

Supporting information

Facile Acylation of Sterically Hindered Alcohols through Ketene Intermediates.

Moshe Nahmany and Artem Melman*

General. Unless otherwise stated, all reagents used are commercially available from Aldrich, Fluka or Merck. All the reactions were performed in dichloromethane or in a mixture of dichloromethane with acetonitrile that were dried and distilled by standard procedures. The ^1H and ^{31}P spectra were acquired by Bruker AMX-300 (300 MHz) and DRX 400 (MHz) instruments in CDCl_3 using the residual solvent peaks for calibration. IR spectra were recorded on Bruker Vector 22 FT-IR spectrometer in thin films.

General procedure of preparations of the *tert* butyl esters 2a-i. To a mixture of 1 mL of a 1M solution of acids **1a-i** in dry dichloromethane (or acetonitrile for acids **1c-d**) and *tert*-butanol (1.25 mmol) were added under stirring at 25 °C 1.1 mL of 1 M solution of DCC. The reaction mixture was stirred for 15 min., filtered through a sintered glass, and evaporated. The residue was analyzed by ^1H NMR (negative identification of **2e-h**) and purified using short-path distillation in a Kugelrohr apparatus or flash chromatography. The products of esterification **2a-d,i** were positively identified by their 300 MHz ^1H NMR using literature data for comparison. No traces of the esters **2e-h** were obtained in these reaction (negative identification by doping experiments with commercial samples of these esters). Compounds **2a-c** were found to be identical to authentic commercial samples, and the identity of compounds **2d, i** was established by comparison with the NMR and IR spectra in the literature

4,8-dimethyl-4-[(phenylsulfonyl)methyl]-2,3-dioxabicyclo[3.3.1]non-8-yl 2-(diethoxyphosphoryl) acetate. To a solution of alcohol **3** (55 mg, 0.17 mmol) in dichloromethane (0.5 mL) were added diethylphosphonoacetic acid (0.19 mL of 1M solution in dichloromethane, 0.19 mmol) and DCC (0.19 mL of a 1M solution in dichloromethane, 0.19 mmol). The reaction mixture was stirred for 15 min., filtered through a sintered glass, and evaporated. The residue was purified by flash chromatography (50 to 70% ethyl acetate-40-60 petroleum ether) to give **4** (80 mg, 92%). ^1H NMR (300 MHz). 1.23 (t, 6H, $J=7.1$ Hz); 1.59 (s, 3H); 1.81 (s, 3H); 1.91-2.14 (m, 7H), 2.91 (d, 2H, $J=21.6$ Hz); 3.03, 3.33 (2xd, 2H; $J=4.1$ Hz); 4.16 (app. quintet, 4H, $J=7$ Hz); 4.39 (br. d., 1H, $J=3.6$ Hz); 7.58 (dt, 2H, $J=1.5, 6.9$ Hz); 7.67 (dt, 1H, $J=1.2, 8.1$ Hz); 7.92 (br. d., 2H, $J=7.5$ Hz) Anal. Calcd. for $\text{C}_{21}\text{H}_{31}\text{O}_9\text{PS}$: C, 52.37; H, 6.59. Found C, 51.96; H, 6.61.

Deuteration experiments. To crystalline potassium *tert*-butoxide (344 mg, 3.1 mmol) was dropwise, under stirring added D₂O (0.2 mL, 10 mmol). The resultant suspension was extracted with dichloromethane (3 mL) to give approx. a 0.8 M solution of *t*-BuOD in dichloromethane (determined by the integration of corresponding peaks in ¹H NMR). A mixture of 0.5 mL of this solution, diethylphosphonoacetic acid (**1a**) (1 mL of a 0.2 M solution in dichloromethane, 0.2 mmol), and DCC (1 mL of 0.2 M solution in dichloromethane) was stirred for 15 min, filtered through a sintered glass, and evaporated. ¹H NMR of the residue shows in addition to a doublet at 2.87 ppm. (*J*=25.5 Hz, PCH₂ group) a doublet of broad triplets at 2.86 ppm (*J*=25.5, Hz, PCHD group). The ³¹P (162 MHz) spectrum of pure **2a** shows a singlet at 25.500 ppm and the spectrum after deuteration shows three singlets at 25.500, 25.518, and 25.536 ppm.

3-Cylohexyl-2-(cyclohexylimino)- 6-ethoxy-5-methyl-2H-1,3-oxazin-4(3H)-one (8). To a solution of monoethyl 2-methylmalonate **1i** in dichloromethane (1 mL of 1M solution) was added a solution of DCC in dichloromethane (2 mL of 1M solution). The reaction mixture was stirred for 1 h at room temperature, filtered through a sintered glass, and evaporated. The residue was purified by flash chromatography (40-60 petroleum ether - ethyl acetate 25:1) to give the title compound (198 mg, 0.59 mmol, 59%). ¹H NMR (300 MHz): 1.13 (t of br. t, *J*=12.9 Hz, 1H), 1.21-1.35 (m, 7H), 1.36 (t, *J*=6.9 Hz, 3H), 1.40-1.80 (m, 10H), 1.72 (s, 3H), 2.48 (q of d, *J*=12.3, 3.3 Hz, 2H), 3.58 (m, 1H), 4.26 (q, *J*=6.9 Hz, 2H), 4.67 (t of t, *J*=3.9, 12 Hz, 1H); IR (film, cm⁻¹): 748, 1205, 1344, 1414, 1645, 1674, 1707, 2924. Anal. Calcd. for C₁₉H₃₀N₂O₃: C, 68.23; H, 9.04; N, 8.38. Found C, 68.51; H, 9.27; N, 8.35.