Tandem Reactions to Construct Heterocycles via Phosphine-Catalyzed Umpolung Addition and Intramolecular Conjugate Addition

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Supporting Information

Compounds **1d**¹, **1e**², **1f**¹, **2a**³, **2b**⁴, **2c**⁵, **3b**⁶, **3c**⁷, **3d**⁸, **3e**⁹, **4a**¹⁰, **4f**¹¹ were prepared by the methods described in the literature cited at the end of the supporting information.

Typical procedure for the phosphine-catalyzed tandem nucleophilic additions:

To a solution of **1a** (56 mg, 0.5 mmol) and triphenylphosphine (6.5 mg, 0.025 mol) in toluene (1.5 mL) at 70°C under nitrogen was added a solution of **2b** (41 mg, 0.5 mmol) in toluene (1 mL). After the reaction was completed as monitored by TLC, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate:petroleum ether = 2:1) to give **5b** as a yellow oil (81mg, 84%).

For the reaction of **1b** or **1c** with **2b** (Table 1, entries 4 and 5), a solution of 1 equiv of **2b** in toluene was added dropwise to the solution of 5 equiv of **1b** or **1c** and 0.05 equiv of triphenylphosphine in toluene at 70°C by a syringe over the indicated

time. For the reaction of **1d** or **1e** with **3b**, **3c**, **3e** or **4f** (Table 1, entries 9, 11, 12 and 14), 1.1 equiv of alkynone in toluene or CH₃CN was added dropwise to the solution of 1 equiv of bifunctional nucleophile and 0.2 equiv of triphenylphosphine in toluene or CH₃CN at 80°C by a syringe over 12 hrs and the mixture was heated for another 12hrs.

2-Ethoxycarbonylmethyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one (5a)

Oil. IR (neat) ν 2947, 1736, 1635, 1404, 1181 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 5.14 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.98 (dd, J = 14.6, 10.1 Hz, 1H), 2.74 (dd, J = 16, 7.7 Hz, 1H), 2.57 (dd, J = 16, 5.7 Hz, 1H), 2.45 (dd, J = 14.6, 5.7 Hz, 1H), 2.37 (t, J = 6.5 Hz, 2H), 2.30 (t, J = 6.5 Hz, 2H), 1.99 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 195.25, 176.71, 169.53, 112.48, 80.91, 60.61, 40.53, 36.09, 31.10, 23.57, 21.36, 13.88. MS (m/z) 224 (M⁺), 179, 178, 150, 137 (100), 108, 81, 48, 41. Anal. Calcd for C₁₂H₁₆O₄: C, 64.27; H, 7.19. Found C, 64.18; H, 7.32.

Cis-(3'-Ethoxycarbonylprop-2'-enyl)-2-hydroxycyclohex-1-en-6-one (6a)

Mp 93-94°C. IR (KBr) ν 2956, 2558, 1722, 1645, 1565, 1359, 1272, 1190, 1076 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 9.80 (s, 1H), 6.29 (dt, J = 11.3, 9.2 Hz, 1H), 5.73 (d, J = 11.3 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.45 (t, J = 9.2 Hz, 2H), 2.39 (t, J = 6.5 Hz, 2H), 2.29 (t, J = 6.5 Hz, 2H), 1.86 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 197.85, 174.35, 170.06, 147.61, 117.97, 110.45, 61.31, 36.34, 29.12, 22.29,

20.51, 13.96. MS (m/z) 224 (M^+), 178, 151, 150(100), 149, 137, 55, 43, 41. Anal.

Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found C, 64.10; H, 7.16.

***Trans*-(3'-Ethoxycarbonylprop-2'-enyl)-2-hydroxycyclohex-1-en-6-one (6b)**

Mp 132-133°C. IR (KBr) ν 2820, 2606, 1714, 1567, 1386, 1273 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 6.92 (dt, $J = 15.6, 6.5$ Hz, 1H), 5.77 (d, $J = 15.6$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.19 (t, $J = 6.5$ Hz, 1H), 2.47 (m, 4H), 1.97 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.52, 147.53, 120.60, 111.93, 60.30, 32.70, 24.71, 20.63, 14.18. MS (m/z) 224 (M^+), 179, 150 (100), 149, 95, 55, 43, 42. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found C, 64.11; H, 7.13.

