Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

for

Angew. Chem. Int. Ed. Z51209

69451 Weinheim, Germany

On the Role of Acyloxyphosphonium ions and the Stereochemical Influence of Base in the Phosphorane Mediated Esterification of Alcohols.

James McNulty,* Alfredo Capretta, Vladimir Laritchev, Jeff Dyck and Al J. Robertson

General Information:

Esterification reactions were performed in flame-dried glassware, assembled and allowed to cool under argon. Silica gel column chromatography was performed using 230-400 mesh silica. Alcohols and amines were used as obtained. Tributylphosphine was obtained from Cytec. Benzene was distilled over calcium hydride and anhydrous DMF used directly (Aldrich *Sure/Seal*^{TM}). ^{1}H-NMR, ^{13}C-NMR were recorded at 300 and 75 mHz in $CDCl_3$. Chiral GC analysis was performed on a HP-6890 with FID under the individual conditions described below. Benzoyl peroxide was obtained from Acros (75% purity). Water was removed before using through warming at 50^{o}C for at least 1.5 hour under vacuum. This process was conducted on a 250mg scale behind a plexiglass shield as a precautionary measure.

General esterification protocol A for inversion of configuration:

(1*S*/1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (Table 1, entry 2). Dried Benzoyl peroxide (232.6 mg, 0.96 mmol, 1.5eq) was dissolved in 1.5 ml dry benzene at 40^{o}C. The BPO solution so obtained was added dropwise via syringe to a magnetically stirred solution of tributylphosphine (240 μL, 0.96 mmol, 1.5eq), L-menthol (100 mg, 0.64, 1.0eq) and tert-octylamine (0.27 ml, 1.6 mmol, 2.5 eq) in 0.5 ml of benzene under Ar at 70^{o}C over a period of 70 min. A thick white precipitate was formed during the reaction. The solution was cooled to room temperature and diluted with EtOAc (10 mL). The organic layer was washed with water (3 x 5 ml), 0.2N $Na_2CO_{3(aq.)}$ (2 x 5 ml) and water (1 x 5 ml). The solvent was removed under reduced pressure and residue was dried under vacuum at 50^{o}C to afford a yellow oil. The product was purified over silica (31 x 1 cm); eluant Hexane/CH_2Cl_2:7/3; to give (1*S*/1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (Table 2, entry 2); colourless oil (91.3 mg, 55%); data below.

General esterification protocol B for retention of configuration:

(1*R*/1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (Table 1, entry 3). Dried Benzoyl peroxide (232.6 mg, 0.96 mmol, 1.5eq) was dissolved in 1.5 ml anhydrous DMF at 40^{o}C. The BPO solution so obtained was added dropwise via syringe to a stirred mixture of tributylphosphine (240 μL, 0.96 mmol, 1.5eq) and L-menthol (100 mg, 0.64, 1.0eq) in 0.5 ml of DMF under Ar at 70^{o}C over a period of 70 min. The solution was cooled to room temperature and diluted with 10 ml of EtOAc. The organic layer was washed with 0.2N $Na_2CO_{3(aq.)}$ (3 x 5 ml) and water (1 x 5 ml). The solvent was removed under reduced pressure and residue dried under vacuum at 50^{o}C to afford a yellow oil. The product was purified over silica (31 x 1 cm); eluant Hexane/CH_2Cl_2:7/3; to give (1*R*/1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (Table 2, entry 3); colourless oil (83.9 mg, 50%); data below.

