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Tetrahedron Letters
Tetrahedron Letters 45 (2004) 2967–2971

Synthesis of some substituted 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene derivatives through the intermediacy of tricarbonyl(η^6-arene)chromium complexes

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Received 30 October 2003; revised 27 January 2004; accepted 5 February 2004

Abstract—5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cyclooctene derivatives with α- and β-substituents are readily accessible from [$Cr(CO)_3$(5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene)] **2** via a two-step sequence, which involves addition of a nucleophile and oxidation of the intermediate anionic cyclohexadienyl complex. Nucleophiles used included $LiCMe_2CN$ (**A**), $LiCH_2CN$ (**B**), and $Li\overline{CHS(CH_2)_3S}$ (**C**). The results show that the primary carbanion $LiCH_2CN$ and the S-stabilized carbanion $Li\overline{CHS(CH_2)_3S}$ give mixtures of α- and β-substituted products and in both cases α-isomers were major, whereas the opposite regioselectivity was obtained with the tertiary carbanion $LiCMe_2CN$.

Tricarbonyl(η^6-arene)chromium complexes have emerged as important intermediates in organic synthesis, the presence of the transition metal facilitating regio- and stereo-selective substitution of positions on or adjacent to the aromatic ring.[1]

Aromatic substitution under mild conditions can be achieved via complexation of the arene to the electron-withdrawing $Cr(CO)_3$ fragment, followed by the addition of a C-nucleophile and oxidative decomplexation.

Substituted arenes when complexed to the $Cr(CO)_3$ fragment, often react with carbon nucleophiles with high regioselectivity, and the addition/oxidation sequence has been developed into a useful synthetic methodology.[2]

This paper describes the synthesis of some substituted 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene derivatives through the intermediacy of [$Cr(CO)_3$(5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene)] **2** and the results of a study of regioselectivity in nucleophilic addition to **2**.

5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cyclooctene **1** was prepared by the Wurtz reaction between α,α′-dibromo-*o*-xylene and sodium in dioxane.[3] Mono(tricarbonylchromium)complex **2** was synthesized by treating **1** with hexacarbonylchromium in di-*n*-butyl ether and tetrahydrofuran (9:1 v/v) at reflux temperature[4] (Scheme 1).

Nucleophilic addition reactions of C-nucleophiles at low temperature, followed by oxidative decomplexation gave α- and β-substituted derivatives of **1**. With the nucleophiles $LiCH_2CN$ and $Li\overline{CHS(CH_2)_3S}$ addition to the site α to the ring junction predominated over that to the β-site. Normally, in $Cr(CO)_3$-mediated reactions, the kinetically preferred site of attack is α to the ring junction, but the bulk of the arene substituent and the carbanion can bring about changes in regioselectivity. S-Stabilized carbanion $Li\overline{CHS(CH_2)_3S}$ added selectively to the C-atom α to the ring junction, a result, which did not vary with time or temperature, showing that 1,3-dithiane-Li adds irreversibly (Table 1). The primary carbanion $LiCH_2CN$ also added selectively to the α-position. In all these cases, product distribution reflects kinetic control, and the observed regioselectivity can be rationalized by assuming either charge or orbital control of addition.[5–7] The opposite β regioselectivity was obtained with the tertiary carbanion $LiC(Me)_2CN$. The

Keywords: Tricarbonylchromium complexes; Regioselectivity; C-Nucleophiles 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene.
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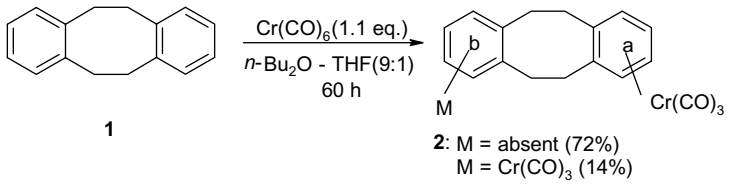
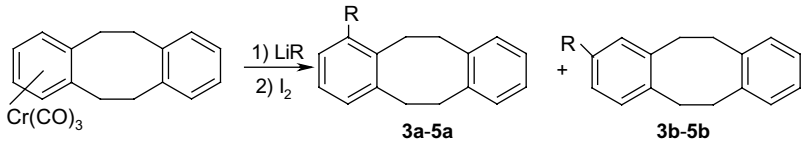
doi:10.1016/j.tetlet.2004.02.050



Scheme 1.