2-Acetylmethyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one (5b)

Oil. IR (neat) ν 2948, 1715, 1628, 1406, 1233, 1181 cm^{-1} . 1H NMR (300 MHz, $CDCl_3$) δ 5.21 (m, 1H), 3.06 (dd, $J = 10.5, 14.7$ Hz, 1H), 2.98 (dd, $J = 17.4, 7.2$ Hz, 1H), 2.75 (dd, $J = 17.4, 4.8$ Hz, 1H), 2.46 (dd, $J = 14.7, 7.2$ Hz, 1H), 2.42 (t, $J = 6.2$ Hz, 2H), 2.35 (t, $J = 6.5$ Hz, 2H), 2.22 (s, 3H), 2.03 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.00, 195.34, 176.84, 112.61, 80.56, 49.26, 36.17, 31.43, 30.36, 23.68, 21.43. MS (m/z) 194 (M^+), 137 (100), 108, 96, 95, 81, 55, 43, 41. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found C, 64.04; H, 7.54.

2-Benzoylmethyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one (5c)

Mp 101-102. IR (KBr) ν 2952, 1679, 1648, 1629, 1412, 1212, 1182, 758, 688 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.96 (d, $J = 7.2$ Hz, 2H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.48 (t, $J = 7.2$ Hz), 5.43 (m, 1H), 3.55 (dd, $J = 17.2, 7.1$ Hz), 3.25 (dd, $J = 17.2, 6.8$ Hz, 1H), 3.13 (dd, $J = 14.6, 7.2$ Hz, 1H), 2.56 (dd, $J = 14.6, 7.2$ Hz, 1H), 2.40 (t, $J = 6.4$ Hz, 2H), 2.35 (t, $J = 6.4$ Hz, 2H), 2.04 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 196.34, 195.33, 176.89, 136.24, 133.39, 128.54, 127.89, 112.74, 81.02, 44.44, 36.22, 31.63, 23.71, 21.46. MS (m/z) 259 ($M^+ + 1$, 100), 258 (M^+), 137, 120, 108, 105, 77, 51. Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{O}_3$: C, 74.98; H, 6.29. Found C, 74.99; H, 6.31.

2-Acetylmethyl-4-acetyl-5-methyl-2,3-dihydrofuran (5d)

Oil. IR (neat) ν 2926, 1716, 1670, 1618, 1602, 1324, 1228 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 5.02 (m, 1H), 3.17 (dd, $J = 11.5, 14.3$ Hz, 1H), 2.96 (dd, $J = 17.0, 7.1$ Hz, 1H), 2.71 (dd, $J = 17.0, 6.2$ Hz, 1H), 2.57 (dd, $J = 14.3, 7.5$ Hz, 1H), 2.21 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 205.40, 194.29, 166.93, 111.61, 77.41, 49.25, 35.95, 30.40, 29.22, 14.73. MS (m/z) 182 (M^+), 125, 109, 97, 43 (100), 41. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3$: C, 68.02; H, 7.27. Found C, 64.04; H, 7.54.

2-Acetylmethyl-4-ethoxycarbonyl-5-methyl-2,3-dihydrofuran (5e)

Mp 43-44°C. IR (KBr) ν 2982, 1716, 1698, 1648, 1602, 1375, 1227, 1068 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 5.04 (m, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.12 (dd, $J = 10.2$, 14.4 Hz, 1H), 2.96 (dd, $J = 17.1$, 7.0 Hz, 1H), 2.71 (dd, $J = 17.1$, 6.0 Hz, 1H), 2.51 (dd, $J = 14.4$, 7.5 Hz, 1H), 2.2 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 205.57, 167.17, 165.90, 101.52, 77.37, 59.32, 49.40, 35.30, 30.48, 14.27, 13.89. MS (m/z) 212 (M^+), 167, 155, 154, 126, 1102, 43 (100). Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_4$: C, 62.25; H, 7.60. Found C, 62.48; H, 7.74.

2-Benzyloxycarbonylmethyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one (5f)

Oil. IR (neat) ν 2948, 1737, 1635, 1404, 1181, 752, 699 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.26-7.38 (m, 5H), 5.21 (m, 1H), 5.16 (s, 2H), 3.02 (dd, $J = 10.2$, 14.7 Hz, 1H), 2.82 (dd, $J = 16.2$, 7.8 Hz, 1H), 2.69 (dd, $J = 16.2$, 5.7 Hz, 1H), 2.51 (dd, $J = 14.7$, 7.2 Hz, 1H), 2.39 (t, $J = 6.3$ Hz, 2H), 2.33 (t, $J = 6.3$ Hz, 2H), 2.02 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 195.38, 176.77, 169.55, 135.33, 128.50, 128.30, 128.18, 112.66, 80.93, 66.60, 40.68, 36.26, 31.30, 23.71, 21.49. MS (m/z) 210 (M^+), 178, 150, 137 (100), 108, 43, 41. Anal. Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4$: C, 71.31; H, 6.34. Found C, 71.60; H, 6.73.

2-Cyclohexanoylmethyl-3,5,6,7-tetrahydro-2H-benzofuran-4-one (5g)

Oil. IR (neat) ν 2932, 2856, 1707, 1648, 1633, 1404, 1231, 1182 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 5.22 (m, 1H), 2.96-3.08 (m, 2H), 2.74 (dd, J = 17.1, 5.8 Hz, 1H), 2.32-2.45 (m, 5H), 2.03 (m, 2H), 1.67-1.88 (m, 5H), 1.18-1.40 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3): δ 210.51, 195.81, 177.36, 112.84, 81.15, 51.09, 46.40, 36.24, 31.64, 28.12, 28.04, 25.67, 25.46, 25.43, 23.88, 21.56. MS (m/z) 264 (M^{+2} , 100), 153, 137, 83, 81, 55, 41. Anal. Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_3$: C, 73.25; H, 8.45. Found C, 72.96; H, 8.05.

***N, N'*-Di-(*p*-toluenesulfonyl)-2-acetylmethyl-piperazine (5h)**

Mp 146-147°C. IR (KBr) ν 2924, 1701, 1341, 1168, 942, 667 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.60 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 4.50 (brd, J = 8.7 Hz, 1H), 3.80 (dd, J = 13.2, 1.5 Hz, 1H), 3.69 (dt, J = 11.7, 1.5 Hz, 1H), 3.50 (dt, J = 11.7, 1.8 Hz, 1H), 3.07-3.20 (m, 2H), 2.45 (s, 3H), 2.41 (s, 3H), 2.21-2.38 (m, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 205.21, 143.93, 143.72, 136.63, 132.21, 129.73, 129.66, 127.29, 126.81, 48.64, 47.97, 45.30, 41.28, 40.61, 30.28, 21.37, 21.32. MS (m/z) 392 ($M^{+}-\text{CH}_3\text{COCH}_3$), 295, 253, 155, 140, 91(100), 65. Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_5\text{S}_2$: C, 55.98; H, 5.82; N, 6.22. Found C, 55.99; H, 5.79; N, 6.05.

***N, N'*-Di-(*p*-toluenesulfonyl)-2-benzoylmethyl-piperazine (5i)**

Workup up procedure: This product precipitated from the reaction mixture and was collected by filtration. Ether was added to the filtrate and the mixture was filtered again. The combined solid was washed with ether and crystallized from CH₂Cl₂-petroleum ether. (The crude product was almost pure when judged from its ¹H NMR.)

