Supplementary Information for

Reactivity of 2-acylaminoacrylates with ketene diethyl acetal; [2+2] cycloadditions vs. tandem condensations

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General Procedures. Melting points are uncorrected. All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous Na2SO4 and, when necessary, concentrated under reduced pressure using a rotary evaporator. NMR spectra were recorded at 300 MHz (1H) and at 75 MHz (13C) and signals are reported in ppm downfield from TMS. Microanalyses were carried out on a CE Instruments EA-1110 analyser and were in good agreement with the calculated values.

1-Benzamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (6). 2-Benzamidoacrylate 3 (307 mg, 1.5 mmol) was dissolved in tBuOH (17 mL) under an inert atmosphere and ketene diethyl acetal 5 (0.4 mL, 3 mmol) was added. The mixture was warmed at 83 °C and then another solution of ketene diethyl acetal 5 (1.6 mL, 12 mmol) in tBuOH (6 mL) was added by a syringe pump (20 min). After 48 h stirring at this temperature, the solvent was evaporated and the crude was purified by silica gel column chromatography, eluting with hexane/EtOAc (7:3), to yield 246 mg (51%) of 6.
as a yellow solid (mp = 64-66 °C). 1H NMR (CDCl$_3$): δ 1.06 (t, 3H, J = 6.0 Hz), 1.24 (t, 3H, J = 6.0 Hz), 1.70-1.77 (m, 1H), 2.18-2.24 (m, 2H), 2.77-2.84 (m, 1H), 3.45 (q, 2H, J = 6.0 Hz), 3.56 (q, 2H, J = 6.0 Hz), 3.70 (s, 3H), 7.34-7.44 (m, 4H), 7.70-7.74 (m, 2H). 13C NMR (CDCl$_3$): δ 15.0, 15.1, 24.7, 28.3, 52.4, 57.8, 58.4, 66.9, 101.6, 127.0, 128.5, 131.6, 133.6, 165.9, 169.9. Anal. Calcd. for C$_{17}$H$_{23}$NO$_5$: C, 63.54; H, 7.21; N, 4.46. Found: C, 63.45; H, 7.19; N, 4.42.

1-Acetamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (7). 2-Acetamidoacrylate 4 (1.43 g, 10 mmol) was dissolved in tBuOH (50 mL) under an inert atmosphere and ketene diethyl acetal 5 (2.6 mL, 20 mmol) was added. The mixture was warmed at 83 °C and then another solution of ketene diethyl acetal 5 (10.4 mL, 80 mmol) in tBuOH (30 mL) was added by a syringe pump (90 min). After 48 h stirring at this temperature, the solvent was evaporated and the crude was purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7), to yield 1.66 g (64%) of 7 as a white solid (mp = 58-60 °C). 1H NMR (CDCl$_3$): δ 1.12 (t, 3H, J = 6.0 Hz), 1.28 (t, 3H, J = 6.0 Hz), 1.64-1.74 (m, 1H), 2.02 (s, 3H), 2.23 (‘t’, 2H, J = 9.0 Hz), 2.74-2.83 (m, 1H), 3.46 (q, 2H, J = 6.0 Hz), 3.58 (q, 2H, J = 6.0 Hz), 3.76 (s, 3H), 6.73 (br s, 1H). 13C NMR (CDCl$_3$): δ 15.0, 15.1, 22.9, 24.7, 28.3, 52.4, 57.7, 58.3, 66.8, 101.4, 169.1, 170.1. Anal. Calcd. for C$_{12}$H$_{21}$NO$_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.46; H, 8.07; N, 5.53.

1-Acetamido-2,2,4,4-tetraethoxycyclohexane-1-carboxylic acid methyl ester (10). First method (from 4): 2,6-di-tert-butyl-4-bromophenol (2.28 g, 8 mmol) was dissolved in CH$_2$Cl$_2$ (10 mL) under an inert atmosphere and AlMe$_3$ (2 mL, 2M solution in hexane) was slowly added. The solution was stirred for 1 h, then 2-acetamidoacrylate 4 (286 mg,
2 mmol) and ketene diethyl acetal 5 (1.32 mL, 10 mmol) were added and the reaction was stirred for 1 h. The reaction was quenched with H₂O and extracted with CH₂Cl₂ (3 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (4:6), to yield 603 mg (80%) of 10 as a colourless oil.

