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Chelation Controlled Intermolecular Hydroacylation: The Direct Addition of Alkyl Aldehydes to Functionalised Alkenes.

Michael C. Willis,*[a] Steven J. McNally[a] and Paul J. Beswick[b]

[a]Department of Chemistry, University of Bath, Bath, BA2 7AY, UK. [b]Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, SG1 2NY, UK.

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Unless otherwise specified, all reactions were performed in anhydrous conditions under a nitrogen atmosphere. All solvents were freshly distilled from sodium (diethyl ether, toluene and tetrahydrofuran) or calcium hydride (acetonitrile, dichloromethane, 1,2-dichloroethane and dimethyl sulfoxide) and stored over molecular sieves under nitrogen or argon. All reactions involving rhodium complexes were performed using standard Schlenk line techniques under argon; substrates for hydroacylation experiments were purified by distillation or recrystallisation before use. The rhodium pre-catalyst complexes were stored in sealed, argon-filled Schlenk tubes in a refrigerator, but they are relatively moisture- and air-stable, so could be weighed on a bench-top balance.

NMR analyses were carried out on Bruker 300AM or Varian 400 instruments. ^{1}H and ^{13}C chemical shifts δ are quoted in parts per million, relative to tetramethylsilane. Multiplicities of the signals are recorded as follows: s = singlet, br = broad signal, d = doublet, t = triplet, q = quartet, quint. = quintet and m = unresolved multiplet. Coupling constants *J* are quoted in Hertz.

Infrared measurements were made as a liquid film in the range 4000–600 cm^{-1}, using a Perkin-Elmer FT-1000 spectrometer; only significant peaks are quoted. The following abbreviations are used: br = broad, w = weak.

Mass spectrometry measurements were performed at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea; values are quoted as *m*/*z* with relative intensity in parentheses.

Thin layer chromatographic analyses were performed on plates coated with Kieselgel $60F_{254}$. Visualisation was achieved with a 254 nm ultraviolet lamp, followed by staining with vanillin or potassium permanganate. Column chromatographic separation was carried out using silica gel (35–70 mesh). Petrol refers to light petroleum ether, boiling point range 40–60 °C.

General procedure for hydroacylation reactions: (Bicyclo[2.2.1]hepta-2,5-diene)(1,2-bis(diphenylphosphino)ethane) rhodium(I) perchlorate[2] (20 mg, 0.029 mmol) was dissolved in 1,2-dichloroethane (4 ml), and hydrogen gas was bubbled through for 15 minutes to generate the catalytically active species **2**. The solution was degassed and purged with argon then the appropriate alkene (0.7 mmol) was added followed by aldehyde **3** (30 mg, 0.29 mmol). The reaction mixture was stirred at 60 ºC for 2 hours then evaporated under reduced pressure. The crude residue was analysed by ^{1}H NMR to measure the conversion of aldehyde to product, using 2,5-dimethylfuran as a quantitative internal standard.[3] Purification by flash chromatography (silica gel, diethyl ether/petrol) provided the pure hydroacylation adducts.

6-Methylsulfanyl-4-oxohexanoic acid methyl ester (Table 2, Entry 1 (linear))

71% Isolated yield; δ_H (300 MHz, $CDCl_3$) 3.68 (3H, s, OMe), 2.78–2.76 (6H, m, $SCH_2CH_2COCH_2$), 2.61 (2H, t, *J* 6.5, CH_2CO_2Me), 2.12 (3H, s, MeS); δ_C (75 MHz, $CDCl_3$) 207.1, 173.2, 51.9, 42.5, 37.3, 27.9, 27.6, 15.8; ν_{max} (film) /cm^{-1} 1738 (C=O); *m/z* (CI+, NH_3) 208 (100 %, M+NH_4), 191 (30 %, M+H), 143 (50 %, M–SCH_3); found $[M+H]^+$ 191.0742, $C_8H_{15}O_3S$ requires 191.0742.

