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Diastereoselective reactions of 1,1,1-trichloro(trifluoro)-3-nitrobut-2-enes with 2-morpholinoalk-1-enes

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Characteristics of compounds **3b**, **4b**, *syn*-**5b**, *anti*-**5b**, **7a**, **8a,b** *and* **9a,b**.

*(4*R**,6*R**)-6-*tert*-Butyl-3-methyl-6-morpholino-4-trifluoromethyl-5,6-dihydro-4*H*-1,2-oxazine-2-oxide* **3b**. This compound was prepared from **1b** and **2** according to the procedure described for compound **3a**. Yield 56%, mp 131–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.10 (s, 9H, *t*-Bu), 2.21 (quint, 3H, Me, *J* 1.2 Hz), 2.23 (dd, 1H, H-5a, *J* 14.8, 10.7 Hz), 2.44 (dd, 1H, H-5b, *J* 14.8, 8.4 Hz), 2.92 (ddd, 2H, N(C*H*H)$_2$, *J* 12.5, 5.0, 3.9 Hz), 3.05–3.22 (m, 3H, N(CH*H*)$_2$, H-4), 3.45–3.58 (m, 4H, O(CH_2)$_2$). ^{19}F NMR (471 MHz, $CDCl_3$) δ: 93.8 (dq, CF_3, *J* 7.8, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 17.3 (q, 3-Me, $^4J_{C,F}$ 2.0 Hz), 23.7 (q, C-5, $^3J_{C,F}$ 2.0 Hz), 26.9 (*Me*$_3$C), 41.5 (q, C-4, $^2J_{C,F}$ 28.1 Hz), 42.8 (Me$_3$*C*), 48.2 (NCH_2), 68.5 (OCH_2), 99.3 (C-6), 115.2 (q, C-3, $^3J_{C,F}$ 1.6 Hz), 125.5 (q, CF_3, $^1J_{C,F}$ 281.5 Hz). IR (KBr, ν/cm^{-1}): 1618. Found (%): C, 51.69; H, 7.14; N, 8.57. Calc. for $C_{14}H_{23}F_3N_2O_3$ (%): C, 51.84; H, 7.15; N, 8.64.

*(3Z,5*R**,6*S**)-2,2-Dimethyl-3-morpholino-6-nitro-5-(trifluoromethyl)hept-3-ene syn*-**4b**. This compound was prepared from **1b** and **2** according to the procedure described for compound **4a** (24 h, ~20 °C). Yield 73%, mp 116–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.14 (s, 9H, *t*-Bu), 1.53 (d, 3H, Me, *J* 6.8 Hz), 2.95 (br s, 4H, N(CH_2)$_2$), 3.70 (t, 4H, O(CH_2)$_2$, *J* 4.5 Hz), 4.49 (dqd, 1H, H-5, *J* 10.6, 8.5, 6.8 Hz), 4.87 (quint, 1H, H-6, *J* 6.8 Hz), 5.16 (d, 1H, H-4, *J* 10.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 15.9 (qt, C-7, 130.6, 2.9 Hz), 30.0 (q.sept, C-1, *J* 126.0, 4.8 Hz), 40.4 (undec, C-2, *J* 3.6 Hz), 45.5 (dqm, C-5, *J* 133.2, 27.5 Hz), 52.7 (tm, N(CH_2)$_2$, *J* 134.7 Hz), 67.7 (tm, O(CH_2)$_2$, *J* 143.1 Hz), 80.9 (dqdq, C-6, $J_{C,H}$ 147.5, 3.9, 3.3 Hz, $^3J_{C,F}$ 1.9 Hz), 110.2 (ddq, C-4, $J_{C,H}$ 156.8, 7.6 Hz, $^3J_{C,F}$ 2.1 Hz), 125.5 (qddd, CF_3, $^1J_{C,F}$ 280.4 Hz, $J_{C,H}$ 7.8, 2.9, 2.0 Hz), 166.3 (m, C-3); ^{19}F NMR (471 MHz, $CDCl_3$) δ: 93.4 (d, CF_3, *J* 8.5 Hz). IR (KBr, ν/cm^{-1}): 1655, 1554, 1393, 1369, 1358. Found (%): C, 51.68; H, 7.42; N, 8.61. Calc. for $C_{14}H_{23}F_3N_2O_3$ (%): C, 51.84; H, 7.15; N, 8.64.

