Diastereoselectivity in the Cycloaddition of 1-Benzyl-2-piperazinone Nitrone with Alkenes

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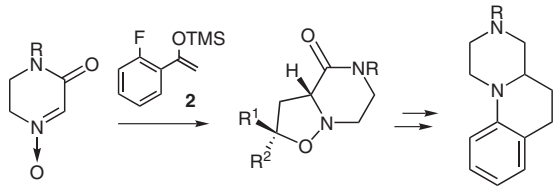
Abstract: The diastereoselectivity of the [2 + 3]-cycloaddition of 1-benzyl-2-piperazinone nitrone with several alkenes has been examined. *exo*-Type cycloadducts predominated for most substrates.

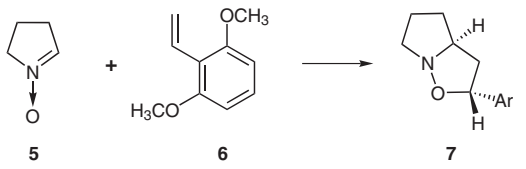
Key words: cycloadditions, diastereoselectivity, heterocycles, substituent effects, bicyclic compounds, nitrone, alkenes

Nitrone cycloadditions are powerful reactions for the assembly of complex structures.[2] Our own interest in nitrones both as radical scavengers[3] and as intermediates for medicinal agents led us to synthesize nitrone **1**. This nitrone readily underwent [2 + 3] cycloaddition reactions with alkynes and alkenes to give isoxazolines and isoxazolidines, respectively.[4] These cycloadducts provided access to 3-substituted 2-piperazinones which served as precursors to more complex heterocyclic systems such as constrained aryl piperazine **4** (Scheme 1).[5] While our initial work focused primarily on substrates in which diastereomeric product mixtures were not possible, cycloaddition with unsymmetrical alkenes could produce diastereomers. For example, reaction of **1** with silyl enol ether **2** gave a 7:1 ratio of **3a** and **3b**, respectively. Our desire to introduce substituents on the 2-piperazinone sidechain, with stereochemical control, led us to investigate the diastereoselectivity of the cycloaddition of nitrone **1** with a variety of unsymmetrical alkenes.



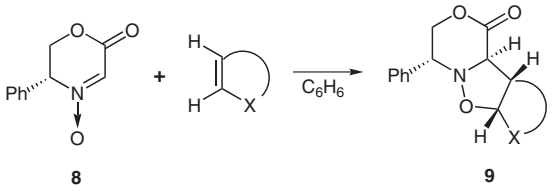
Scheme 1 R = CH_2Ph

Diastereoselectivity in the reaction of cyclic nitrones and alkenes has been extensively investigated by other workers.[6] In an early example, Tufariello and Ali obtained a single product **7** from the cycloaddition of 1-pyrrolidine 1-oxide (**5**) with styrene (**6**) (Scheme 2).[7] This diastereomer, which arises from an *exo*-type addition, was carried on to (±)-elaeocarpine and (±)-isoelaeocarpine.



Scheme 2

Tamura and coworkers reported good to excellent diastereoselectivity in the reaction of chiral nitrone **8** with a variety of alkenes to give cycloadducts **9** as the major or exclusive stereoisomer (Scheme 3).[8] Again, *exo*-mode addition predominated. Cleavage of the morpholinone ring in **9** removed the chiral auxiliary to reveal an amino acid. From these reports, we expected to observe high diastereoselectivity favoring *exo*-mode addition in the cycloaddition of **1** with unsymmetrical alkenes.



Scheme 3 X = O, NR′

Nitrone **1** was prepared in a straightforward manner (Scheme 4).[4] Protected 2-piperazinone **10** was alkylated with benzyl bromide to afford **11** which was deprotected with neat TFA to provide **12**. The secondary amine was oxidized regioselectively to nitrone **1** using hydrogen peroxide with sodium tungstate as a catalyst.[9] Although stable at ambient temperatures for at least several months, nitrone **1** readily reacts with monosubstituted alkenes under very mild conditions. Typically, the reactions were run in dichloromethane for 2–4 days at ambient temperatures using a 3:1 ratio of alkene–nitrone. In the case of 1-hexene, additional alkene was added. The reaction mixtures were simply concentrated in vacuo and purified by flash chromatography to afford isoxazolidines **13**–**19**. Diastereomeric mixtures were separable by this method.