2-Methyl-5-methylsulfanyl-3-oxopentanoic acid methyl ester (Table 2, Entry 1 (branched))

16% Isolated yield; δ_H (300 MHz, $CDCl_3$) 3.74 (3H, s, OMe), 3.56 (1H, q, *J* 5, C*H*Me), 2.93–2.81 (2H, m, CH_2CO), 2.78–2.72 (2H, m, SCH_2), 2.12 (3H, s, SMe), 1.36 (3H, d, *J*

5, CH*Me*); δ_C (75 MHz, $CDCl_3$) 204.5, 171.1, 53.2, 52.9, 41.6, 28.2, 16.2, 13.1; ν_{max} (film) /cm^{-1} 1747, 1716 (C=O); *m/z* (EI+) 190 (15 %, M^+), 143 (25 %, M–MeS), 103 (40 %, $MeSCH_2CH_2CO$), 87 (40 %, $CHMeCO_2Me$), 75 (60 %, $MeSCH_2CH_2$), 61 (100 %, $MeSCH_2$), 59 (60 %, CO_2Me); found $[M+H]^+$ 191.0739, $C_8H_{15}O_3S$ requires 191.0742.

6-Methylsulfanyl-4-oxohexanoic acid *tert*-butyl ester (Table 2, Entry 2)

81% Isolated yield; δ_H (300 MHz, $CDCl_3$) 2.69 (4H, br s, SCH_2CH_2), 2.62 (2H, t, *J* 6.5, $COCH_2$), 2.45 (2H, t, *J* 6.5, $CH_2CO_2{}^tBu$), 2.04 (3H, s, MeS), 1.37 (9H, s, t-Bu); δ_C (75 MHz, $CDCl_3$) 207.7, 172.3, 81.0, 42.8, 37.8, 29.5, 28.4 (3 □ CH_3), 28.2, 16.1; ν_{max} (film) /cm^{-1} 1719 (br, C=O); *m/z* (CI+, NH_3) 250 (40 %, M+NH_4), 233 (15 %, M+H), 194 (100 %, M–CH_2=$C(Me)_2$ +NH_4); found $[M+H]^+$ 233.1208, $C_{11}H_{21}O_3S$ requires 233.1206.

6-Methylsulfanyl-4-oxohexanoic acid dimethylamide (Table 2, Entry 3)

82% Isolated yield; δ_H (300 MHz, $CDCl_3$) 2.97 (3H, s, NMe), 2.86 (3H, s, NMe), 2.79–2.74 (2H, m, SCH_2CH_2CO), 2.71–2.65 (4H, m, SCH_2+$COCH_2$), 2.57–2.51 (2H, m, CH_2CONMe_2), 2.04 (3H, s, SMe); δ_C (75 MHz, $CDCl_3$) 208.8, 171.8, 43.1, 37.8, 37.5, 37.4, 28.3, 27.6, 16.1; ν_{max} (film) /cm^{-1} 1714, 1645 (C=O); *m/z* (CI+, NH_3) 204 (100 %, M+H), 156 (40 %, M–MeS); found $[M+H]^+$ 204.1054, $C_9H_{18}NO_2S$ requires 204.1053.

1-Methyl-3-(3-methylsulfanylpropionyl)pyrrolidine-2,5-dione (Table 2, Entry 4)

73% Isolated yield; δ_H (300 MHz, $CDCl_3$) 3.89 (1H, dd, *J* 7 and 3, COCHCO), 2.85 (3H, s, NMe), 2.8–2.4 (6H, m, $MeSCH_2CH_2$+CH_2CONMe), 2.05 (3H, s, SMe); δ_C (75 MHz, $CDCl_3$) 200.4, 176.5, 176.2, 52.9, 34.6, 30.8, 30.5, 29.4, 15.8; ν_{max} (film) /cm^{-1} 1714, 1654 (C=O); *m/z* (CI+, NH_3) 233 (60 %, M+NH_4) 97 (100 %); found $[M+H]^+$ 233.0955, $C_9H_{13}O_3NS$ requires 233.0954.

1-Methylsulfanyl-5-phenyl-pentan-3-one (Table 2, Entry 5)

41% Isolated yield; δ_H (300 MHz, $CDCl_3$) 7.24–7.19 (2H, m, 2 □ Ph), 7.14–7.10 (3H, m, 3 □ Ph), 2.95–2.75 (2H, m, PhC*H*$_2$), 2.72–2.68 (2H, m, SC*H*$_2$), 2.65–2.61 (4H, m, C*H*$_2$COC*H*$_2$), 2.02 (3H, s, MeS); δ_C (75 MHz, $CDCl_3$) 207.2, 139.8, 127.5 (2 □ CH), 127.3 (2 □ CH), 125.2, 43.5, 41.6, 28.6, 26.9, 14.8; ν_{max} (film) /cm^{-1} 1713 (C=O); *m*/*z* (CI+, NH_3) 226 (100 %, M+NH_4), 209 (25 %, M); 178 (30 %, M+NH_4–MeS); found $[M+H]^+$ 209.1000, $C_{12}H_{17}OS$ requires 209.1000.

