A Synthetic Alternative to the Type-II Intramolecular 4+3 Cycloaddition Reaction

*Richard S. Grainger, * Richard B. Owoare, Patrizia Tisselli and Jonathan W. Steed[†]*

Department of Chemistry, King's College London, Strand, London WC2R 2LS

E-mail: richard.grainger@kcl.ac.uk

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[†] To whom correspondence regarding X-ray crystal structure should be addressed.

EXPERIMENTAL

General procedures

Solvents were dried as follows: THF was refluxed over sodium wire and benzophenone, CH₂Cl₂ was refluxed from calcium hydride, diethyl ether was dried over sodium wire for 2 days. Commercially available NaH (60% in mineral oil) was freed of mineral oil by repeated washings with petroleum ether (60-80°C) under nitrogen. All other commercially available reagents were used as received. All reactions were carried out in oven-dried glassware under nitrogen atmosphere unless otherwise stated. Infra-red spectra were recorded on a Fourier transform I.R. spectrometer. ¹H NMR were recorded using a 360 MHz spectrometer in deuteriochloroform referenced to TMS (0 ppm) or CHCl₃ (7.26 ppm). Chemical shifts are in parts per million (δ ppm). Coupling constants are in Hertz (*J* Hz). The following abbreviations are used: s-singlet, d-doublet, dd-double doublet, t-triplet, m-multiplet. ¹³C NMR were recorded at 90 MHz in deuteriochloroform using CDCl₃ (77.0 ppm) as standard unless otherwise stated. Chemical shifts are in parts per million (δ ppm). Mass spectra were recorded by electron impact (EI) or chemical ionization (CI). High resolution mass spectra were recorded using fast atom bombardment (FAB). Melting points are uncorrected. Analytical TLC was carried out on Merck (aluminium sheets) silica gel plates using short wave (254 nm) UV light, KMnO₄ and anisaldehyde to visualise components. Silica gel (silica gel 60, 230-400 mesh, Merck) was used for flash column chromatography, according to the method of Still.¹

¹ Still, W.C; Kahn, M.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *43*, 2923.

4-(3'-Furyl)-1-bromobutane. Triphenylphosphine (13.2 g, 115.0 mmol) was added portionwise to a stirred solution of alcohol **3** (9.21 g, 50 mmol) and carbon tetrabromide (12.5 g, 112.0 mmol) in CH₂Cl₂ (30 mL) at 0 °C. The mixture was stirred for 2 h while warming to room temperature. The reaction was quenched with water and the aqueous layer extracted with CH₂Cl₂. The combined organic extracts were washed with brine and dried over MgSO₄, filtered, and concentrated in vacuo to give a residue that was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to afford the title compound (10 g, 89%) as a colorless oil; *R_f* 0.55 (1:4 diethyl ether/60-80 petroleum ether); ν_{max} (neat); 2937, 2862, 1501 cm⁻¹; δ_{H} (360 MHz; CDCl₃) 1.77 (m, 2 H), 1.95 (m, 2 H), 2.51 (t, *J* = 7.5 Hz, 2 H), 3.48 (t, *J* = 6.7 Hz, 1 H), 6.32 (d, *J* = 0.9 Hz, 1 H), 7.28 (d, *J* = 0.9 Hz, 1 H), 7.41 (t, *J* = 1.7 Hz, 1 H); δ_{C} (90 MHz, CDCl₃) 24.3 (CH₂), 28.9 (CH₂), 33.3 (2 × CH₂), 115.4 (CH), 124.9 (C) 139.3 (CH), 143.1 (CH); *m/z* (EI) 204 (*M* + 1; 10.5%), 123 (28.5), 81 (100), 67 (10.8); HRMS calcd for C₈H₁₂OBr 203.0066, found 254.1125.