The [2 + 3] cycloadditions gave good to excellent yields and only one regioisomer was isolated. The high regioselectivity is well precedented in related nitrone reactions

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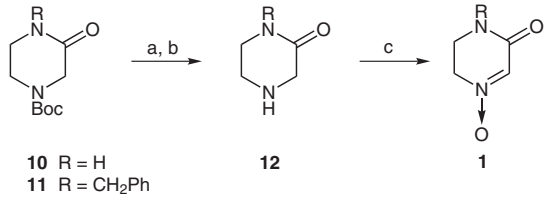
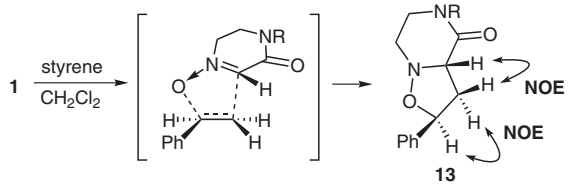


Scheme 4 a) NaH–DMF–$PhCH_2Br$; b) TFA; c) $Na_2WO_4 \cdot 2\ H_2O$–30% H_2O_2–EtOH

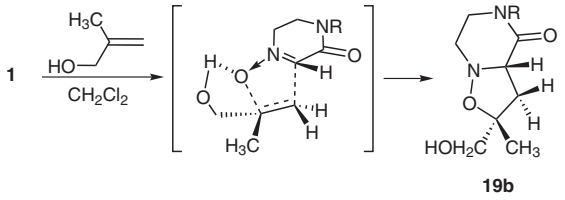
and is consistent with HOMO–LUMO arguments made by others.[10] In reactions using simple hydrocarbons such as styrene and 1-hexene, the cycloaddition was highly diastereospecific. Based on the NOE pattern exhibited by the isoxazolidine protons, the relative stereochemical assignments of the newly formed asymmetric centers were as shown for styrene in Scheme 5. The diastereomer produced for each of the hydrocarbon substrates was that expected from an *exo*-mode of addition, consistent with the well-precedented preference of cyclic nitrones for this mode of addition.[6–8]



Scheme 5 R = CH_2Ph

The cycloaddition of nitrone **1** with hydroxy-bearing substrates was also investigated. Slightly lower diastereoselectivity was observed with allyl alcohol and with its one carbon homolog, 3-buten-1-ol, although the product resulting from an *exo*-mode addition still predominated. This slight erosion in selectivity may have arisen from hydrogen bonding between the substrate hydroxy group and the nitrone oxygen, which would tend to reverse the orientation of the alkene and thus enhance *endo*-mode addition. In the final cycloaddition, 3-hydroxy-2-methyl-1-propene was chosen as a hydroxy-bearing substrate in which the steric requirements of the alkene substituents are more balanced. With the steric effects minimized, the contribution of the hydroxy group to diastereoselectivity should be enhanced. In this case, the *endo*-mode of cycloaddition was favored (13:87 ratio of **19a**–**19b**) indicating hydrogen bonding played a major role in determining the facial selectivity (Scheme 6). The reaction still proceeded in high yield.

In conclusion, we have shown that the cycloaddition of nitrone **1** with several alkenes proceeded regiospecifically. High diastereoselectivity was observed in cycloadditions of the nitrone with mono-substituted alkenes lacking a hydroxy group, consistent with *exo*-mode addition. The diastereoselectivity decreased somewhat for mono-substituted alkenes, allyl alcohol and 3-buten-1-ol, while for the more sterically balanced geminally substituted alkene, hydrogen-bonding effects apparently favored an *endo*-type addition. Applications of nitrone **1** are currently under investigation.