5-(4-Cyanophenyl)-1-methylsulfanyl-pentan-3-one (Table 2, Entry 6)

66% Isolated yield; δ_H (300 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8, 2 □ Ar), 7.23 (2H, d, *J* 8, 2 □ Ar), 2.90 (2H, t, *J* 7, ArC*H*$_2$), 2.72 (2H, t, *J* 7, ArCH_2C*H*$_2$), 2.65–2.60 (4H, m, SC*H*$_2$C*H*$_2$), 2.03 (3H, s, MeS); δ_C (75 MHz, $CDCl_3$) 207.6, 147.0, 132.7, 129.6, 119.5, 110.5, 44.0, 42.9, 29.9, 28.3, 16.2; ν_{max} (film) /cm^{-1} 2244 (C≡N), 1715 (C=O); *m*/*z* (CI+, NH_3) 251 (100 %, M+NH_4), 234 (5 %, M+H); 203 (30 %, M+NH_4–MeS); found $[M+NH_4]^+$ 251.1214, $C_{13}H_{19}N_2OS$ requires 251.1213.

1-Methylsulfanylundecan-3-one (Table 2, Entry 7)

33% Isolated yield; δ_H (300 MHz, $CDCl_3$) 2.69-2.65 (4H, m, SC*H*$_2$C*H*$_2$), 2.35 (2H, t, *J* 7.5, CO*CH*$_2$), 2.05 (3H, s, SMe), 1.52–1.20 (12H, m, 6 □ CH_2), 0.81 (3H, t, *J* 6, Me); δ_C (75 MHz, $CDCl_3$) 209.8, 43.5, 42.7, 32.2, 29.7, 29.6, 29.5, 28.4, 24.1, 23.0, 16.2, 14.5; ν_{max} (film) /cm^{-1} 1711 (C=O); *m*/*z* (EI+) 216 (15 %, M), 141 (20 %, M–$CH_3SCH_2CH_2$), 103 (42 %, M–C_8H_{17}), 71 (85 %, C_5H_{11}), 61 (85 %, CH_3SCH_2), 57 (65 %, C_4H_9), 43 (65 %, C_3H_7); found M^+ 216.1548, $C_{12}H_{24}OS$ requires 216.1546.

(*E*)-4-Methyl-7-methylsulfanyl-5-oxohept-3-enoic acid methyl ester (Table 2, Entry 8)

45% Isolated yield; δ_H (300 MHz, $CDCl_3$) 6.75 (1H, tq, *J* 7 and 1.5, C=CH), 3.68 (3H, s, OMe), 3.24 (2H, d, *J* 7, C*H*$_2$CO$_2$Me), 2.96 (2H, t, *J* 7 SCH_2), 2.71 (2H, t, *J* 7, SCH_2CH_2CO), 2.06 (3H, s, SMe), 1.73 (3H, d, *J* 1.5, Me); δ_C (75 MHz, $CDCl_3$) 171.2, 162.0, 139.7, 133.6, 52.6, 37.7, 34.6, 29.2, 16.2, 12.1; *m*/*z* (CI+, NH_3) 234 (30 %, M+NH_4), 217 (15 %, M+H), 202 (50 %, M+NH_3–OMe), 186 (100 %, M+NH_3–MeS); found $[M+NH_4]^+$ 234.1157, $C_{10}H_{20}NO_3S$ requires 234.1158; the geometry of the double bond was not confirmed.