Table 1. Substituted 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctenes via addition of C-nucleophiles



Nucleophile LiR	Conditions[a] [°C, h]	Product distribution[b]		Yield [%]
$LiC(Me)_2CN$	−30/1.3		100 (**3b**)	62
$LiC(Me)_2CN$	−55/0.7	35 (**3a**)	65 (**3b**)	65
$LiCH_2CN$	−20/1	61 (**4a**)	39 (**4b**)	23
$Li\overline{CHS(CH_2)_3S}$	−10/1	75 (**5a**)	25 (**5b**)	96
$Li\overline{CHS(CH_2)_3S}$	−25/2.5	75 (**5a**)	25 (**5b**)	96
$Li\overline{CHS(CH_2)_3S}$	−50/2.5	75 (**5a**)	25 (**5b**)	96

[a] All reactions conducted in THF/HMPA 10:1.
[b] Ratio determined by ^1H NMR.

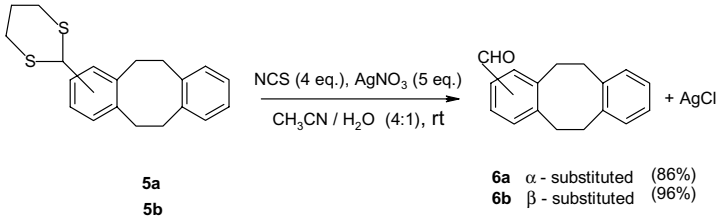
substitution patterns were deduced by inspection of ^1H NMR and (H,H-COSY) spectra.

Hydrolysis of the isomeric dithiane derivatives **5a**,**b** gave α- and β-carbaldehyde derivatives **6a**,**b** (Scheme 2). Reaction of **6a** with MeLi gave alcohol **7**, dehydration of which in the presence of *p*-toluenesulfonic acid in refluxing benzene is presumed to give 5,6,11,12-tetrahydrodibenzo[*a*,*e*]cycloocten-1-ylethene, which dimerized under the reaction conditions giving **8** (Scheme 3). The GC-mass analysis indicated the presence of only a single dimer. The FT-IR and ^1H NMR spectra showed no olefinic signals, thus it is proposed that elimination of water and in situ dimerization of the resulting alkene leads to indane derivative **8**.

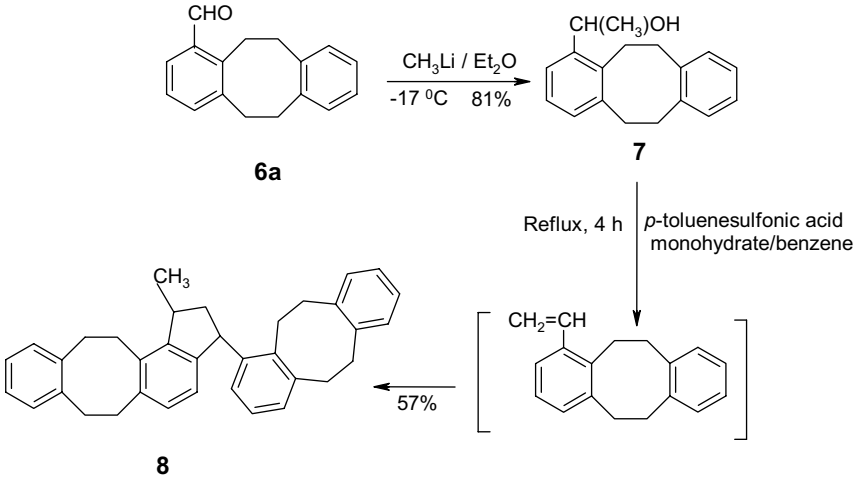
1. Experimental

1.1. $[Cr(CO)_3$(5,6,11,12-tetrahydrodibenzo[*a*,*e*]cyclooctene)] 2

Mp 186 °C; IR (KBr): $\nu = 3022$ (w), 3068 (w), 2950–2850 (w), 1945 (s), 1850 (br, s), 760 (m), 669 (s), 630 (s), 531 (m) cm^{-1}; IR (THF): $\nu = 1960$ and 1885 cm^{-1} (CO); ^1H NMR (400 MHz, DMSO-d_6): δ 2.64–2.74 (m, 2H), 2.78–2.83 (m, 2H), 2.97–3.08 (m, 2H), 3.22–3.31 (m, 2H), 5.4–5.45 (m, 2H, ArH[a]), 5.47–5.52 (m, 2H, ArH[a]), 7 (s, 4H, ArH[b]); ^{13}C NMR (50 MHz, DMSO-d_6): δ 32.6 (2×CH_2), 33.2 (2×CH), 93.5 (2×CH), 96.6 (2×CH), 113.1 (2×C), 126.2 (2×CH), 129.6 (2×CH), 139 (2×C), 234.3 (3×CO); MS (EI): m/z (%) = 344 (10) [M^+], 269



Scheme 2.