Scheme 6 R = CH_2Ph

Reaction solvents were Aldrich anhyd grade except for CH_2Cl_2, which was obtained from EM Sciences and used as received. Mps were determined using a Thomas–Hoover apparatus and are uncorrected. ^1H NMR spectra were obtained on Varian Gemini-300, Unity-300 and Unity-400 spectrometers. Chromatography refers to flash chromatography on silica gel.

4-Benzyl-3-oxopiperazine-1-carboxylic Acid *tert*-Butyl Ester (11)

A stirred solution of **10**[11] (10.01 g, 50.0 mmol) in anhyd DMF (50 mL) under nitrogen was treated with benzyl bromide (6.00 mL, 50.0 mmol). Sodium hydride (60% in an oil dispersion, unwashed, 2.00 g, 50.0 mmol) was added in portions over 10 min. Gas and heat evolved. After 18 h, Et_2O (400 mL) and H_2O (200 mL) were added to the reaction mixture and the layers were separated. The ethereal layer was washed with H_2O (100 mL) and brine (100 mL) and then dried ($MgSO_4$), suction filtered and concentrated in vacuo to a white solid. This product was stirred with hexanes (100 mL) for 30 min, and then suction filtered. The white solid was air-dried and then vacuum-dried to afford **11**.

Yield: 10.8 g (37.2 mmol, 74%); mp 85–87 °C.

IR (KBr): 1701, 1688, 1643, 1425, 1248, 1171 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.26 (5 H), 4.62 (2 H, s), 4.16 (2 H, s), 3.58 (2 H, app. t, *J* = 5.4 Hz), 3.25 (2 H, app. t, *J* = 5.3 Hz), 1.45 (9 H, s).

^{13}C NMR ($CDCl_3$): δ = 165.7, 153.8, 136.1, 128.7, 128.2, 127.7, 80.6, 49.9, 47.8 (br), 45.5, 40.1 (br), 28.3.

MS (CI; CH_4): *m/z* (%) = 291 (10), 263 (20), 235 (100).

Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.33; H, 7.77; N, 9.68.

1-Benzylpiperazin-2-one (12)

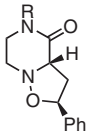
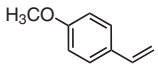
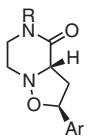
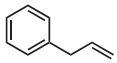
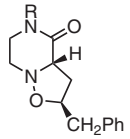
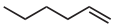
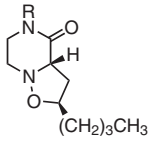
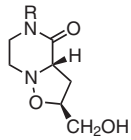
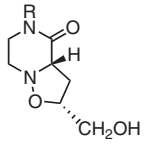
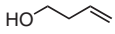
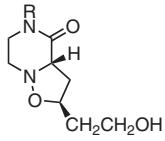
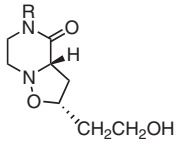
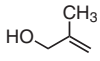
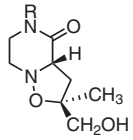
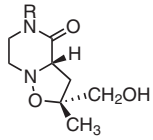
Compound **11** (10.7 g, 36.9 mmol) in a flask cooled to 0 °C was treated with TFA (40 mL). Gas evolved. After 20 min, the reaction was concentrated in vacuo at ca. 40 °C and the resulting viscous liquid was carefully treated with sat. aq $NaHCO_3$ (150 mL). Gas evolved. Additional solid $NaHCO_3$ was added until gas evolution had ceased and the solution was basic (pH ca. 9). The reaction mixture was diluted with H_2O (ca. 50 mL) and extracted with 40–60 EtOH–CH_2Cl_2 (4 × 250 mL). The combined extracts were washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated in vacuo to give **12** as a viscous liquid.

Yield: 5.95 g (31.3 mmol, 85%).

IR ($CHCl_3$): 1636 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.25 (5 H), 4.60 (2 H, s), 3.59 (2 H, s), 3.22 (2 H, app. t, *J* = 6.5 Hz), 3.03 (2 H, app. t, *J* = 6.5 Hz), 1.83 (1 H, br s).