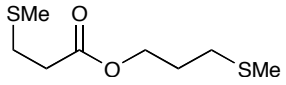
4-Benzenesulfonyl-1-methylsulfanylpentan-3-one (Table 2, Entry 9)

84% Isolated yield; δ_H (300 MHz, $CDCl_3$) 7.77–7.71 (2H, m, Ph), 7.65–7.60 (1H, m, Ph), 7.59–7.46 (2H, m, Ph), 4.14 (1H, q, *J* 7, COC*H*Me), 3.20 (1H, dt, *J* 18 and 7, 1 □ CH_2CO), 2.89 (1H, dt, *J* 18 and 7, 1 □ CH_2CO), 2.67 (2H, t, *J* 7, SCH_2), 2.06 (3H, s, MeS), 1.33 (3H, d, *J* 7, Me); δ_C (75 MHz, $CDCl_3$) 201.1, 134.8, 129.8, 129.8, 128.2, 70.4, 43.9, 28.0, 16.1, 12.2; ν_{max} (film) /cm^{-1} 1716 (C=O), 1308, 1148 (S=O); *m*/*z* (EI+) 272 (10 %, M), 225 (10 %, M–SMe), 141 (20 %, SO_2Ph), 131 (60 %, M–SO_2Ph), 77 (100 %, Ph), 61 (60 %, $MeSCH_2$); found $[M+NH_4]^+$ 290.0881, $C_{12}H_{20}NO_3S_2$ requires 290.0879.

6-Methylsulfanyl-4-oxohex-2-enoic acid methyl ester (Table 2, Entry 10)

82% Isolated yield; δ_H (400 MHz, $CDCl_3$) 7.00 (1H, d, *J* 16, *H*C=CH), 6.62 (1H, d, *J* 16, HC=C*H*), 3.74 (3H, s, OMe), 2.88 (2H, t, *J* 7, SCH_2CH_2), 2.72 (2H, t, *J* 7, SCH_2), 2.06 (3H, s, SMe); δ_C (75 MHz, $CDCl_3$) 198.2, 166.2, 139.4, 131.2, 52.9, 14.8, 28.1, 16.3; ν_{max} (film) /cm^{-1} 1733, 1710 (C=O); *m*/*z* (EI+) 189 (100%, M+H), 158 (10%), 141 (M–SMe); found $[M+H]^+$ 341.1243, $C_8H_{13}O_3S$ requires 341.1240.

3-Methylsulfanylpropanoic acid 3-methylsulfanylpropyl ester (Tischenko adduct)



δ_H (300 MHz; $CDCl_3$) 4.14 (2H, t, *J* 6, OCH_2), 2.70 (2H, td, *J* 7 and 1.5, SCH_2 CH_2CO_2), 2.56 (2H, td, *J* 7 and 1.5, $SCH_2CH_2CO_2$), 2.50 (2H, t, *J* 7, CH_2S), 2.06 (3H, s, SMe), 2.04 (3H, s, SMe), 1.87 (2H, quint., *J* 7, OCH_2CH_2); δ_C (75 MHz, $CDCl_3$) 170.9, 62.3, 33.4, 29.6, 28.1, 27.1, 14.5, 14.49; ν_{max} (film) /cm^{-1} 1732 (C=O), 1244 (C–O); *m/z* (CI+, NH_3) 226 (100 %, M+NH_4), 209 (20 %, M+H), 89 (30 %, $(CH_2)_3$SMe); found: $[M+NH_4]^+$ 226.0933, $C_8H_{20}NO_2S_2$ requires 226.0935.

4-Oxo-hex-5-enoic acid methyl ester (5)

Ketone **4** (37 mg, 0.19 mmol) was dissolved in dichloromethane (2 ml). Methyl triflate (25 μl, 0.23 mmol) was added *via* syringe, and the mixture stirred at room temperature for 20 minutes. Potassium hydrogen carbonate (40 mg, 0.29 mmol) was added and stirred for a further 10 minutes. The mixture was washed with water and brine, dried with sodium sulfate and evaporated to give *enone* **5** as a colourless oil (20 mg, 76 %); δ_H (300 MHz, $CDCl_3$) 6.32 (1H, dd, *J* 18 and 10, CH=CH_{trans}), 6.20 (1H, dd, *J* 18 and 2, CH=CH_{cis}), 5.82 (1H, dd, *J* 10 and 2, C*H*=CH_2), 4.15 (3H, s, OMe), 2.87 (2H, t, *J* 7, $COCH_2$), 2.58 (2H, t, *J* 7, CH_2CO_2Me); data in agreement with literature example.[4]

References

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