Scheme 3.

(100) [M^+-3CO], 208 (18) [$M^+-Cr(CO)_3$], 52 (81) [Cr^+]; Anal. Calcd for $C_{19}H_{16}CrO_3$: C, 66.28; H, 4.83. Found: C, 66.47; H, 4.53.

1.2. General procedure for the nucleophilic additions to complex 2

The [Cr(arene)$(CO)_3$] complex (1.0 mmol) in THF (10 ml) at −78 °C was added in one portion to a solution of the nucleophile (1–1.1 mmol in THF, 10 ml, −78 °C). HMPA (2 ml) was added dropwise at this stage. The mixture was then stirred for the time and at the temperature indicated in the Table 1. After recooling to −78 °C, a cold (−78 °C) solution of I_2 (5–6 mmol in THF (10 ml)) was added rapidly via cannula. After a few minutes the cooling bath was removed, and the temperature slowly (1 h) raised to 20 °C and stirred at this temperature for 4 h. The mixture was diluted with Et_2O (40 ml) and washed with aq $NaHSO_3$ (10%, 3×30 ml), aq HCl (1 N, 3×30 ml), satd $NaHCO_3$ (20 ml), H_2O (2×30 ml), and brine (30 ml). The organic layer was dried ($MgSO_4$) and the solvent removed on a rotavapor to give the crude product.

1.3. 2-(5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-1-yl)-2-methylpropionitrile 3a

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 6H, $C(CH_3)_2CN$), 3.08 (m, 8H), 6.95–7.12 (m, 7H, ArH).

1.4. 2-(5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-2-yl)-2-methylpropionitrile 3b

Mp 57.5–58.5 °C; IR (KBr): ν = 3066 (w), 3015 (m), 2975 (m), 2931 (w), 2235 (m), 1500 (m), 1489 (m), 1462 (m), 1450 (m), 893 (m), 829 (s), 735 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 6H, $C(CH_3)_2CN$), 3.08 (m, 8H), 6.95–7.12 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.16 (CH_3), 34.85 (CH_2), 34.96 (CH_2), 35.14 (CH_2), 35.34 (CH_2), 36.7 (C), 122.50 (CH), 124.72 (CN), 126.19 (CH), 126.44 (CH), 129.64 (CH), 129.79 (CH), 130.23 (CH), 139.14 (C), 140.35(C), 140.41 (C), 140.46 (C), 141.44 (C); MS (70 eV): m/z (%) = 275 (100) [M^+], 260 (45), 248 (25), 235 (9), 207 (86), 192 (50), 179 (14), 156 (13), 130 (17), 115 (23), 104 (37), 91 (13), 78 (11); Anal. Calcd for $C_{20}H_{21}N$: C, 87.22; H, 7.68; N, 5.08. Found: C, 87.17; H, 7.91; N, 4.68.

1.5. 5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-1-yl-acetonitrile 4a

Mp 104 °C; IR (KBr): ν = 3061 (w), 3015 (m), 2930 (s), 2893 (m), 2235 (m), 1491 (s), 1457 (s),760 (s), 737 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.1 (m, 8H), 3.65 (s, 2H, CH_2CN), 6.9–7.1 (m, 7H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.02 (CH_2), 29.2 (CH_2), 33.82 (CH_2), 34.14 (CH_2), 35.51 (CH_2), 118.07 (CN), 126.24 (CH), 126.45 (CH), 126.59 (CH), 127.22 (CH), 127.66 (C), 129.45 (CH), 129.57 (CH), 130.48 (CH), 138.51 (C), 139.52 (C), 139.83 (C), 141.9 (C); MS (70 eV): m/z (%) = 247 (100) [M^+], 232 (48), 220 (15), 207 (46), 192 (30), 178 (8), 155 (8), 128 (12), 115 (28), 104 (54), 91 (18), 91 (18), 78 (21); Anal. Calcd for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.07; H, 6.92; N, 5.85.