Table 1 Diastereoselectivity of the Reaction of Nitrone **1** with Alkenes

Entry	Alkene	Reaction time (h)	Cycloadducts (R = CH_2Ph) *exo*	*endo*	Ratio *exo–endo*	Combined yield (%)
1		72	 **13**	not detected[a]	>98:2[a]	87
2		90	 **14**	not detected[a]	>98:2[a]	90
3		72	 **15**	not detected[a]	>98:2[a]	91
4		90	 **16**	not detected[a]	>98:2[a]	91
5		48	 **17a**	 **17b**	92:8	92
6		48	 **18a**	 **18b**	96:4	95
7		48	 **19a**	 **19b**	13:87	90

[a] Proton NMR showed essentially one diastereomer.

^{13}C NMR ($CDCl_3$): δ = 167.8, 136.6, 128.6, 128.1, 127.4, 50.3, 49.7, 47.1, 43.1.

MS (CI; CH_4): *m*/*z* (%) = 191 (100).

1-Benzyl-4-oxy-5,6-dihydro-1*H*-pyrazin-2-one (1)

To a stirred solution of **12** (5.88 g, 30.9 mmol) in EtOH (150 mL) was added $Na_2WO_4 \cdot 2\,H_2O$ (0.50 g, 1.54 mmol), aq hydrogen peroxide (30%; 7.0 mL, 68 mmol), and H_2O (7.5 mL). After 6 h, the reaction mixture was treated with brine (75 mL) and extracted with CH_2Cl_2 (2 × 150 mL). The combined extracts were dried ($MgSO_4$), filtered through a pad of Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography [EtOAc and then EtOH–EtOAc (10:90) to give **1** (5.13 g; R_f ca. 0.25 in EtOAc] as a viscous oil with trace contaminants by TLC analysis. This product partially solidified on standing. Trituration with Et_2O (ca. 100 mL) afforded **1**.

Yield: 4.40 g (21.6 mmol, 70%); very slightly yellow solid; mp 72–73 °C.

IR (KBr): 1649, 1566, 1217 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.25 (5 H), 7.19 (1 H, s), 4.65 (2 H, s), 4.01 (2 H, t, *J* = 6.3 Hz), 3.53 (2 H, t, *J* = 6.5 Hz).

^{13}C NMR ($CDCl_3$): δ = 159.1, 135.5, 129.0, 128.2, 128.2, 58.7, 49.1, 42.0.

MS (EI): *m*/*z* (%) = 204 (100), 132 (85), 91 (100).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.67; H, 5.90; N, 13.66.

Cycloaddition of Nitrone 1 with Alkenes; General Procedure

A stirred solution of alkene (3.00 mmol) in CH_2Cl_2 (2.0 mL) under nitrogen at r.t. (ca. 18 °C) was treated with nitrone **1** (204 mg, 1.00 mmol). The reaction mixtures were concentrated in vacuo when TLC analysis using EtOAc as eluent indicated complete (or near complete) consumption of nitrone. Reaction times were as shown in Table 1. The residue after concentration was purified by flash chromatography to give the products. Ratios of diastereomers were determined based on isolated products.

5-Benzyl-2-phenyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (13)

The product was purified by chromatography (EtOAc–hexane, 75:25) to give **13**.

Yield: 270 mg (87%); off-white solid; R_f ca. 0.38 in EtOAc; mp 94.5–96.0 °C.

IR (KBr): 3437, 3031, 1635, 1497, 1260, 747, 698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.26 (10 H), 5.24 (1 H, dd, *J* = 6.1, 8.3 Hz), 4.69 (1 H, d, *J* = 14.5 Hz), 4.59 (1 H, d, *J* = 14.6 Hz), 4.30 (1 H, dd, *J* = 6.8, 8.3 Hz), 3.46 (1 H, m), 3.35–3.25 (3 H, m), 3.04 (1 H, ddd, *J* = 6.5, 8.5, 12.9 Hz), 2.74 (1 H, ddd, *J* = 6.1, 8.6, 12.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 168.1, 141.1, 136.2, 128.8, 128.6, 128.1, 127.9, 127.7, 126.1, 78.2, 64.3, 49.7, 48.2, 42.6, 42.0.