Table 1, Entry 1: Following general method A, (1*R*/1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate was obtained, colourless oil 95 mg (57%); ratio of retention/inversion 0.7/99.3 determined by chiral GC: (1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (inversion): ^{1}H-NMR ($CDCl_3$) δ 0.80-2.2 (m, 17H), 5.49 (broad s, 1H), 7.4-7.65 (m, 3H), 8.08 (d, 2H, *J*=8.3 Hz); ^{13}C-NMR ($CDCl_3$) δ, 21.2, 22.4, 22.6, 25.8, 27.2, 29.8, 35.3, 39.6, 47.4, 72.1, 128.7, 129.9, 131.4, 133.1, 166.3. (1*R*, 2*S*, 5*R*) 2-isopropyl-5-methylcyclohexyl benzoate (retention) had similar chemical shifts except for the C-1 proton ^{1}H-NMR δ 4.97 (m). HREIMS: calcd. for $C_{17}H_{24}O_2$ 260.1777; found 260.1771. FTIR: 2950, 2922, 2869, 1715, 1585, 1451, 1369, 1313, 1273, 1198, 1175, 1114, 1069, 1027, 923, 712 cm^{-1}. The diastereomeric purity was determined by chiral GC on an Astec β-PM capillary column (30m x 0.25mm, flow rate=2.0 ml/min, temperature 150 ^{o}C). Standard retention times were 9.36 min (1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate and 10.64 min for (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate. Standard samples of each ester were prepared from L-menthol and neomenthol (1-epimer) and benzoyl chloride for direct confirmation.

Table 1 Entry 2: Following general method A, (1*R*/1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate was obtained, colourless oil 91.3 mg (55%); ratio of retention/inversion 1.1/98.9 determined by chiral GC as above: The NMR data were identical to Table 2, Entry 1 except for the ratio of the C-1 protons at δ 4.97 and 5.49.

Table 1, Entry 3: Following general method B, (1*R*/1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate was obtained, colourless oil 95 mg (57%); ratio retention/inversion 97/3 determined by chiral GC: (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (retention): ^{1}H-NMR ($CDCl_3$) δ 0.80-2.2 (m, 17H), 4.97(m, 1H), 7.4-7.65 (m, 3H), 8.08 (d, 2H, *J*=7.5 Hz); ^{13}C-NMR ($CDCl_3$) δ,16.9, 21.2, 22.5, 24.0, 26.9, 31.8, 34.7, 41.4, 47.7, 75.2, 128.7, 129.9, 131.2, 133.1, 166.5. FTIR: 2955, 2929, 2870, 1714, 1603, 1584, 1452, 1369, 1314, 1274, 1160, 1098, 1070, 1027, 963, 711 cm^{-1}. HREIMS: calcd. for $C_{16}H_{21}O_2$ 245.1541; found 245.1542 (M^{+}-CH_3). (1*S*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl benzoate (inversion) had similar chemical shifts except for the C-1 proton ^{1}H-NMR δ 5.49 (broad s).

Table 1, Entries 4 and 5: Following general methods A and B respectively, 2-Hexyl benzoate was obtained, colourless oil 96.3 mg (73%) entry 4, and 87.8 mg (67 %) entry 5: ^{1}H-NMR ($CDCl_3$) δ 0.93 (t, 3H, *J*= 6.7 Hz), 1.3-1.5 (m, 4H), 1.36 (d, 3H, *J*= 6.7 Hz), 1.54-1.85 (m, 2H), 5.18 (m, 1H), 7.4-7.6 (m, 3H), 8.07 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 14.4, 20.5, 23.0, 28.0, 36.2, 72.1, 128.7, 129.9, 131.3, 133.1, 166.6. FTIR: 2958, 2935, 2863, 1714, 1603, 1585, 1452, 1379, 1354, 1314, 1276, 1175, 1109, 1070, 1026, 920, 854, 712 cm^{-1} HREIMS: calcd. for $C_{13}H_{18}O_2$ 206.1307; found 260.1299. The enantiomeric purity was determined by reductive liberation of the scalemic alcohol and conversion to the 2-hexyl 4'-nitrobenzoate derivative. Thus, a 1M solution of $LiAlH_4$ in THF (0.1 ml) was added to a solution of 5 mg of scalemic ester in 0.1 ml THF. After 1 h the reaction mixture was decomposed with 0.05 ml of water followed by extraction into CH_2Cl_2. The organic phase was dried with Na_2SO_4, filtered and solutions of 4-nitrobenzoyl chloride (2 mg in 50 μL) and 4-dimethylaminopyridine (1.5 mg in 50 μL) were injected sequentially. After 2h the reaction mixture was diluted with CH_2Cl_2 (5 ml) and washed with 0.2M Na_2CO_3 (3 x 1ml), dried with Na_2SO_4 and evaporated. The white solid so obtained was dissolved in 0.5 ml of CH_2Cl_2 and analyzed by chiral GC on an Astec β-PM capillary column (30m x0.25mm, flow rate=0.5 ml/min, temperature 130 ^{o}C, standard retention times were 102.1 min for (2*S*)-2-hexyl-4'-nitrobenzoate, 103.5 min for (2*R*)-2-hexyl-4'-nitrobenzoate).