Mp 210-211°C. IR (KBr) ν 2922, 1682, 1341, 1170, 938, 670 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.59 (d, J = 8.4 Hz, 2H), 7.53-7.61 (m, 5H), 7.44 (t, J = 7.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 4.73 (brd, J = 8.7 Hz, 1H), 3.88 (d, J = 13.2 Hz, 1H), 3.74 (d, J = 11.7, 1H), 3.52-3.65 (m, 2H), 3.21 (dt, J = 3.0, 13.2 Hz, 1H), 2.73 (d, J = 13.2 Hz, 2H), 2.42 (s, 3H), 2.35-2.46 (m, 2H), 2.32 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 196.64, 144.10, 143.82, 136.75, 136.27, 133.48, 132.41, 129.89, 128.57, 127.97, 127.55, 127.01, 49.30, 48.64, 45.67, 40.96, 36.67, 21.54, 21.43. MS (m/z) 407 (M⁺-PhCO), 393, 392, 357, 237, 105 (100). Anal. Calcd for C₂₆H₂₈N₂O₅S₂: C, 60.92; H, 5.51; N, 5.46. Found C, 60.95; H, 5.35; N, 5.66.

***N,N'*-Di-(*p*-toluenesulfonyl)-2-cyclohexanoylmethyl-piperazine (5j)**

Mp 142-143°C IR (KBr) ν 2931, 2855, 1702, 1344, 1162, 941 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.59 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.51 (brd, J = 8.4 Hz, 1H), 3.82 (d, J = 12.9 Hz, 1H), 3.69 (d, J = 11.7, 1H), 3.45 (d, J = 11.7 Hz, 1H), 3.18 (dd, J = 10.5, 18 Hz, 1H), 3.12

(dt $J = 3.3, 12.9$ Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H), 2.12-2.31 (m, 4H), 1.63-1.77 (m, 5H), 1.18-1.27(m, 5H). ^{13}C NMR (75 MHz, CDCl_3): δ 210.59, 143.97, 143.69, 136.76, 132.16, 129.77, 127.38, 126.88, 50.82, 48.79, 47.99, 45.53, 40.69, 38.23, 28.11, 28.06, 25.59, 25.37, 25.36, 21.45, 21.38. MS (m/z) 363 (M^+ -Ts), 253, 237, 208 (100), 154, 91, 83, 55. Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_5\text{S}_2$: C, 60.21; H, 6.61; N, 5.40. Found C, 60.17; H, 6.49; N, 5.19.

***N*-(*p*-Toluenesulfonyl)-2-acetylmethylmorpholine (5k)**

Mp 86-87°C IR (KBr) ν 2922, 2899, 1722 1344, 1160, 752 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.63 (d, $J = 8.1$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 4.02 (m, 1H), 3.87 (dq, $J = 1.7, 11.7$ Hz, 1H), 3.68 (dt, $J = 2.7, 11.7$, 1H), 3.53 (m, 2H), 2.59 (dd, $J = 7.6, 18.0$ Hz, 1H), 2.45 (s, 3H), 2.39-2.48 (m, 2H), 2.16 (s, 3H), 2.15 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 205.14, 143.85, 131.90, 129.64, 127.61, 71.15, 65.59, 49.54, 46.33, 45.12, 30.55, 21.36. MS (m/z) 407 (M^+ -PhCO), 393, 392, 357, 237, 105 (100). Anal. Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_4\text{S}$: C, 56.55; H, 6.44; N, 4.71. Found C, 56.40; H, 6.42; N, 4.57.

***N*-(*p*-Toluenesulfonyl)-2-cyclohexanoylmethylmorpholine (5l)**

Mp 99-100°C IR (KBr) ν 2931, 2854, 1712 1348, 1168, 979, 756 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, $J = 8.1$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 4.03 (m, 1H), 3.86 (dt, $J = 10.2, 1.5$ Hz, 1H), 3.66 (dt, $J = 2.7, 11.4$, 1H), 3.58 (d, $J = 11.4$ Hz, 1H), 3.49 (d, $J = 11.4$ Hz, 1H), 2.66 (dd, $J = 7.5, 16.5$ Hz, 1H), 2.45 (s, 3H), 2.40-2.49 (m, 2H), 2.16

(s, 3H), 2.31 (m, 1H), 2.17 (t, $J = 10.7$ Hz), 1.76-1.83 (m, 4H), 1.66 (m, 1H), 1.16-1.36 (m, 5H). ^{13}C NMR (75 MHz, CDCl_3): δ 210.08, 143.77, 131.99, 129.59, 127.61, 71.14, 65.52, 50.99, 49.63, 45.15, 43.33, 27.91, 27.87, 25.59, 25.35, 25.31, 21.36. MS (m/z) 366 ($M^+ + 1$), 254, 239 (100), 210, 91, 81, 55, 41. Anal. Calcd for $\text{C}_{19}\text{H}_{27}\text{NO}_4\text{S}$: C, 62.44; H, 3.83; N, 4.71. Found C, 62.45; H, 7.23; N, 3.71.

Crystallographic data for **5l**: $\text{C}_{19}\text{H}_{27}\text{NO}_4\text{S}$, F.W. = 365.48, monoclinic, space group C2/c , $a = 17.4458(17)$ Å, $b = 14.1729(13)$ Å, $c = 16.0903(15)$ Å, $V = 3906.8$ (6) Å³, $Z = 8$, $\mu(\text{MoK}\alpha) = 1.243\text{g/cm}^3$, $F(000) = 1568$, $T = 293\text{K}$. The intensity data were collected on a Rigaku AFC7R diffractometer with $\text{MoK}\alpha$ radiation ($\lambda = 0.71073$ Å, graphite monochromator) and 12 kW rotating anode generator. 2θ range (3.72 – 56.56); 11587 measured reflections. The 4583 reflections [$R(\text{int}) = 0.0487$] were used in refinement; good of fit indicator, 0.740; R (R_w) = 0.0451 (0.0776); $p_{\text{max}}, p_{\text{min}} = 0.173, -0.134$ e/Å³.

Ethyl *N,N'*-di-(*p*-toluenesulfonyl)piperazine-2-carboxylate (**5m**)

Mp 146-147°C. (150.9-154.9 °C lit.¹²) ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, $J = 8.4$ Hz), 7.61 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 4.74 (m, 1H), 4.22 (dt, $J = 11.7, 1.8$ Hz, 1H), 4.09 (q, $J = 7.2$ Hz), 3.71 (m, 2H), 3.45 (dt, $J = 12.3, 3.3$ Hz, 1H), 2.54 (dd, $J = 3.6, 11.7$ Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.36 (dd, $J = 3.6, 11.7$ Hz, 1H), 1.20 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 167.53, 143.97, 143.44, 136.00, 131.88, 129.62, 129.29, 127.36, 126.95, 61.62, 54.65, 48.10, 45.31, 41.40, 21.24, 13.70.

***N,N'*-Di-(*p*-toluenesulfonyl)-2-butyrylpiperazine (5n)**

Mp 142-143°C IR (KBr) ν 2938, 2935, 1724, 1341, 1169, 942 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.60-7.63 (m, 4H), 7.32 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 4.60 (m, 1H), 4.22 (dt, J = 12.6, 1.5 Hz, 1H), 3.71 (dt, J = 13.2, 1.5 Hz, 1H), 3.56 (dt, J = 11.5, 1.5 Hz, 1H), 3.33 (dd, J = 3.3, 12.6 Hz, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.37-2.59 (m, 3H), 2.31 (dt, J = 3.3, 11.5 Hz, 1H), 1.59 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 204.21, 144.32, 143.68, 136.40, 131.82, 129.85, 129.54, 127.64, 127.15, 61.15, 46.87, 45.37, 41.77, 40.81, 21.48, 16.68, 13.48. MS (m/z) 394 ($\text{M}^+ - \text{C}_3\text{H}_6\text{CO}$), 393, 238 (100), 155, 91, 83, 55. Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5\text{S}_2$: C, 56.87; H, 6.07; N, 6.03. Found C, 56.76; H, 6.15; N, 5.91.

