The Tandem Heck – allylic substitution reaction; a Novel Route to lactams

Pedro Pinho, Adriaan J. Minnaard and Ben L. Feringa

Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.

General experimental information: Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. THF was dried and distilled from sodium/benzophenone, CH₃CN and DME were dried and distilled from CaH₂ and ether was dried and distilled from P₂O₅. The *n*-Bu₄NCl was crystallized by addition of dry ether to a saturated solution in reagent grade acetone and upon removal of the solvents dried at 70 °C under vacuum for 32h. The needed volume of dry CH₃CN to afford a 1M solution was then added and the reagent kept and used as such. Na₂CO₃ was purchased dry from commercial suppliers and stored in a Schlenk flask after further drying under vacuum at 120 °C for 24h. Thin-Layer Chromatography was performed on precoated plates, silica gel 60 F254 and flash chromatography on silica gel Merck Type 9385 230-400 mesh. All NMR spectra were recorded on a Varian XL 300 MHz in CDCl₃ solutions using the residual solvent peak as internal reference. Mass spectra and HRMS were obtained using an AEI MS-902. Melting points were determined on a Mettler FP1.

General procedure for the preparation of the *N*-tosylamides: The corresponding carboxylic acid was dissolved in dry THF under argon and tosyl isocyanate (1 equivalent) was added to the solution. After stirring at rt for 10 min the inert atmosphere was disconnected and Et₃N (1 equivalent) was added drop-wise to the open flask, allowing the release of the formed CO₂. After stirring for 1h at rt the solution was diluted with an equal volume of EtOAc and washed with 2M HCl and brine. After drying, the organic phase was concentrated and the product crystallized by addition of hexane to a saturated ether solution followed by filtration and washing with hexane.

This compound was obtained in 94 % yield as a white solid. Mp = 70 – 71 °C. ¹H NMR 2.38 (3H, s), 2.97 – 3.02 (2H, m), 5.08 – 5.21 (2H, m), 5.66 – 5.84 (1H, m), 7.27 – 7.34 (2H, m), 7.82 – 7.89 (2H, m) and 8.87 (1H, br s); ¹³C NMR 21.7, 41.2, 121.0, 128.4, 128.8, 129.6, 135.3, 145.3 and 168.6. MS (EI) *m/z* (rel intensity) 239 (M⁺, 1%), 155 (44), 108 (44), 91 (100) and 65 (36). HRMS: calcd for C₁₁H₁₃NO₃S (M⁺) *m/z* 239.0616, found 239.0611.

This compound was obtained in 96 % yield as a white solid. Mp = 88 – 89 °C. ¹H NMR 2.24 – 2.42 (4H, m), 2.43 (3H, s), 4.89 – 4.99 (2H, m), 5.61 – 5.78 (1H, m), 7.29 – 7.37 (2H, m), 7.91 – 7.97 (2H, m) and 9.20 (1H, br s); ¹³C NMR 21.6, 28.0, 35.3, 116.0, 128.2, 129.6, 135.4, 135.8, 145.1 and 170.7. MS (EI) *m/z* (rel intensity) 253 (M⁺, 5%), 155 (17), 108 (84), 92 (17), 91 (100) and 65 (56). HRMS: calcd for C₁₂H₁₅NO₃S (M⁺) *m/z* 253.0773, found 253.0767.

General procedure for the tandem cyclizations: A sealable Schlenk tube was loaded with dry Na_2CO_3 that was suspended in dry CH_3CN under argon. To the stirring mixture was then added $\text{P}(o\text{-tolyl})_3$ (11 mol%), $\text{Pd}(\text{OAc})_2$ (0.025M in CH_3CN , 5 mol%), the amide substrate (approx. 1 mmol), $n\text{-Bu}_4\text{NCl}$ (1M in CH_3CN , 200 mol%) and the vinyl bromide (200 mol%). The total amount of solvent was adapted to afford a 0.1M solution of the substrate. The mixture was then frozen in a nitrogen/ EtOH bath and the tube sealed under vacuum. After allowing to reach rt, the reaction was heated to 86°C and kept at that temperature for 16h. The mixture was then transferred to a roundbottom flask and silica gel was added just prior to solvent evaporation. The solid residue was then purified by flash chromatography to afford the pure product.

This compound was obtained in 41 % yield as a pale yellow oil. ^1H NMR 1.56 (3H, dd, $J = 6.6, 1.8$ Hz), 1.81 – 1.94 (1H, m), 2.24 – 2.72 (3H, m), 4.52 – 4.66 (1H, m), 5.28 (1H, ddq, $J = 15.6, 7.8, 1.8$ Hz), 5.54 (1H, ddq, $J = 15.6, 6.6, 0.9$ Hz) and 7.06 – 7.48 (5H, m); ^{13}C NMR 17.6, 26.5, 31.2, 62.2, 123.1, 125.1, 128.6, 128.7, 130.4, 132.1 and 174.4. MS (EI) m/z (rel intensity) 201 (M^+ , 100%), 186 (81), 161 (16), 160 (28), 146 (14), 144 (11) 93 (13) and 93 (13). HRMS: calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$ (M^+) m/z 201.1154, found 201.1158.

This compound was obtained in 82 % yield as a white solid. $\text{Mp} = 132 - 133^\circ\text{C}$. ^1H NMR 1.65 (3H, dd, $J = 6.6, 1.8$ Hz), 1.72 – 1.80 (1H, m), 2.17 – 2.53 (3H, m), 2.37 (3H, s), 4.76 – 4.84 (1H, m), 5.31 (1H, ddq, $J = 15.3, 8.1, 1.8$ Hz), 5.75 (1H, ddq, $J = 15.3, 6.6, 0.9$ Hz), 7.22 – 7.27 (2H, m) and 7.81 – 7.86 (2H, m); ^{13}C NMR 17.5, 21.6, 26.1, 30.7, 61.7, 128.6, 129.2, 129.5, 129.7, 136.1, 144.8 and 173.1. MS (EI) m/z (rel intensity) 280 ($\text{M}+1$, 21%), 215 (100), 200 (59), 155 (25), 124 (31) and 91 (57). MS (CI^+) m/z 297 ($\text{M}^+ + \text{NH}_4^+$) HRMS: calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3\text{S}$ ($\text{M}^+ + 1$) m/z 280.1007, found 280.1020.

This compound was obtained in 77 % yield as a white solid. $\text{Mp} = 138 - 139^\circ\text{C}$. ^1H NMR 1.58 (3H, s), 1.73 – 1.84 (1H, m), 2.14 – 2.57 (3H, m), 2.36 (3H, s), 4.72 – 4.80 (1H, m), 4.80 – 4.91 (2H, m), 7.21 – 7.30 (2H, m) and 7.81 – 7.90 (2H, m); ^{13}C NMR 18.4, 21.6, 24.5, 30.6, 64.2, 113.2, 128.5, 129.3, 135.5, 142.7, 145.0 and 173.4. MS (EI) m/z (rel intensity) 280 ($\text{M}+1$, 25%), 215 (100), 200 (53), 174 (38), 155 (39), 123 (28) and 91 (82). MS (CI^+) m/z 297 ($\text{M}^+ + \text{NH}_4^+$) HRMS: calcd for $\text{C}_{14}\text{H}_{18}\text{NO}_3\text{S}$ ($\text{M}^+ + 1$) m/z 280.1007, found 280.1016.

This compound was obtained in 53 % yield as a white solid. $\text{Mp} = 116 - 117^\circ\text{C}$. ^1H NMR 1.35 (3H, s), 1.59 (3H, d, $J = 6.6$ Hz), 1.74 – 1.84 (1H, m), 2.22 – 2.58 (3H, m), 2.43 (3H, s), 4.80 (1H, d, $J = 7.2$ Hz), 5.46 (1H, q, $J = 6.6$ Hz), 7.27 – 7.31 (2H, m) and 7.86 – 7.90 (2H, m); ^{13}C NMR 11.7, 13.1, 21.6, 24.2, 31.0, 66.0, 122.9, 128.5, 129.15, 129.24, 133.2, 144.8 and 173.6. MS (EI) m/z (rel intensity) 293 (M^+ , 43%), 229 (22), 214 (22), 155 (43), 138 (76), 110 (16), 95 (29), 91 (100), 81 (15) and 65 (30). HRMS: calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3\text{S}$ (M^+) m/z 293.1085, found 293.1082.

5d

This compound was obtained in 55 % yield as a white solid. Mp = 149 – 150 °C. ^1H NMR 1.28 – 1.66 (5H, m), 1.76 – 1.89 (2H, m), 1.94 – 2.30 (2H, m), 2.22 – 2.59 (3H, m), 2.43 (3H, s), 4.78 (1H, d, J = 8.4 Hz), 5.61 (1H, br s), 7.28 – 7.32 (2H, m) and 7.88 – 7.92 (2H, m); ^{13}C NMR 18.4, 21.7, 22.0, 23.8, 24.6, 24.8, 31.3, 65.1, 125.6, 128.5, 129.2, 135.3, 136.2, 144.8 and 177.5. MS (EI) m/z (rel intensity) 319 (M^+ , 31%), 254 (21), 164 (84), 155 (15), 147 (20), 91 (100), 84 (15), 79 (23) and 65 (25). HRMS: calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_3\text{S}$ (M^+) m/z 319.1242, found 319.1240.

6a

This compound was obtained in 81 % yield as a white solid. Mp = 115 – 116 °C. ^1H NMR 1.62 (3H, dd, J = 6.6, 1.5 Hz), 1.67 – 1.92 (3H, m), 2.18 – 2.52 (3H, m), 2.32 (3H, s), 5.01 – 5.16 (1H, m), 5.39 (1H, ddq, J = 15.3, 6.6, 1.5 Hz), 5.60 (1H, ddq, J = 15.3, 6.6, 1.2 Hz), 7.18 – 7.23 (2H, m) and 7.80 – 7.85 (2H, m); ^{13}C NMR 16.2, 17.6, 21.6, 29.1, 33.3, 58.0, 128.86, 128.94, 129.3, 129.6, 136.4, 144.4 and 170.3. MS (EI) m/z (rel intensity) 294 ($\text{M}+1$, 24%), 229 (85), 214 (37), 155 (22), 122 (17), 108 (72), 107 (43) and 91 (100). MS (CI^+) m/z 311 ($\text{M}^+ + \text{NH}_4^+$) HRMS: calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{S}$ ($\text{M}^+ + 1$) m/z 294.1163, found 294.1156.