Second method (from 7): 2,6-di-tert-butyl-4-bromophenol (570 mg, 2 mmol) was dissolved in CH₂Cl₂ (10 mL) under an inert atmosphere and AlMe₃ (0.5 mL, 2M solution in hexane) was slowly added. The solution was stirred for 1 h, then compound 7 (130 mg, 0.5 mmol) and ketene diethyl acetal 5 (0.33 mL, 2.5 mmol) were added and the reaction was stirred for 10 min. The reaction was quenched with H₂O and extracted with CH₂Cl₂ (3 × 10 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to give a residue that was purified by silica gel column chromatography, eluting with hexane/EtOAc (4:6), to yield 115 mg (61%) of 10 as a colourless oil.

1H NMR (CDCl₃): δ 1.06-1.15 (m, 12H), 1.44-1.52 (m, 1H), 1.72 (d, 1H, J = 15.0 Hz), 1.91-2.00 (m, 4H), 2.23 (d, 1H, J = 15.0 Hz), 2.32-2.36 (m, 2H), 2.36-3.58 (m, 7H), 3.66-3.75 (m, 4H), 6.26 (br s, 1H). 13C NMR (CDCl₃): δ 14.6, 15.1, 15.3, 15.4, 23.7, 25.6, 27.4, 38.7, 52.0, 55.0, 55.1, 56.9, 57.7, 65.6, 99.3, 101.3, 170.2, 171.5. Anal. Calcd. for C₁₈H₃₃NO₇: C, 57.58; H, 8.86; N, 3.73. Found: C, 57.69; H, 8.78; N, 3.70.

N-(1-Hydroxymethyl-2-oxocyclobutyl)acetamide (11). To a solution of LiBH₄ (1.93 mL, 2M solution in THF) in dry Et₂O (35 mL), a solution of 7 (500 mg, 1.93 mmol) in dry Et₂O (15 mL) was added under an inert atmosphere, at 0 ºC. The reaction was warmed up to rt and stirred at this temperature for 7 h. The reaction was filtered and washed with Et₂O and EtOH. The organic solution was evaporated, dissassembled in
CHCl₃/iPrOH (4:1) and washed with brine. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to give a residue, which was purified by silica gel column chromatography, eluting with hexane/EtOAc (2:8). This compound was dissolved in THF (40 mL) and 1N HCl (10 mL) was added. The mixture was stirred for 5 h at rt and the solvent evaporated. The crude was purified by silica gel column chromatography, eluting with MeOH/EtOAc (1:9) to give 182 mg (60% yield for two steps) of 11 as a white solid (mp = 110-112 ºC). ¹H NMR (CD₃OD): δ 1.86 (s, 3H), 2.08 (td, 1H, J = 6.0 Hz, J = 12.0 Hz), 2.27-2.36 (m, 1H), 2.66-2.78 (m, 1H), 2.87-2.97 (m, 1H), 3.53 (d, 1H, J = 9.0 Hz), 3.64 (d, 1H, J = 9.0 Hz). ¹³C NMR (CD₃OD): δ 21.8, 22.8, 42.1, 63.5, 77.5, 173.0, 209.9. Anal. Calcd. for C₇H₁₁NO₃: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.39; H, 7.17; N, 8.83.

**N-[1-(tert-Butyldiphenylsilanyloxymethyl)-t-2-hydroxycyclobutyl]-r-acetamide (12).** Alcohol 11 (306 mg, 1.95 mmol) was dissolved in DMF (25 mL). Then, imidazole (397 mg, 5.85 mmol) and TBDPSCI (1.47 mL, 6.06 mmol) were added and the mixture was stirred at rt for 20 h. Subsequently, the reaction was evaporated to low pressure and an aqueous solution of 5% NaHCO₃ and EtOAc (15 mL) were added. The organic layer was separated and the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1). This residue, corresponding to the protected ketone (520 mg, 1.32 mmol), was dissolved in THF (20 mL) and the resulting solution was added to a suspension of NaBH₄ (55 mg, 1.45 mmol) at 0 ºC in EtOH (30 mL). The suspension was stirred at rt for 3 h and HCl 2N (2 mL) was added dropwise. The mixture was diluted with CHCl₃/iPrOH (4:1) (40 mL) and washed with brine (30 mL). The organic layer was dried, filtered and evaporated. The crude was
purified by silica gel column chromatography, eluting with hexane/EtOAc (4:6) to give 399 mg of the pure alcohol 12 (52%) as a white solid (mp = 117-119 °C). $^1$H NMR (CDCl$_3$): $\delta$ 1.07 (s, 9H), 1.43-1.48 (m, 1H), 1.73-1.86 (m, 4H), 2.08-2.23 (m, 2H), 3.96-4.04 (m, 2H), 4.27 (t, 1H, $J = 9.0$ Hz), 5.89 (br s, 1H), 7.36-7.43 (m, 6H), 7.60-7.65 (m, 4H). $^{13}$C NMR (CDCl$_3$): $\delta$ 19.4, 21.2, 23.2, 24.2, 26.7, 26.9, 29.7, 62.6, 63.1, 71.8, 127.7, 127.8, 129.7, 129.8, 133.3, 133.5, 135.5, 135.5, 170.2. Anal. Calcd. for C$_{23}$H$_{31}$NO$_3$Si: C, 69.48; H, 7.86; N, 3.52. Found: C, 69.61; H, 7.72; N, 3.47.