***Ethyl N,N'*-di-(*p*-toluenesulfonyl)diazepane-2-carboxylate (5o)**

Oil. IR (neat) ν 1716, 1342, 1160, 736 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 7.71 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.5 Hz, 4H), 4.88 (t, J = 6.0 Hz, 1H), 4.10 (m, 2H), 3.84 (dt, J = 15.3, 4.2 Hz, 1H), 3.72 (dd, J = 6.6, 14.7 Hz, 1H), 3.60 (dd, J = 5.1, 14.7 Hz, 1H), 3.42 (ddd, J = 3.6, 7.2, 15.3 Hz, 1H), 3.24 (m, 2H), 2.43 (s, 3H), 2.42 (s, 3H), 1.81 (m, 2H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 169.12, 143.53, 143.34, 136.79, 135.44, 129.70, 129.39, 127.07, 126.82, 61.53, 59.29, 51.19, 49.16, 43.58, 29.14, 21.30, 13.74. MS (m/z) 407 ($\text{M}^+ - \text{CO}_2\text{Et}$), 325 (100), 252, 210, 155, 116, 97, 91. Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_6\text{S}_2$: C, 54.98; H, 5.87; N, 5.83.

Found C, 54.62; H, 5.82; N, 5.80.

Synthesis of piperazine-2-carboxylic acid:

A suspension of **5m** (290mg, 0.62mmol) in 48% HBr (3mL) was heated under reflux for 48hrs. The reactant disappeared and white solid precipitated during this period. The mixture was then cooled and the solid was collected by filtration. The filtrate was concentrated (ca 1mL) and white solid precipitated again. The combined solid was recrystallized from acetone-water to give piperazine-2-carboxylic acid dihydrobromide 128 mg (71 %). Mp 275°C(d) (282°C lit.¹³) ¹H NMR (300 MHz, D₂O) δ 4.21 (m, 1H) 3.94 (dd, J = 3.9, 14.1 Hz, 1H), 3.72 (m, 2H), 3.34-3.52 (m, 3H).

N,N'-Di-(*p*-toluenesulfonyl)-5-methylene-6,9-diazanonan-4-one (**6c**)

This product (α -adduct) was isolated (22%) from the reaction of bifunctional nitrogen nucleophile **1d** with electron-deficient alkyne **4f** (the reaction condition was similar to that described in Table 1, No. 14, except that the reaction time was shortened to 10 hrs). Cyclized product **5n** was isolated in 62% yield in this reaction. The α -adduct was used in the control experiment described below.

Oil. IR (neat) ν 3284, 2965, 1695, 1336, 1263cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 8.1 Hz, 4H), 6.10 (d, J = 1.5 Hz, 1H), 5.64 (t, J = 6.0 Hz, 1H), 5.53 (t, J = 1.5 Hz, 1H), 3.40 (t, J = 6.0 Hz, 2H), 3.02 (dd, J = 6.0, 11.1 Hz, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.42 (s, 3H), 1.61 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 198.99, 144.57, 144.25, 143.28, 136.74, 134.44, 129.59, 127.80, 127.06, 124.74, 49.55, 41.56, 40.14, 21.52, 21.44, 17.32,

13.56. MS (m/z) 393 (M^+ -COC₃H₇), 309, 280, 155, 126, 91, 65. Anal. Calcd for C₂₂H₂₈NO₅S₂: C, 56.87; H, 6.07; N, 6.03. Found C, 56.77; H, 6.12; N, 5.91.

Control experiment:

Reaction of 6a in the presence or in the absence of Ph₃P:

A solution of **6a** (25mg, 0.11mmol) and Ph₃P (5.8mg, 0.022mmol) in toluene was heated at 110°C for 48 hrs. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate:petroleum ether = 2:1) to give **5a** (23mg), 92%.

Heating a solution of **6a** in toluene at 110°C in the absence of Ph₃P gave disordered results.