MS (CI; CH_4): *m*/*z* (%) = 309 (100).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.97; H, 6.68; N, 9.07.

5-Benzyl-2-(4-methoxyphenyl)tetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (14)

Crude product was chromatographed (EtOAc–hexane, 75:25) to give **14**.

Yield: 300 mg (90%); off-white solid; R_f ca. 0.34 in EtOAc; mp 106.0–107.5 °C.

IR (KBr): 3432, 2930, 1638, 1514, 1493, 1251, 1174, 1031, 834, 698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.38–7.25 (7 H), 6.89 (2 H, br d, *J* = 8.8 Hz), 5.19 (1 H, dd, *J* = 6.7, 8.4 Hz), 4.70 (1 H, d, *J* = 14.4 Hz), 4.58 (2 H, d, *J* = 14.4 Hz), 4.32 (1 H, br d, *J* = 7.7 Hz), 3.80 (3 H, s), 3.43 (1 H, m), 3.35–3.21 (3 H), 2.98 (1 H, ddd, *J* = 6.7, 8.3, 12.8 Hz), 2.72 (1 H, ddd, *J* = 6.2, 8.5, 12.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 168.2, 159.4, 136.2, 132.8, 128.8, 128.1, 127.8, 127.6, 114.0, 78.0, 64.6, 55.3, 49.7, 48.2, 42.6, 41.9.

MS (CI; CH_4): *m*/*z* (%) = 339 (100).

Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.75; H, 6.69; N, 8.08.

2,5-Dibenzyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (15)

The product was purified by chromatography (EtOAc–hexane, 75:25) to give **15**.

Yield: 294 mg (91%); off-white solid; R_f ca. 0.40 in EtOAc; mp 92.0–93.5 °C.

IR (KBr): 3437, 2929, 1634, 1498, 1453, 1259, 1073, 701 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35–7.19 (10 H), 4.66 (1 H, d, *J* = 14.7 Hz), 4.48 (1 H, d, *J* = 14.7 Hz), 4.48 (1 H, m), 4.08 (1 H, app. t, *J* = 7.7 Hz), 3.36–3.17 (4 H), 3.10 (1 H, m), 2.99 (1 H, dd, *J* = 6.5, 13.8 Hz), 2.80 (1 H, dd, *J* = 6.5, 13.8 Hz), 2.66–2.46 (2 H).

^{13}C NMR ($CDCl_3$): δ = 168.2, 137.6, 136.2, 129.4, 128.7, 128.5, 128.0, 127.7, 126.6, 77.5, 64.0, 49.6, 48.0, 42.7, 41.1, 38.4.

MS (CI; CH_4): *m*/*z* (%) = 323 (100), 203 (35).

5-Benzyl-2-butyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (16)

An additional portion of 1-hexene (0.37 mL, 3.0 mmol) was added after 42 h. The crude product was purified by chromatography (EtOAc) (to remove a small amount of unreacted nitrone **1**) to give **16**.

Yield: 263 mg (91%); R_f ca. 0.52 in EtOAc); off-white solid; mp 89–90 °C.

IR (KBr): 2935, 1637, 1499, 1454, 1264, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35–7.22 (5 H), 4.69 (1 H, d, *J* = 14.6 Hz), 4.50 (1 H, d, *J* = 14.6 Hz), 4.23 (1 H, m), 4.12 (1 H, app. t, *J* = 8 Hz), 3.35–3.06 (4 H), 2.64 (1 H, m), 2.38 (1 H, m), 1.65 (1 H, m), 1.52 (1 H, m), 1.45–1.35 (4 H), 0.90 (3 H, t, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$): δ = 168.3, 136.1, 128.6, 127.9, 127.5, 76.6, 63.9, 49.4, 47.8, 42.6, 38.8, 34.6, 27.9, 22.4, 13.8.

MS (CI; CH_4): *m*/*z* (%) = 289 (100), 203 (27).

HRMS (TOF ESI+): *m*/*z* calcd for $C_{17}H_{24}N_2O_3$ (+H): 289.1910; found: 289.1903.