2-(3'-Furyl-4-butyl)-dimethyl malonate. To a solution of NaH (1.4 g, 1.35 mmol) in DMF (30 mL) and THF (86 mL) at 0 °C was added dimethyl malonate (16 mL, 143 mmol). The mixture was allowed to stir while warming to room temperature for 15 min, and then 4-(3'-furyl)-1-bromobutane (5.8 g, 28.6 mmol) was added. The resulting mixture was brought to reflux for 1.5 h before concentrating in vacuo to give a residue that was diluted with water and extracted three times with *n*-pentane (50 mL) and once with a mixture of *n*-pentane/diethyl ether (1:1, 50 mL). The combined organic extracts were dried (MgSO₄) and concentrated. The excess dimethyl malonate was removed by short-path distillation using a Kugelröhr apparatus (2 mm/Hg, 68 °C) to afford the title compound (5.1 g, 70%) as a pale yellow oil; *R_f* 0.32 (3:1 60-80 petroleum ether/diethyl ether); ν_{max} (neat); 2929, 1743, 1459 cm⁻¹; δ_{H} (360 MHz;

CDCl₃) 1.28 (m, 2 H), 1.53 (m, 2 H), 1.86 (m, 2 H), 2.35 (t, $J = 7.5$ Hz, 2 H), 3.29 (t, $J = 7.5$ Hz, 1 H), 3.66 (s, 6 H), 6.18 (d, $J = 0.9$ Hz, 1 H), 7.13 (d, $J = 0.9$ Hz, 1 H), 7.27 (t, $J = 1.6$ Hz, 1 H); δ_C (90 MHz, CDCl₃) 24.7 (CH₂), 27.2 (CH₂), 29.0 (CH₂), 29.9 (CH₂), 52.0 (CH), 52.9 (2 $\times$ CH₃), 111.3 (CH), 125.1 (C), 139.2 (CH), 143.1 (CH), 170.3 (C); m/z (EI) 254 (M⁺; 61.6%), 191 (33.9), 135 (39), 81 (100); HRMS calcd for C₁₃H₁₈O₅ 254.1154, found 254.1125.

6-(Furan-3'-yl)-hexanoic acid methyl ester (4). A mixture of the freshly prepared diester (3.1 g, 12.3 mmol), DMSO (13 mL), NaCl (0.4 g, 15.3 mmol) and distilled water (0.8 g, 45.5 mmol) were refluxed for 3 h. After cooling, the reaction mixture was poured into cold water (20 mL), followed by extraction with diethyl ether/hexanes (1:1, 3 $\times$ 20 mL). The organic layers were washed with brine, dried (MgSO₄) and concentrated in vacuo to give a residue that was purified by column chromatography (1:3 diethyl ether/hexane) to give compound **4** (2.2 g, 90%) as a colorless oil; R_f 0.56 (3:1 60-80 petroleum ether/diethyl ether); $\nu_{\max}$ (neat); 2930, 1804, 1739 cm⁻¹; δ_H (360 MHz; CDCl₃) 1.38 (m, 2 H), 1.62 (m, 4 H), 2.33 (t, $J = 7.5$ Hz, 2 H), 2.43 (t, $J = 7.5$ Hz, 2 H), 3.68 (s, 3 H), 6.27 (d, $J = 0.8$ Hz, 1 H), 7.22 (d, $J = 0.9$ Hz, 1 H), 7.36 (t, $J = 1.6$ Hz, 1 H); δ_C (90 MHz, CDCl₃) 25.02 (CH₂), 29.1 (CH₂), 30.0 (CH₂), 34.4 (CH₂), 51.1 (CH₃), 111.4 (CH), 125.4 (C), 139.2 (CH), 143.1 (CH), 175.6 (C); m/z (EI) 196 (M⁺; 51.2%), 165 (22.5), 95 (50.1), 82 (100); HRMS calcd for C₁₁H₁₆O₃ 196.1099, found 196.1103.

1,1-Dichloro-7-furan-3'-yl-heptan-2-one (5). To a solution of CH₂Cl₂ (1.8 g, 21.4 mmol) and **4** (2.1 g, 10.7 mmol) in THF (22 mL) was added a solution of lithium dicyclohexylamide [prepared by addition of *n*-BuLi (8.6 mL, 2.5 M, 21.4 mmol) to dicyclohexylamine (3.9 g, 21.4 mmol) at -78 °C] over 10 min at -78 °C. The combined mixture was stirred for 20 min at -78 °C before aqueous hydrolysis with HCl (6 M, 11