Reaction of 6c in the presence or in the absence of Ph₃P:

A solution of **6c** (28mg, 0.06mmol) and Ph₃P (3.1mg, 0.012mmol) in 0.5 ml toluene-CH₃CN (v:v=4:1) was heated at 80°C for 17hrs. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate:petroleum ether = 2:1) to give **5n** (23mg), 82%.

No reaction occurred in the absence of Ph₃P.

References:

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1c6-30-2
 Archive directory: /export/home/tu-xy/vmr/sys/data
 Sample directory:
 Pulse Sequence: s2pu1
 Solvent: CDCl3
 Ambient temperature
 F1: 500.13602418
 Mercury-30088 "NMK390"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.500 sec
 SFO 1282.43 Hz
 48 repetitions
 OBSERVE C13: 75.442103 MHz
 DECOUPLE H1: 500.0294698 MHz
 Power 41 dB
 Comments: 17.09
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 F1 size 65536
 Total time 11 hr, 59 min, 18 sec

1c6-30-1
 Archive directory: /export/home/ju-xy/vnmr2ys/data
 Sample directory:
 Pulse Sequence: s2put
 Solvent: CDCl3
 Ambient temperature: 197.847
 Frequency: 125.761 MHz
 Mercury-3000B "OMC300"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 7.500 sec
 Width 1867.4 Hz
 72 repetitions
 OBSERVE C13 75.442105 MHz
 DECOUPLE H1 300.029638 MHz
 SAMPLE 18
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line processing 1.0 Hz
 F1 size 4533
 F2 size 4533
 Total time 11 hr, 59 min, 18 sec

z1g9-24
 Archive directory: /export/home/ju-xy/vnmr/sy5/data
 Sample directory:
 Pulse Sequence: szput1
 Solvent: CDCl3
 Ambient temperature
 F1 frequency: 125.761 MHz
 F2 frequency: 62.901 MHz
 Mercury-300B8
 Relax, delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.000 sec
 Vth 237.800 sec
 104 repetitions
 OBSERVE C13: 75.442099 MHz
 DECOUPLE H1: 300.0294698 MHz
 CONTINUOUSLY ON
 WALTZ-16 modulated
 DATA PROCESSING
 F1 freq 125.761072 MHz
 F2 freq 62.901072 MHz
 Total time 12 hr, 44 min, 18 sec

fgb2102403c
 Archive directory: /export/home/lu-xy/vnmr/sys/data
 Sample directory:
 Pulse Sequence: szpu1
 Solvent: CDCl3
 F1 (nucl1): 13C
 F2 (nucl2): 13C
 Mercury-300MHz "NMR300"
 Relax. delay 1.000 sec
 Pulse 45.0 degrees
 Acq. time 1.500 sec
 Nucl1 freq 125.761 MHz
 72 repetitions
 OBSERVE C13, 75.4421036 MHz
 DECOUPLE H1, 300.0234638 MHz
 Power 14.8
 Continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 F1 size 131.2
 Total time 12 hr, 44 min, 15 sec

t3-50
 Archive directory: /export/home/lu-xy/vnmr/sy/data
 Sample directory:
 File: PROTON
 Pulse Sequence: szpu1

1c5-41-c13
 Archive directory: /export/home/ju-xy/vnmr/sys/data
 Sample directory:
 Pulse Sequence: zgpg30
 Solvent: CDCl3
 Ambient temperature
 File: 1c5-41-c13
 Mercury-300BS "MERCURYx300"
 Relax delay: 1.000 sec
 Pulse: 51.1 deg
 Acq. time: 2.000 sec
 Width: 18867.9 Hz
 28 repetitions 75.4421076 MHz
 DECOUPLE H1: 300.0294698 MHz
 Power: 39 dB
 Continuously on
 300.0294698 MHz
 Data: 280 scans
 Line broadening 0.7 Hz
 FT size 131072
 Total time 14 hr, 55 min, 8 sec