5-Benzyl-2-hydroxymethyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (17a) and 5-Benzyl-2-hydroxymethyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (17b)

The crude product was purified eluting with EtOH–EtOAc (10:90) to separate the two diastereomers.

Compound 17a

Yield: 222 mg (85%); tan solid; R_f ca. 0.21 in EtOAc; mp 129–131 °C.

IR (KBr): 3204, 2929, 1646, 1492, 1449, 1352, 1260, 1092, 748, 700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.37–7.22 (5 H), 4.60 (2 H, s), 4.35 (1 H, m), 4.10 (1 H, dd, *J* = 5.9, 8.7 Hz), 3.73 (1 H, dd, *J* = 2.7, 11.9 Hz), 3.62 (1 H, dd, *J* = 5.0, 11.7 Hz), 3.49 (1 H, m), 3.25–3.15 (3 H), 2.64 (2 H, m), 1.32 (1 H, br s).

^{13}C NMR ($CDCl_3$): δ = 168.3, 135.2, 128.8, 128.0, 127.8, 77.1, 64.5, 63.8, 49.7, 42.6, 42.0 35.0.

MS (CI; CH_4): *m*/*z* (%) = 263 (100).

HRMS (TOF ESI+): *m*/*z* calcd for $C_{14}H_{18}N_2O_3$ (+H): 263.1390; found: 263.1389.

Compound 17b

Yield: 17.7 mg (7%); slightly yellow oil; R_f ca. 0.71 in EtOAc. By ^1H NMR, the sample contained 5% (ca.1 mg) of diastereomer **17a**.

IR (KBr): 3403, 2925, 1637, 1496, 1453, 1355, 731 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.36–7.23 (5 H), 4.70 (1 H, d, *J* = 14.6 Hz), 4.50 (1 H, d, *J* = 14.6 Hz), 4.20 (1 H, m), 4.11 (1 H, dd, *J* = 5.6, 8.7 Hz), 3.77 (1 H, dd, *J* = 2.9, 12.2 Hz), 3.58 (2 H, m), 3.39–3.21 (2 H), 3.10 (1 H, m), 2.72 (1 H, m), 1.87 (1 H, br s).

^{13}C NMR ($CDCl_3$): δ = 168.7, 136.2, 128.7, 128.1, 127.7, 78.5, 63.4, 63.2, 50.0, 48.3, 41.7, 35.2.

MS (CI; CH_4): *m*/*z* (%) = 263 (100).

5-Benzyl-2-(2-hydroxyethyl)tetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (18a) and 5-Benzyl-2-(2-hydroxyethyl)tetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (18b)

The crude product was eluted with EtOH–EtOAc (10:90, then 20:80) to separate the diastereomers. The combined mixed fractions were rechromatographed using EtOH–EtOAc (15:85).

Compound 18a
Yield: 251 mg (91%); waxy, off-white solid; R_f ca. 0.42 in EtOH–EtOAc (20:80); mp 81.5–82.5 °C.

IR (KBr): 3467, 1643, 1494, 1258, 1052, 1032, 704 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.35–7.22 (5 H), 4.64 (1 H, d, *J* = 14.5 Hz), 4.56 (1 H, d, *J* = 14.5 Hz), 4.46 (1 H, m), 4.13 (1 H, dd, *J* = 6.4, 8.8 Hz), 3.77 (2 H, br m), 3.41 (1 H, m), 3.26–3.12 (3 H), 2.73 (1 H, ddd, *J* = 6.2, 8.1, 12.7 Hz), 2.48 (1 H, ddd, *J* = 5.5, 8.9, 12.9 Hz), 2.30 (1 H, br s), 1.86 (2 H, m).

^{13}C NMR ($CDCl_3$): δ = 168.3, 136.2, 128.8, 128.0, 127.7, 75.2, 63.7, 60.0, 49.7, 47.8, 42.3, 38.9, 37.4.

MS (CI; CH_4): *m*/*z* (%) = 277 (100), 203 (32).

HRMS (TOF ESI+): *m*/*z* calcd for $C_{15}H_{20}N_2O_3$ (+H): 277.1547; found: 277.1541.