$N$-[t-2-Benzyloxy-1-(tert-butyldiphenylsilanyloxymethyl)cyclobutyl]-r-acetamide (13). To a stirred solution of alcohol 12 (120 mg, 0.30 mmol) in dry Et$_2$O under an inert atmosphere, benzyl-2,2,2-trichloroacetimidate (67 µL, 0.36 mmol) was added. The solution was cooled to 0 °C and triflic acid (5 µL, 0.06 mmol) was added dropwise, whereupon a white solid precipitated, which redissolved on warming to rt over 5 h. The reaction was quenched with aqueous saturated NaHCO$_3$ (5 mL), extracted with Et$_2$O (3 × 5 mL), and the combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (7:3) to give 59 mg (40% yield) of 13 as a colourless oil. $^1$H NMR (CDCl$_3$): $\delta$ 1.08 (s, 9H), 1.52-1.65 (m, 1H), 1.77-1.86 (m, 4H), 2.10-2.29 (m, 2H), 3.90-3.98 (m, 2H), 4.46, (s, 2H), 4.83 (t, 1H, $J = 9.0$ Hz), 5.73 (br s, 1H), 7.21-7.24 (m, 5H), 7.36-7.45 (m, 6H), 7.63-7.67 (m, 4H). $^{13}$C NMR (CDCl$_3$): $\delta$ 19.3, 20.8, 23.4, 24.3, 26.9, 63.1, 64.2, 71.9, 76.7, 127.5, 127.8, 128.2, 129.8, 129.9, 133.0, 133.2, 135.6, 135.6, 138.5, 170.1. Anal. Calcd. for C$_{30}$H$_{37}$NO$_3$Si: C, 73.88; H, 7.65; N, 2.87. Found: C, 73.72; H, 7.61; N, 2.92.

$N$-[t-2-Acetoxy-1-(tert-butyldiphenylsilanyloxymethyl)cyclobutyl]-r-acetamide (14). To a stirred solution of alcohol 12 (173 mg, 0.44 mmol) in pyridine (4 mL) under an inert atmosphere, Ac$_2$O (1.25 mL, 13 mmol) and DMAP (53 mg, 0.44 mmol) were
added. After stirring for 5 h at rt, Et₂O (15 mL) was added and the organic layer was washed with aqueous 0.5% HCl, aqueous saturated NaHCO₃ and brine, dried, filtered and concentrated. The residue was purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7) to give 166 mg (87%) of 14 as a white solid (mp = 108-110 ºC). \(^1\)H NMR (CDCl₃): \(\delta\) 1.06 (s, 9H), 1.90, (s, 3H), 1.91, (s, 3H), 1.97-2.10, (m, 3H), 2.20-2.26 (m, 1H), 3.86 (d, 1H, \(J\) = 12.0 Hz), 3.98 (d, 1H, \(J\) = 12.0 Hz), 4.98-5.10 (m, 1H), 6.49 (br s, 1H), 7.37-7.44 (m, 6H), 7.62-7.67 (m, 4H). \(^1^3\)C NMR (CDCl₃): \(\delta\) 19.1, 20.6, 22.7, 23.0, 23.4, 26.6, 61.9, 62.8, 72.6, 127.5, 127.6, 129.5, 129.6, 132.6, 133.3, 135.3, 135.4, 168.9, 171.5. Anal. Calcd. for C₂₅H₃₃NO₄Si: C, 68.30; H, 7.57; N, 3.19. Found: C, 68.42; H, 7.68; N, 3.07.