Table 1, Entries 6 and 7: Following general methods A and B respectively, **(**1*R*/1*S*)-1-Phenyl-1-propyl benzoate was obtained, colourless oil 42 mg (54%) Entry 5, and 33.8 mg (56%) Entry 6: ^{1}H-NMR ($CDCl_3$) δ 0.99 (t, 3H, *J*= 7.5 Hz), 1.9-2.2 (m, 2H), 5.95 (t, 1H, *J*= 6.8 Hz), 7.28-7.65 (m, 8H), 8.12(m, 2H); ^{13}C-NMR ($CDCl_3$) δ 10.4, 30.0, 78.3, 126.9, 128.2, 128.7, 128.8, 130.0, 130.9, 133.3, 141.0, 166.3. FTIR: 3064, 3033, 2971, 2937, 2878,1766, 1720, 1602, 1493, 1452, 1314, 1272, 1177, 1111, 1070, 1026, 998, 944, 910, 756, 712 cm^{-1} HREIMS: calcd. for $C_{16}H_{16}O_2$ 240.1151; found 240.1144. The enantiomeric purity was determined on the alcohol liberated on reduction of the scalemic ester. Thus, a 1M solution of $LiAlH_4$ in THF (0.1 ml) was added to a solution of 5 mg of the scalemic ester in 0.1 ml THF. After 1 h the reaction mixture was decomposed

with 0.05 ml of water. The crude alcohol mixture was extracted with 2 ml of CH_2Cl_2 and dried with Na_2SO_4. The solution of 1-phenylpropan-1-ol so obtained was analyzed by chiral GC on an Astec β-PM capillary column (30m x 0.25mm, flow rate=0.5 ml/min, temperature 120 ^oC). Standard retention times were 6.8 min for (1*R*)-1-phenyl-1-propan-1-ol and 7.0 min for (1*S*)-1-phenyl-1-propan-1-ol.

Table 1, Entry 8 and 9: Following general methods A and B respectively, **(**2*S*/2*R*)-Ethyl-2-benzoyloxypropanoate was obtained, colourless oil 104.5 mg (73%) Entry 8, and 100.2 mg (70%) Entry 9: ^{1}H-NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*= 6.8 Hz), 1.63 (d, 3H, *J*= 7.5 Hz), 4.24 (q, 2H, *J*= 7.5 Hz), 5.31 (q, 1H, *J*= 6.8 Hz), 7.4-7.65 (m, 3H), 8.10 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 14.5, 17.4, 61.8, 69.6, 128.8, 129.9, 130.2, 133.7, 166.3, 171.2. FTIR: 3065, 2988, 2942, 2908, 1727, 1602, 1585, 1452, 1380, 1350, 1317, 1272, 1208, 1114, 1046, 1025, 856, 714 cm^{-1} HREIMS: calcd. for $C_{12}H_{14}O_4$ 222.0892; found 222.0888. The enantiomeric purity was determined by chiral GC on an Astec β-PM capillary column (30m x 0.25mm, flow rate=0.5 ml/min, temperature 130 ^oC). Standard retention times were 19.0 min **(**2*R*)-ethyl-2-benzoyloxypropanoate and 19.3 min **(**2*S*)-ethyl-2-benzoyloxypropanoate.