1.6. 5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-2-yl-acetonitrile 4b

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.1 (m, 8H), 3.55 (s, 2H, CH_2CN), 6.9–7.1 (m, 7H, ArH).

1.7. 2-(5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-1-yl)-1,3-dithiane 5a

Mp 138 °C; IR (KBr): ν 3050 (w), 3018 (w), 2978 (w), 2930 (m), 2903 (m), 858 (w), 1489 (w), 1465 (m), 1448 (m), 1275 (m), 772 (m), 761 (s), 750 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.8–2.0 (m, 1H –C(5)), 2.1–2.3 (m, 1H–C(5)), 2.85 (dt, J_1 = 13.9 Hz, J_2 = 3.5 Hz, 2H–C(4,6)), 3.05 (m, 8H), 3.17 (t, J = 6.8 Hz, 2H), 5.45 (s,

1H–C(2)), 6.78 (d, $J = 7.3$ Hz, 1H, ArH), 6.9 (m, 5H, ArH), 7.3 (d, $J = 7.3$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 25.3$ (CH_2), 28.8 (CH_2), 32.6 (CH_2), 34.1 (CH_2), 35.4 (CH_2), 36.1 (CH_2), 48.7 (CH), 126.0 (CH), 126.2 (CH), 126.4 (CH), 126.5 (CH), 129.3 (CH), 130.24 (CH), 130.27 (CH), 136.5 (C), 137.7 (C), 139.8 (C), 140.1 (C), 141.2 (C); MS (70 eV): m/z (%) = 326 (32) [M^+], 251 (100), 219 (15), 205 (7), 147 (42), 91 (7); Anal. Calcd for $C_{20}H_{22}S_2$: C, 73.57; H, 6.79. Found: C, 73.75; H, 6.81.

1.8. 2-(5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-2-yl)-1,3-dithiane 5b

Mp 132.5–133.5 °C; IR (KBr): $v = 3018$ (w), 2948 (m), 2928 (m), 2855 (w), 1494 (m), 1458 (m), 1436 (m), 1411 (m), 1281 (s), 1171 (m), 779 (m), 759 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.8–2.0 (m, 1H), 2.05–2.25 (m, 1H), 2.86 (dt, $J_1 = 13.8$ Hz, $J_2 = 3.4$ Hz, 2H–C(4, 6)), 3.03 (m, 10H), 5.05 (s, 1H–C(2)), 6.8–7.2 (m, 7H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3 (CH_2), 32.1 (CH_2), 35.09 (CH_2), 35.11 (CH_2), 35.2 (CH_2), 35.26 (CH_2), 51.3 (CH), 125.4 (CH), 126.2 (CH), 128.98 (CH), 129.6 (CH), 129.76 (CH), 130.1 (CH), 136.8 (C), 140.6 (C), 141.17 (C), 141.3 (C); MS (70 eV): m/z (%) = 326 (100) [M^+], 252 (69), 237 (18), 219 (14), 207 (8), 205 (8), 192 (7), 147 (14), 115 (12), 104 (23), 91 (16).

1.9. 5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cyclooctene-1-carboxaldehyde 6a

Mp 94–95 °C; IR (KBr): $v = 3080$ (w), 3015 (w), 2978 (w), 2937 (w), 2891 (w), 2842 (w), 2718 (m), 1691 (s), 1583 (m), 1474 (m), 1448 (m), 762 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10–3.23 (m, 6H), 3.56 (t, $J = 7$ Hz, 2H), 6.80–7.15 (m, 6H, ArH), 7.47–7.53 (dd, $J_1 = 7$ Hz, $J_2 = 2$ Hz, 1H, ArH), 10.2 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 27.8 (CH_2), 33.6 (CH_2), 34.8 (CH_2), 35.4 (CH_2), 126.14 (CH), 126.22 (CH), 126.34 (CH), 129.36 (CH), 129.92 (CH), 130.97 (CH), 134.0 (C), 135.59 (CH), 139.41(C), 139.69 (C), 142.3 (C), 142.76 (C), 192.96 (CHO); MS (70 eV): m/z (%) = 236 (100) [M^+], 221 (34), 207 (9), 203 (12), 193 (15), 178 (16), 131 (32), 115 (15), 104 (32), 104 (32), 91 (16); Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.17; H, 6.84.

