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# Arenetricarbonylchromium complexes in the synthesis of 6,7-benzomorphanes

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## Abstract

The action of sodium amide on tricarbonyl-$\eta^6$-[1′,2′,3′,4′-tetrahydro-spiro(1,3-dioxolane-2,1′-naphthalene)]chromium followed by reaction with sodium bromoacetate gives tricarbonyl-$\eta^6$-[1-(1,2,3,4-tetrahydro-4-oxonaphthalene)acetic acid]chromium (**4**). Some procedures to transform **4** into 1-(*N*-benzyl-2-aminoethyl)-1,2-dihydronaphthalene (**10**)—a synthon to 6,7-benzomorphanes—are described. