl-isoxazolidine (*exo* 5c). Yellow solid; 0.139 g; mp 44 °C; R_f 0.40 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 2878, 1597, 1498, 1200, 1114, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=7.6 Hz, OCH_2CH_3), 2.43 (ddd, 1H, J=13.0, 6.1, 2.3 Hz, C4–Ha), 2.98 (ddd, 1H, J=13.0, 9.2, 6.1 Hz, C4–Hb), 3.64 (dq, 1H, J=9.9, 6.8 Hz, OCH_2CH_3), 3.84 (s, 3H, OCH_3), 4.02 (dq, 1H, J=9.9, 6.9 Hz, OCH_2CH_3), 4.61 (dd, 1H, J=9.2, 6.1 Hz, C3–H), 5.43 (dd, 1H, J=6.1, 2.3 Hz, C5–H), 6.95–6.98 (m, 3H, Ar–H), 7.02 (d, 2H, J=8.4 Hz, Ar–H), 7.19 (t, 2H, J=8.4 Hz, Ar–H), 7.25 (t, 1H, J=7.6 Hz, Ar–H), 7.43 (t, 2H, J=7.6 Hz, Ar–H), 7.56 (d, 2H, J=8.4 Hz, Ar–H), 7.74 (d, 2H, J=8.4 Hz, Ar–H), 8.23 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4, 45.3, 55.4, 61.0, 64.1, 101.5, 114.1, 116.9, 118.9, 121.5, 123.0, 125.7, 126.3, 127.5, 128.7, 129.4, 129.7, 140.1, 150.1, 150.9, 159.7; MS m/z=442 M^+. Anal. Calcd for $C_{27}H_{27}N_3O_3$ (441.53): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.48; H, 6.11; N, 9.50.

4.3.4. 5-Ethoxy-3-[3-(4-ethoxy-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-phenyl-isoxazolidine (*exo* 5d). Yellow solid; 0.141 g; mp 104 °C; R_f 0.43 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 2977, 1597, 1493, 1241, 1112, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=7.6 Hz, OCH_2CH_3), 1.41 (t, 3H, J=6.9 Hz, OCH_2CH_3), 2.44 (ddd, 1H, J=13.0, 6.1, 2.3 Hz, C4–Ha), 2.97 (ddd, 1H, J=13.0, 8.4, 6.1 Hz, C4–Hb), 3.62 (dq, 1H, J=9.1, 7.6 Hz, OCH_2CH_3), 4.02 (dq, 1H, J=9.1, 7.6 Hz, OCH_2CH_3), 4.05(q, 2H, J=6.9 Hz, OCH_2CH_3), 4.64 (dd, 1H, J=8.4, 6.1 Hz, C3–H), 5.45 (dd, 1H, J=6.1, 2.3 Hz, C5–H), 6.97–6.99 (m, 3H, Ar–H), 7.01 (d, 2H, J=8.6 Hz, Ar–H), 7.18 (t, 2H, J=8.6 Hz, Ar–H), 7.28 (t, 1H, J=7.9 Hz, Ar–H), 7.41 (t, 2H, J=7.9 Hz, Ar–H), 7.59 (d, 2H, J=8.4 Hz, Ar–H), 7.76 (d, 2H, J=8.4 Hz, Ar–H), 8.24 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8, 15.3, 45.2, 60.9, 63.5, 63.9, 101.4, 114.1, 116.9, 118.8, 121.4, 122.9, 125.5, 126.2, 127.4, 128.7, 129.3, 129.6, 140.1, 150.0, 150.9, 158.9; MS m/z=455 M^+. Anal. Calcd for $C_{28}H_{29}N_3O_3$ (455.55): C, 73.82; H, 6.42; N, 9.22. Found: C, 73.78; H, 6.48; N, 9.32.

4.3.5. 3-[3-(4-Bromo-phenyl)-1-phenyl-1*H*-pyrazol-4-yl]-5-ethoxy-2-phenyl-isoxazolidine (*exo* 5e). Colorless solid; 0.166 g; mp 102 °C; R_f 0.48 (20% ethylacetate–petroleum ether); ν_{max} (KBr): 2878, 1597, 1498, 1200, 1114, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (t, 3H, J=6.9 Hz, OCH_2CH_3), 2.42 (ddd, 1H, J=13.0, 6.1, 2.3 Hz, C4–Ha), 2.96 (ddd, 1H, J=13.0, 9.2, 6.1 Hz, C4–Hb), 3.63 (dq, 1H, J=9.1, 6.8 Hz, OCH_2CH_3), 4.01 (dq, 1H, J=9.1, 6.8 Hz, OCH_2CH_3), 4.56 (dd, 1H, J=9.1, 6.1 Hz, C3–H), 5.43 (dd, 1H, J=6.9, 2.3 Hz, C5–H), 6.97–7.01 (m, 3H, Ar–H), 7.20 (t, 2H, J=8.4 Hz, Ar–H), 7.27 (t, 1H, J=6.9 Hz, Ar–H), 7.44 (t, 2H, J=8.4 Hz, Ar–H), 7.49 (d, 2H, J=6.9 Hz, Ar–H), 7.54 (d, 2H, J=8.4 Hz, Ar–H), 7.73 (d, 2H, J=7.6 Hz, Ar–H), 8.24 (s, 1H, pyrazolyl–H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4, 45.1, 61.2, 64.1, 101.4, 117.1, 118.9, 121.6, 122.4, 123.3, 126.7, 127.9, 128.8, 129.5, 130.0, 131.8, 132.1, 139.9, 149.9; MS m/z=490 M^+. Anal. Calcd for $C_{26}H_{24}BrN_3O_2$ (489.40): C, 63.68; H, 4.93; N, 8.57. Found: C, 63.78; H, 4.85; N, 8.69.

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17. Crystallographic data for the structure **5d** in this paper have been deposited with the Cambridge Crystallographic Data centre as supplemental publication no. CCDC-655418. Copies of the data can be obtained, free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 01223 336033 or email: deposit@ccdc.cam.ac.uk).