mL). The solid precipitate was filtered off and the filtrate extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated to give a residue that was purified by column chromatography (1:9 diethyl ether/60-80 petroleum ether) to afford the title compound (1.69 g, 64%) as a colorless oil; *R_f* 0.57 (3:1 60-80 petroleum ether/diethyl ether); *ν*_{max} (neat); 2932, 1735, 781 cm⁻¹; *δ*_H (360 MHz; CDCl₃) 1.32 (m, 2 H), 1.51 (m, 2 H), 1.63 (m, 2 H), 2.36 (t, *J* = 7.5 Hz, 2 H), 2.75 (t, *J* = 7.3 Hz, 2 H), 5.73 (s, 1 H), 6.19 (d, *J* = 0.9 Hz, 1 H), 7.14 (d, *J* = 1.4 Hz, 1 H), 7.28 (t, *J* = 1.6 Hz, 1 H); *δ*_C (90 MHz, CDCl₃) 23.9 (CH₂), 24.9 (CH₂), 28.9 (CH₂), 30.0 (CH₂), 35.2 (CH₂), 70.3 (CH), 111.3 (CH), 125.3 (C) 139.2 (CH), 143.1 (CH), 197.7 (C); *m/z* (EI) 248 (M⁺; 29%), 165 (60.9), 95 (20), 82 (100), 81 (76.4); HRMS calcd for C₁₁H₁₄O₂Cl₂ 248.0348, found 248.0345.

1,1-Dibromo-7-furan-3'-yl-heptan-2-one (6). To a solution of ester **4** (500 mg, 2.55 mmol) and dibromomethane (0.88 g, 5.10 mmol) in THF (5.2 mL), was added a solution of lithium diisopropylamide [prepared by addition of *n*- BuLi (2.7 mL, 2.5 M, 5.1 mmol) to diisopropylamine (0.72 mL, 5.10 mmol) in THF (5.2 mL) at -78 °C] over 10 min at -78 °C. The mixture was stirred at this temperature for 20 min and then hydrolysed with HCl (6 M, 2.6 mL). The solid precipitate was filtered and the filtrate extracted with ether (3 × 10 mL). The combined ethereal layer was dried (MgSO₄) and concentrated in vacuo. The crude product was purified by column chromatography (4:1 60-80 petroleum ether/diethyl ether) to give **6** (540 mg, 63%) as a colorless oil; *R_f* 0.50 (4:1 60-80 petroleum ether/diethyl ether); *ν*_{max} (neat); 2930, 2856, 1718, 778 cm⁻¹; *δ*_H (360 MHz; CDCl₃) 1.33 (m, 2 H), 1.53 (m, 2 H), 1.64 (m, 2 H), 2.35 (t, *J* = 7.5 Hz, 2 H), 2.86 (t, *J* = 7.3 Hz, 2 H), 5.71 (s, 1 H), 6.19 (d, *J* = 0.8 Hz, 1 H), 7.14 (t, *J* = 1.2 Hz, 1 H), 7.27 (t, *J* = 1.6 Hz, 1 H); *δ*_C (90 MHz, CDCl₃) 24.5 (CH₂), 24.7 (CH₂), 29.3 (CH₂), 30.3 (CH₂), 35.2 (CH₂), 43.3 (CH), 111.4 (CH), 125.3

(C), 139.2 (CH), 143.1 (CH), 197.3 (C); m/z (EI) 338 (M^+ ; 12.7%), 165 (57.1), 121 (12), 81 (100); HRMS calcd for $C_{11}H_{14}O_2Br_2Na$ ($M + Na^+$) 360.9232, found 360.9218.

Favorskii rearrangement of dichloroketone (5): trifluoroethyl acrylic esters (7 & 8). To a solution of **5** (50 mg, 0.20 mmol) in 1,1,1-trifluoroethanol (0.25 mL, 0.8 M) was added triethylamine (60 μ L, 0.44 mmol) at room temperature. The reaction was heated at 50 °C (oil bath) for 24h before quenching with water and extracting with CH_2Cl_2 . The organic layer was dried ($MgSO_4$) and concentrated to give a residue that was purified by column chromatography (5:1 hexane/ethyl acetate) to give an inseparable mixture of **7** and **8** (31.3 mg, 57%) in a 4:1 ratio; R_f 0.68 (5:1 hexane/ethyl acetate); ν_{max} (neat) 2933, 1734, 1636 cm^{-1} ; δ_H (360 MHz; $CDCl_3$) 1.47 (m, 4 H), 2.36 (t, $J = 7.3$ Hz, 2 H), 2.62 (m, 2 H), 4.44 (m, 2 H), 5.59 (d, $J = 1.1$ Hz, 2 H), 5.77 (d, $J = 11.45$ Hz, 1 H), 6.19 (s, 1 H), 6.30 (m, 1 H), 7.13 (s, 1 H), 7.27 (t, $J = 1.6$ Hz, 1 H); δ_C (90 MHz, $CDCl_3$) 24.1 (CH_2), 28.0 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 59.7 (C), 110.7 (CH), 117.6 (CH) 124.6 (C), 128.6 (CH_2), 138.5 (CH), 138.8 (C), 142.3 (CH), 153.3 (C), 164.0 (C), 165.1 (C); m/z (EI) 276 (M^+ ; 100%), 248 (18.1), 149 (77), 82 (99); HRMS calcd for $C_{13}H_{15}O_3F_3$ 276.0973, found 276.0945.