Compound 18b
Yield: 11.1 mg (4%); slightly orange oil; R_f ca. 0.28 in EtOH–EtOAc (20:80). By ^1H NMR, the sample contained 10% ca. 1 mg) of diastereomer **18a**.

IR ($CHCl_3$): 4311, 1632, 730, 705 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.37–7.23 (5 H), 4.61 (2 H, s), 4.20 (1 H, m), 4.09 (1 H, dd, *J* = 5.4, 9.0 Hz), 3.72 (2 H, br t, *J* = 5.9 Hz), 3.63 (1 H, ddd, *J* = 3.9, 9.3, 12.9 Hz), 3.36 (1 H, app. dt, *J* = 4.0, 13.6 Hz), 3.26 (1 H, ddd, *J* = 4.1, 9.4, 13.5 Hz), 3.07 (1 H, dt, *J* = 4.2, 12.0 Hz), 2.87 (1 H, ddd, *J* = 7.3, 9.0, 12.9 Hz), 2.25 (1 H, ddd, *J* = 5.4, 8.3, 12.7 Hz), 1.94–1.74 (2 H), 1.68 (1 H, br s).

^{13}C NMR ($CDCl_3$): δ = 169.1, 136.3, 128.7, 128.1, 127.7, 76.6 (coincident with the upfield line of $CDCl_3$), 63.0, 60.5, 50.1, 48.3, 41.5, 40.0, 37.2.

MS (CI; CH_4): *m*/*z* (%) = 277 (100), 203 (80).

5-Benzyl-2-hydroxymethyl-2-methyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (19a) and 5-Benzyl-2-hydroxymethyl-2-methyltetrahydroisoxazolo[2,3-*a*]pyrazin-4-one (19b)
The crude product was purified eluting with EtOH–EtOAc (10:90).

Compound 19a
Yield: 31.1 mg (11%); slightly orange solid; R_f ca. 0.18 in EtOAc; mp 102–104 °C (softened at ca. 85 °C).

IR (KBr): 3416, 1648 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.37–7.23 (5 H), 4.69 (1 H, d, *J* = 14.6 Hz), 4.57 (1 H, d, *J* = 14.6 Hz), 4.07 (1 H, dd, *J* = 3.2, 9.0 Hz), 3.74 (1 H, m), 3.56 (2 H, s), 3.40 (1 H, app. dt, *J* = 3.2, 14.2 Hz), 3.24 (1 H, ddd, *J* = 4.4, 10.5, 14.0 Hz), 3.02 (1 H, ddd, *J* = 2.8, 4.4, 12.2 Hz), 2.80 (1 H, dd, *J* = 9.1, 13.0 Hz), 2.47 (1 H, dd, *J* = 3.2, 12.9 Hz), 1.72 (1 H, br s), 1.23 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 169.1, 136.3, 128.7, 128.1, 127.7, 81.9, 70.0, 63.9, 50.2, 47.4, 41.6, 41.1, 22.3.

MS (CI; CH_4): *m*/*z* (%) = 277 (100).

Compound 19b
Yield: 217 mg (79%); waxy, slightly orange solid; R_f ca. 0.21 in EtOAc; mp 89–91 °C.

IR (KBr): 3396, 1617, 1498, 1048, 698 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.36–7.23 (5 H), 4.71 (1 H, d, *J* = 14.3 Hz), 4.48 (1 H, d, *J* = 14.3 Hz), 4.18 (1 H, app. t, *J* = 7.0 Hz), 3.57–3.43 (3 H), 3.34–3.22 (2 H), 3.15 (1 H, m), 2.68 (1 H, dd, *J* = 6.4, 12.5 Hz), 2.39 (1 H, dd, *J* = 8.1, 12.6 Hz), 1.84 (1 H, br s), 1.29 (3 H, s).

^{13}C NMR ($CDCl_3$): δ = 168.5, 136.2, 128.8, 128.2, 127.8, 83.3, 67.1, 64.2, 49.9, 48.5, 42.0, 40.7, 23.6.

MS (CI; CH_4): *m*/*z* (%) = 277 (100).

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.89; H, 7.31; N, 10.20.

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