13C OBSERVE

Archive directory: /export/home/zhang-zg/vmr/sys/data
Sample directory:

Pulse Sequence: zgpg30

Solvent: CDCl3

Ambient temperature

File: 1c4-81-c13

Mercury-3000B "MERCURY-3000"

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 2.080 sec

Width 18867.9 Hz

Observed C13 125.442064 MHz

DECOUPLE H1, 300.024558 MHz

Power 42 dB

Continuously on

Waltz-16 modulation

DATA PROCESSING

Line broadening 1.0 Hz

FT size 131072

Total time 14 hr. 55 min. 8 sec

144.101
143.815
136.747
136.274
133.484
132.412
129.893
129.813
128.565
127.966
127.546
127.012
77.424
77.000
76.576
49.298
48.638
45.669
40.955
36.666
21.535
21.432

1c4-66
Pulse Sequence: zgpg30
Solvent: CDCl3
Amplitude: 12.00 dB
Frequency: 125.76 MHz
Mercury-3000B
Pulse: 67.8 degrees
Acq. Time: 2.000 sec
X1: 125.76 MHz
X2: 125.76 MHz
OBSERVE: C13, 125.4421043 MHz
DECOUPLE: H1, 300.0294698 MHz
Power: 12.00 dB
Modulation: WALTZ-16 modulated
Data Processing: Line broadening 0.5 Hz
F2: 125.76 MHz
Total Time: 1204 hr, 57 min, 4 sec

1c5-42-c13
 Archive directory: /export/home/tu-xy/vnmr/sy/s/data
 Sample directory:
 Pulse Sequence: zgpg30
 Solvent: DMSO-d6
 Acquire: 120 min
 File: 1c5-42-c13
 Mercury-300BB "MERCURYv3.00"
 Relax: delay 1.000 sec
 Pulse: 45.0 degrees
 Acq: 120.0 sec
 Width: 18867.9 Hz
 32 repetitions
 OBSERVE: c13, 75.1421076 MHz
 DPM: 1.000000000
 Power: 59.000000000
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 F2 size 131072
 Total time 14 hr, 55 min, 7 sec

210.062

143.767

131.992

129.583

127.606

77.425

77.000

76.571

71.143

65.523

50.992

49.626

45.148

43.327

27.914

27.870

25.585

25.345

25.311

21.358

1c4-76-cl3
Pulse Sequence: zgpg30
Solvent: CDCl3
Acquisition Temperature
File: 1c4-76-cl3
MERCURY-3000B "MERCURY-3000"
Relax. delay 1.000 sec
Pulse 2.200 sec
Acq. time 50.386 sec
Width 18757.0 Hz
16384 points
0.16384 sec
300.136372 MHz
DECOUPLE H1 300.0291638 MHz
Power 45 dB
on during acquisition
off during acquisition
WALTZ-16 applied
DATA PROCESSING
Line broadening 2.0 Hz
File size 65536
Total time 50 hr, 31 min, 38 sec

STANDARD 1H OBSERVE
 Archive directory: /export/home/lu-xy/vnmr/sys/data
 Sample directory:
 Pulse Sequence: szpu1

2108-28-c13
 Archive directory: /export/home/ju-sy/vnmr/sy/data
 Sample directory:
 Pulse Sequence: zgpg30

1c5-77-2-c13
 Archive directory: /export/home/tu-xy/vnmr/sy/s/date
 Sample directory:
 Pulse Sequence: szpu182
 Solvent: CDCl3
 Acquisition Temperature: 188.98
 File: 1c5-77-2-c13
 Mercury-3000B "MERCURY-VX300"
 Relax. delay 1.000 sec
 Pulse: 45.0 degrees
 Delay: 1.000 sec
 Width: 1867.30 Hz
 162 repetitions
 OBSERVE C13, 75.442093 MHz
 DECOUPLE H1, 300.0298938 MHz
 Relax: 1.000 sec
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line processing 1.0 Hz
 F2: 75.442093 MHz
 Total time 119 hr, 55 min, 5 sec