6b

This compound was obtained in 75 % yield as a white solid. Mp = 126 – 127 °C. ^1H NMR 1.58 – 1.84 (2H, m), 1.76 (3H, s), 1.95 – 2.04 (1H, m), 2.22 – 2.48 (3H, m), 2.35 (3H, s), 4.66 (1H, br s), 4.96 – 5.02 (2H, m), 7.20 – 7.24 (2H, m) and 7.82 – 7.86 (2H, m); ^{13}C NMR 15.9, 20.5, 21.6, 26.0, 33.0, 61.0, 113.6, 128.9, 129.4, 136.2, 143.1, 144.6 and 170.4. MS (EI) m/z (rel intensity) 294 ($\text{M}+1$, 21%), 229 (100), 214 (22), 188 (59), 155 (25), 108 (55) and 91 (77). MS (CI^+) m/z 311 ($\text{M}^+ + \text{NH}_4^+$) HRMS: calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3\text{S}$ ($\text{M}^+ + 1$) m/z 294.1163, found 294.1164.

6c

This compound was obtained in 50 % yield as a white solid. Mp = 136 – 137 °C. ^1H NMR 1.51 (3H, d, J = 6.6 Hz), 1.58 (3H, s), 1.60 – 1.86 (3H, m), 2.22 – 2.24 (3H, m), 2.37 (3H, s), 4.94 (1H, br s), 5.03 (1H, q, J = 6.6 Hz), 7.19 – 7.24 (2H, m) and 7.78 – 7.83 (2H, m); ^{13}C NMR 13.1, 14.6, 16.0, 21.6, 26.4, 33.3, 62.0, 121.6, 128.7, 129.5, 133.4, 136.2, 144.4 and 170.7. MS (EI) m/z (rel intensity) 307 (M^+ , 2%), 244 (19), 243 (94), 188 (20), 155 (25), 152 (41), 136 (20), 124 (27), 108 (54), 107 (36) and 91 (100). HRMS: calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{S}$ (M^+) m/z 307.1242, found 307.1244.

6d

This compound was obtained in 49 % yield as a white solid. Mp = 153 – 154 °C. ^1H NMR 1.50 – 2.20 (12H, m), 2.34 – 2.56 (2H, m), 2.46 (3H, s), 5.02 (1H, br s), 5.28 (1H, br s), 7.29 – 7.34 (2H, m) and 7.93 – 7.98 (2H, m); ^{13}C NMR 16.1, 21.6, 22.2, 24.7, 26.4, 26.7, 33.3, 61.2, 124.4, 128.8, 129.6, 135.5, 136.2, 144.4 and 170.7. MS (EI) m/z (rel intensity) 333 (M^+ , 13%), 314 (23), 270 (20), 269 (92), 178 (100), 162 (18), 155 (16), 150 (19), 149 (19), 108 (23), 107 (31), 91 (81) and 79 (26). HRMS: calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_3\text{S}$ (M^+) m/z 333.1399, found 333.1409.

Desulfonylation procedure: Naphthalene (6 equiv with respect to **5a**) was dissolved in dry and degassed DME under argon. To the solution was then added sodium metal (1 equiv with respect to the naphthalene) in small pieces and the mixture sonicated until a deep-green solution of sodium-naphthalenide was obtained (10 – 15 min). The solution was further stirred at rt for 2h before being cooled to 0 °C and treated with a solution of **5a** in the same solvent. After addition the system was kept at 0 °C for 20 min, after which the reaction was quenched by addition of saturated NH_4Cl solution. Extraction with three portions of EtOAc afforded a residue that was purified first by filtration through silica to remove the excess naphthalene and then by preparative TLC to yield **7** in 79%.²

7

^1H NMR 1.69 (3H, dd, J = 6.6, 1.8 Hz), 1.72 – 1.85 (1H, m), 2.22 – 2.43 (3H, m), 4.02 – 4.18 (1H, m), 5.39 (1H, ddq, J = 15.3, 7.8, 1.8 Hz), 5.52 (1H, br s) and 5.63 (1H, ddq, J = 15.3, 6.6, 0.9 Hz); ^{13}C NMR 17.5, 28.5, 30.1, 56.4, 127.5, 131.8 and 178.2. MS (EI) m/z (rel intensity) 125 (M^+ , 51%), 110 (100). HRMS: calcd for $\text{C}_7\text{H}_{11}\text{NO}$ (M^+) m/z 125.0841, found 125.0872.

¹ A melting point of 93.5–94.5 °C for compound **3** has been reported, although without further characterization, see: Biloski, A.J.; Wood, R.D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233.

² Compound **7** has been prepared before, but no spectroscopic details were reported, see: Vedejs, E.; Meier, G.P. *Tetrahedron Lett.* **1979**, 4185.