*(5*R**,6*S**)-2,2-Dimethyl-6-nitro-5-trifluoromethyl-3-heptanone syn-***5b**. A mixture of **4b** (3.24 g, 10.0 mmol), 25 ml of 0.5M HCl solution and 20 ml of ethanol was stirred for 4 h at 50 °C, cooled, and extracted with dichloromethane (3×3 ml). The combined extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to a yellow oil. Distillation (bp 76–78 °C, 2 Torr) afforded 1.73 g (68% yield) of *syn*-**5b** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (s, 9H, *t*-Bu), 1.59 (d, 3H, Me, *J* 6.8 Hz), 2.83 (dd, 1H, H-4a, *J* 18.6, 6.0 Hz), 2.89 (dd, 1H, H-4b, *J* 18.6, 5.5 Hz), 3.80–3.88 (m, 1H, H-5), 4.86 (qd, 1H, H-6, *J* 6.8, 4.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: 93.2 (d, CF_3, *J* 9.2 Hz). IR (neat, ν/cm^{-1}): 1710, 1561, 1369. Found (%): C, 47.06; H, 6.22; N, 5.47. Calc. for $C_{10}H_{16}F_3NO_3$ (%): C, 47.06; H, 6.32; N, 5.49.

*(5*R**,6*R**)-2,2-Dimethyl-6-nitro-5-trifluoromethyl-3-heptanone anti-***5b**. This compound was not obtained in pure form. Treatment of **3b** with water and then with diluted HCl gave a mixture of composition *anti*-**5b**/*syn*-**5b**/*syn*-**3b** = 28:38:34. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (s, 9H, *t*-Bu), 1.60 (d, 3H, Me, *J* 7.0 Hz), 2.81 (dd, 1H, H-4a, *J* 18.7, 5.7 Hz), 2.95 (dd, 1H, H-4b, *J* 8.7, 5.6 Hz), 3.64–3.74 (m, 1H, H-5), 4.83–4.90 (m, 1H, H-6). ^{19}F NMR (376 MHz, $CDCl_3$) δ: 93.6 (d, CF_3, *J* 9.2 Hz).

*(4*R**,6*R**)-6-*tert*-Butyl-3-methyl-6-piperidino-4-trichloromethyl-5,6-dihydro-4*H*-1,2-oxazine-2-oxide* **7a**. This compound was prepared by the procedure described for compound **3a**. Yield 48%, mp 118–119 °C. ^{1}H NMR (500 MHz, C_6D_6): ^{1}H NMR, δ: 0.93 (s, 9H, *t*-Bu), 1.13–1.30 (m, 6H, 3 CH_2), 2.20 (d, 3H, Me, *J* 0.6 Hz), 2.35 (dd, 1H, H-5a, *J* 15.0 9.27 Hz), 2.44.(dd, 1H, H-5a, *J* 15.0 8.31 Hz), 2.55–2.64 [m, 2H, N(C*H*H)$_2$], 2.73–3.00 [m, 2H, N(CH*H*)$_2$], 3.18 (m, H-4). IR (KBr, ν/cm^{-1}): 1599. Found (%): C, 48.46; H, 6.85; N, 7.46. Calc. for $C_{15}H_{25}Cl_3N_2O_3$ (%): C, 48.47; H, 6.78; N, 7.54.

*(4*R**,4a*R**,8a*R**)-3-Methyl-8a-morpholino-4-trichloromethyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine-2-oxide* **8a**. This compound was prepared from **1a** and *N*-cyclohexenylmorpholine according to the procedure described for compound **3a**.Yield 57%, mp 145–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.16 (tdd, 1H, H-6a, *J* 13.5, 12.8, 3.7 Hz), 1.38 (qd, 1H, H-7a, *J* 12.8, 2.6 Hz), 1.45 (td, 1H, H-8a, *J* 13.3, 2.9 Hz), 1.69 (m, 2H, H-6b, H-7b), 1.88 (tt, 1H, H-5a, *J* 13.7, 4.4 Hz), 1.97 (d, 1H, H-5b, *J* 13.7 Hz), 2.17 (br d, 1H, H-8b, *J* 13.3 Hz), 2.34 (s, 3H, Me), 2.94 (dt, 2H, N(C*H*H)$_2$, *J* 12.2, 4.8 Hz), 3.07 [dt, 2H, N(CH*H*)$_2$, *J* 12.2, 4.8 Hz], 3.12 (m, 1H, H-4a), 3.29 (d, 1H, H-4, *J* 4.5 Hz), 3.72 [t, 4H, O(CH$_2$)$_2$, *J* 4.8 Hz]. ^{1}H NMR (400 MHz, C_6D_6) δ: 0.6–1.9 (m, 8H, CH_2), 2.10 (s, 3H, Me), 2.59 [dt, 2H, N(C*H*H)$_2$, *J* 12.2, 4.8 Hz], 2.78 [dt, 2H, N(CH*H*)$_2$,