1.10. 5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cyclooctene-2-carboxaldehyde 6b

Mp 89–91 °C; IR (KBr): $v = 3080$ (w), 3040 (w), 2954 (m), 2853 (m), 2830 (w), 2784 (w), 2739 (w), 1684 (s), 1604 (m), 1446 (m), 1249 (s), 1172 (s), 835 (s), 767 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08–3.25 (m, 8H), 6.95 (m, 4H, ArH), 7.12 (d, $J = 7.4$ Hz, 1H, ArH), 7.45 (m, 2H, ArH), 9.85 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.56 (CH_2), 34.64 (CH_2), 34.82 (CH_2), 35.26 (CH_2), 126.38 (CH), 126.47 (CH), 128.15 (CH), 129.68 (CH), 129.85 (CH), 130.43 (CH), 130.73 (CH), 134.91 (C), 139.57 (C), 139.70 (C), 141.36 (C), 147.96 (C), 191.98 (CHO); MS (70 eV): m/z (%) = 236 (100) [M^+], 221 (29), 207 (29), 193 (25), 178 (17), 131 (6), 115 (14), 104 (42), 91 (15).

1.11. 1-(5,6,11,12-Tetrahydrodibenzo[*a*,*e*]cycloocten-1-yl)ethanol 7a

Mp 65 °C; IR (KBr): $v = 3258$ (s, br), 3060 (w), 3015 (w), 2971 (m), 2925 (w), 2891 (w), 2837 (w), 1491 (s), 1452 (s), 1369 (m), 1304 (m), 1112 (s), 1087 (s), 1067 (s), 1015 (m), 999 (m), 760 (s), 735 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, 3H, $J = 6.5$ Hz), 1.6 (br d, 1H, $J = 3$ Hz), 3.0–3.2 (m, 8H), 5.1–5.3 (m, 1H), 6.8–7.1 (m, 6H, ArH), 7.25 (d, 1H, $J = 7$ Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 24.55$ (CH_3), 28.23 (CH_2), 34.43 (CH_2), 35.11 (CH_2), 35.67 (CH_2), 66.91 (CH), 122.92 (CH), 126.08 (CH), 126.25 (CH), 126.29 (CH), 129.3 (CH), 129.43 (CH), 129.58 (CH), 137.21 (C), 140.28 (C), 140.34 (C), 141.25 (C), 143.02 (C); MS (70 eV): m/z (%) = 252 (14) [M^+], 234 (100), 219 (40), 205 (28), 193 (16), 178 (8), 129 (20), 105 (28), 91 (19); Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.40; H, 7.92.

1.12. Dimer 8

Mp 65 °C; IR (KBr): $v = 3061$ (w), 3015 (m), 2950 (s), 2890 (m), 1490 (s), 1453 (s), 756 (s), 736 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.2 (d, $J = 7.2$ Hz), 3H, 1.3 (m, 2H), 2.9–3.2 (m, 18H), 6.8–7.0 (m, 13H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.12 (CH_3), 28.87 (CH_2), 30.33 (CH_2), 34.47 (CH_2), 34.91 (CH_2), 35.09 (CH_2), 35.32 (CH_2), 35.59 (CH_2), 37.34 (CH), 38.41 (CH_2), 43.51 (CH_2), 46.22 (CH), 123.14 (CH), 125.65 (CH), 125.91 (CH), 125.94 (CH), 126.09 (CH), 126.17 (CH), 127.83 (CH), 128.76 (CH), 129.51 (CH), 129.54 (CH), 129.65 (CH), 129.68 (CH), 136.90 (C), 138.28 (C), 140.17 (C), 140.45 (C), 141.15 (C), 144.08 (C), 144.94 (C), 147.39 (C); MS (70 eV): m/z (%) = 469 (39) [M^++1], 468 (100) [M^+, dimer], 453 (3.5), 349 (13.6), 261 (5.3), 245 (5.4), 234 (6.2), 219 (4.7) 205 (3.3), 193 (3.3), 105 (7.7), 91 (5.7).

Acknowledgements

The author sincerely acknowledges all the members of the Organic Chemistry Department of Justus Liebig University of Giessen, especially Prof. J. Ipaktschi, for their kind and valuable cooperation.

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