**1-Acetamido-c-2-benzyloxy cyclobutane-r-1-carboxylic acid methyl ester (15).** To a solution of compound 13 (58 mg, 0.12 mmol) in dry THF (5 mL), tetrabutylammonium fluoride (147 µL, 1M solution in THF) was added. The mixture was stirred for 4 h at rt, quenched by addition of aqueous saturated NH₄Cl and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1) to give the corresponding alcohol. A 1.5-fold excess of Jones reagent was dropwise added to a solution of this alcohol in acetone (5 mL) at 0 ºC over 5 min. The mixture was stirred at 0 ºC for 2 h. The excess of Jones reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with EtOAc (4 × 20 mL). The combined organic layers were dried and concentrated. In order to purified it, we transformed the carboxylic acid in its methyl ester by addition of diazomethane to a solution of the carboxylic acid in Et₂O. The mixture was stirred for 10 min, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (1:1) to give 17 mg
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(50%) of 15 as a colourless oil. $^1$H NMR (CDCl$_3$): $\delta$ 1.92 (s, 3H), 2.18-2.31 (m, 3H), 2.44-2.52 (m, 1H), 3.82 (s, 3H), 4.46-4.49 (m, 2H), 4.52-4.62 (m, 1H), 6.14 (br s, 1H), 7.24-7.37 (m, 5H). $^{13}$C NMR (CDCl$_3$): $\delta$ 22.7, 23.6, 24.4, 52.7, 66.4, 71.6, 76.9, 127.9, 127.9, 128.4, 137.6, 169.8, 171.6. Anal. Calcd. for C$_{15}$H$_{19}$NO$_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.83; H, 7.02; N, 5.12.

1-Acetamido-c-2-acetoxycyclobutane-r-1-carboxylic acid methyl ester (16). To a solution of compound 14 (166 mg, 0.37 mmol) in dry THF (15 mL), tetrabutylammonium fluoride (370 $\mu$L, 1M solution in THF) was added. The mixture was stirred for 30 min at rt, quenched by addition of aqueous saturated NH$_4$Cl and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with a gradient of MeOH/EtOAc (0:10→1:9) to give the corresponding alcohol. A 1.5-fold excess of Jones reagent was dropwise added to a solution of this alcohol in acetone (10 mL) at 0 $^\circ$C over 5 min. The mixture was stirred at 0 $^\circ$C for 1 h. The excess of Jones reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were dried and concentrated. In order to purified it, we transformed the carboxylic acid in its methyl ester by addition of diazomethane to a solution of the carboxylic acid in Et$_2$O. The mixture was stirred for 10 min, evaporated and purified by silica gel column chromatography, eluting with hexane/EtOAc (3:7) to give 33 mg (38%) of 16 as a colourless oil. $^1$H NMR (CDCl$_3$): $\delta$ 1.82-1.92 (m, 1H), 1.99 (s, 3H), 2.04 (s, 3H), 2.27-2.40 (m, 2H), 2.86-2.94 (m, 1H), 3.76 (s, 3H), 5.05 (t, 1H, $J = 9.0$ Hz), 6.82 (br s, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ 20.4, 22.9, 23.3, 24.8, 52.6, 65.2, 71.4, 170.1, 170.2, 171.7. Anal. Calcd. for C$_{10}$H$_{15}$NO$_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.28; H, 6.73; N, 6.13.
1-Acetamido-2-ethoxy-4-oxocyclohex-2-ene-1-carboxylic acid ethyl ester (17). To a solution of compound 10 (603 mg, 1.61 mmol) in THF (40 mL), an aqueous 1 N HCl solution (10 mL) was added. The solution was stirred at rt for 12 h and then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried, filtered and concentrated. The crude was dissolved in EtOH (50 mL) and DBU (2.0 mL, 13 mmol) was added. The reaction was stirred for 1 h and 1 N HCl (4 mL) was added and the excess of solvent was removed. The aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried, filtered, evaporated and purified by silica gel column chromatography, eluting with MeOH/EtOAc (5:95) to give 336 mg (78%) of compound 17 as a colourless oil. ¹H NMR (CDCl₃): δ 1.22-1.30 (m, 6H), 2.00 (s, 3H), 2.21-2.27 (m, 1H), 2.41-2.50 (m, 1H), 2.54-2.64 (m, 1H), 2.82-2.90 (m, 1H), 3.84-3.92 (m, 2H), 4.22-4.29 (m, 2H), 5.50 (s, 1H), 6.66 (br s, 1H). ¹³C NMR (CDCl₃): δ 13.8, 13.9, 23.5, 29.9, 33.6, 61.1, 63.0, 65.1, 105.5, 169.1, 169.9, 170.5, 197.7. Anal. Calcd. for C₁₃H₁₉NO₅: C, 57.98; H, 7.11; N, 5.20. Found: C, 58.10; H, 7.01; N, 5.12.
1-Benzamido-2,2-diethoxycyclobutane-1-carboxylic acid methyl ester (6).
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N-(1-Hydroxymethyl-2-oxoclobutyl)acetamide (11)
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$N$-[2-Benzyl-(tert-butyldiphenylsiloxymethyl)cyclobutyl]-$r$-acetamide (13)
$N\text{-}[r\text{-}2\text{-Acetoxy-1-(}\text{tert-butyldiphenylsilanyloxymethyl})\text{cyclobutyl}]-r\text{-acetamide (14)}$
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