J 12.2, 4.8 Hz], 2.84 (d, 1H, H-4, *J* 4.5 Hz), 2.94–2.99 (m, 1H, H-4a), 3.38 [t, 4H, $O(CH_2)_2$, *J* 4.8 Hz]; ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4 (C-6), 21.5 (Me), 22.5 (C-7), 22.7 (C-8), 29.3 (C-5), 39.4 (C-4a), 45.1 (NCH_2), 62.6 (C-4), 67.6 (OCH_2), 102.0 (CCl_3), 102.4 (C-8a), 119.6 (C-3). IR (KBr, ν/cm^{-1}): 1596. Found (%): C, 45.26; H, 5.82; N, 7.65. Calc. for $C_{14}H_{21}Cl_3N_2O_3$ (%): C, 45.24; H, 5.69; N, 7.54.

*(4*R**,4a*R**,8a*R**)-3-Methyl-8a-morpholino-4-trifluoromethyl-4a,5,6,7,8,8a-hexahydro-4*H*-1,2-benzoxazine-2-oxide* **8b**. This compound was prepared from **1b** and *N*-cyclohexenylmorpholine in hexane according to the procedure described for compound **3a**.Yield 71%, mp 99–100 °C. ^1H NMR (400 MHz, C_6D_6) δ: 0.84 (m, 1H, CH), 0.98–1.50 (m, 6H, $3CH_2$), 1.50 (d, 1H, CH, *J* 13.0 Hz), 1.95 (s, 3H, Me), 2.36–2.57 [m, 6H, H-4, H-4a, $N(CH_2)_2$], 3.38 [t, 4H, $O(CH_2)_2$, *J* 4.4 Hz]. ^{19}F NMR (376 MHz, C_6D_6) δ: 96.3 (br s, CF_3). IR (KBr, ν/cm^{-1}): 1621. Found (%): C, 52.13; H, 6.60; N, 8.39. Calc. for $C_{14}H_{21}F_3N_2O_3$ (%): C, 52.17; H, 6.57; N, 8.69.

*(5*R**,6*R**)-4-Nitro-1-phenyl-3-trichloromethyl-1-pentanone anti-***9a**.Yield 86%, mp 103–104 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.64 (d, 3H, Me, *J* 7.0 Hz), 3.66 (dd, 1H, H-2a, *J* 19.1, 3.6 Hz), 3.96 (dd, 1H, H-2b, *J* 19.1, 5.4 Hz), 4.08 (ddd, 1H, H-3, *J* 5.4, 3.6, 2.6 Hz), 5.54 (qd, 1H, H-4, *J* 7.0, 2.6 Hz), 7.51–7.60 (m, 2H, H_m), 7.65 (tt, 1H, H_p, *J* 7.4, 1.3 Hz), 8.05–8.08 (m, 2H, H_o). IR (KBr, ν/cm^{-1}): 1687, 1554, 1359. Found (%): C, 44.40; H, 3.84; N, 4.34. Calc. for $C_{12}H_{12}Cl_3NO_3$ (%): C, 44.40; H, 3.73; N, 4.32.