[4+3] Cyclization of dichloroketone (5) to oxatricyclic chloroketone (9). A solution of $NaOCH(CF_3)_2$ (0.5 mL, 0.8 M) in $(CF_3)_2CHOH$ (0.5 mL) was added dropwise to dichloroketone **5** (101 mg, 0.41 mmol) over a period of 1h at room temperature. The resulting mixture was stirred at room temperature for 5 days and then quenched with water. The aqueous layer was extracted twice with diethyl ether and CH_2Cl_2 . The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction was purified by column chromatography (10:1 hexane/ethyl acetate) to give **9** (10.5 mg, 12 %) and traces of **10**; R_f 0.42 (3:1 60-80 petroleum ether

/ ethyl acetate); $\nu_{\max}$ (neat) 2936, 1725, 1195 cm^{-1} ; δ_{H} (360 MHz; CDCl_3) 1.24 (m, 4 H), 1.73 (m, 2 H), 2.41 (t, $J = 2.8$ Hz, 2 H), 3.01 (m, 1 H), 4.51 (d, $J = 4.40$ Hz, 1 H), 4.84 (d, $J = 4.46$ Hz, 1 H), 4.95 (m, 1 H), 5.85 (d, $J = 1.1$ Hz, 1 H); δ_{C} (90 MHz, CDCl_3) 23.7 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 27.0 (CH_2), 56.6 (CH), 64.2 (CH), 83.0 (CH), 83.5 (CH), 124.1 (CH), 150.7 (C), 199.8 (C); m/z (EI) 212 (M^+ ; 18%), 178 (15), 177 (100), 107 (41); HRMS calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{ClNa}$ 235.0496, found 235.0494.

Favorskii rearrangement of dibromoketone (6) in hexafluoropropan-2-ol. Triethylamine (0.2 mL, 1.41 mmol) was added dropwise to a solution of dibromoketone **6** (216 mg, 0.64 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (0.8 mL) at room temperature. The reaction was monitored (by TLC) over 7 days by which time there was complete disappearance of starting material. The mixture was quenched with water and the aqueous layer extracted with diethyl ether. The organic layer was dried (MgSO_4), concentrated in vacuo and purified by column chromatography (7:1 hexane/ethyl acetate) to give **10** (141 mg, 65%) along with traces of **11**; R_f 0.57 (6:1 hexane/ethyl acetate); $\nu_{\max}$ (neat) 2934, 2862, 1760, 1636 cm^{-1} ; δ_{H} (360 MHz; CDCl_3) 1.49 (m, 4 H), 2.37 (t, $J = 7.3$ Hz, 2 H), 2.64 (m, 2 H), 5.73 (m, 1 H), 5.84 (t, $J = 11.4$ Hz, 1 H), 6.18 (s, 1 H), 6.46 (m, 1 H), 7.13 (s, 1 H), 7.27 (t, $J = 1.6$ Hz, 1 H); δ_{C} (90 MHz, CDCl_3) 24.8 (CH_2), 28.6 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 66.3 (CH), 111.3 (CH), 116.8 (CH), 125.1 (C), 139.2 (CH), 143.1 (CH), 156.8 (CH), 162.6 (C); m/z (EI) 344 (M^+ ; 45%), 276 (13), 149 (30), 89 (100); HRMS calcd for $\text{C}_{13}\text{H}_{15}\text{O}_3\text{F}_3$ 344.0847, found 344.0848.