*(5*R**,6*R**)-4-Nitro-1-phenyl-3-trifluoromethyl-1-pentanone anti-***9b** *and (5*R**,6*S**)-4-nitro-1-phenyl-3-trifluoromethyl-1-pentanone syn-***9b**. Yield 75%, bp 142–144 °C, 2 Torr. ^1H NMR (400 MHz, $CDCl_3$) δ: *syn*-**9b** (52%): 1.64 (dq, 3H, Me, *J* 6.9, 0.5 Hz), 3.36 (AB-system, 2H, CH_2, *J* 18.7, 5.5 Hz), 4.02–4.13 (m, 1H, H-3), 4.90–5.00 (m, 1H, H-4), 7.52 (t, 2H, H_m, *J* 7.6 Hz), 7.64 (tt, 1H, H_p, *J* 7.5, 1.4 Hz), 7.97 (d, 2H, H_o, *J* 7.5 Hz), *anti*-**9b** (48%): 1.65 (dq, 3H, Me, *J* 7.0, 0.8 Hz), 3.40 (dd, 1H, H-2a, *J* 18.7, 5.6 Hz), 3.42 (dd, 1H, H-2b, *J* 18.7, 5.0 Hz), 3.90–4.00 (m, 1H, H-3), 4.90–5.00 (m, 1H, H-4), 7.51 (t, 2H, H_m, *J* 7.6 Hz), 7.63 (tt, 1H, H_p, *J* 7.5, 1.4 Hz), 7.99 (d, 2H, H_o, *J* 7.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: *syn*-**9b** (52%): 93.1 (dq, CF_3, *J* 9.2, 0.5 Hz), *anti*-**9b** (48%): 93.7 (dq, CF_3, *J* 9.3, 0.8 Hz). IR (neat, ν/cm^{-1}): 1692, 1598, 1582, 1559, 1394, 1360. Found (%): C, 52.36; H, 4.50; N, 5.06. Calc. for $C_{12}H_{12}F_3NO_3$ (%): C, 52.37; H, 4.39; N, 5.09.

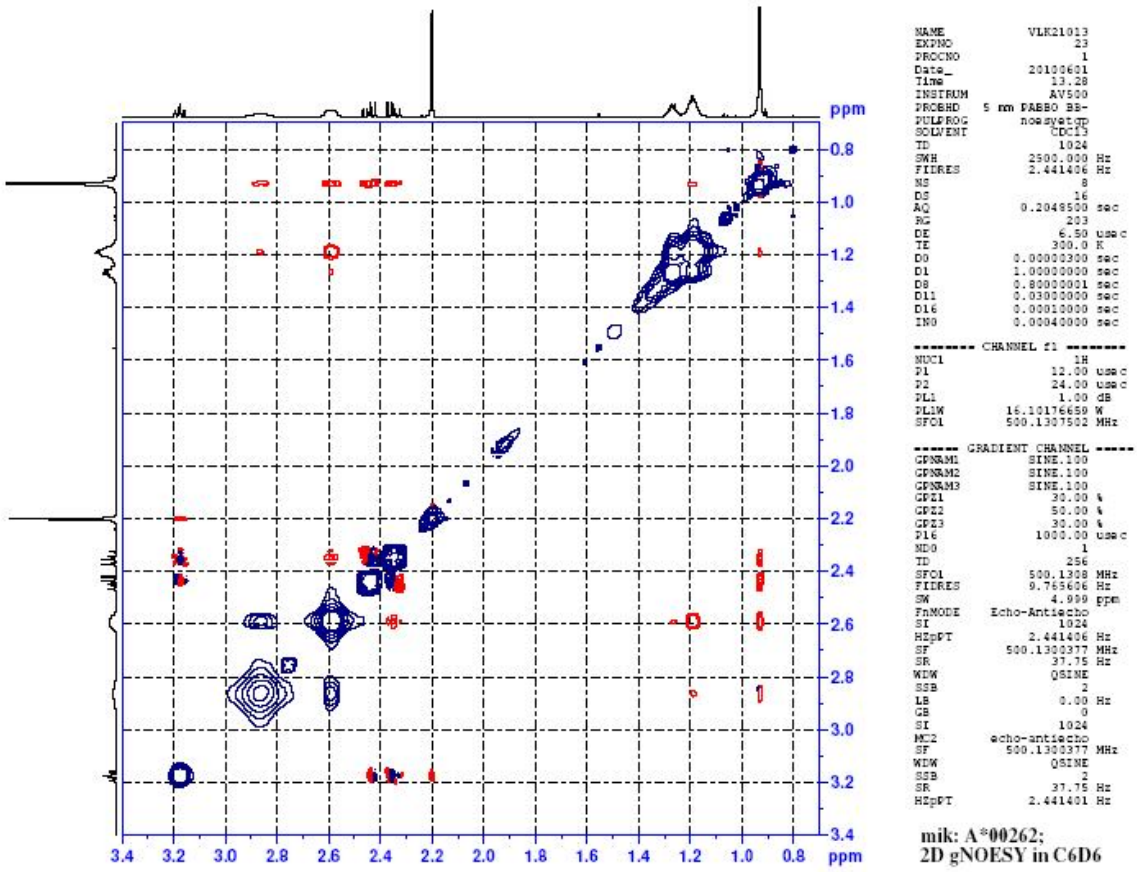

Figure 1S 2D NOESY experiment of **7a.**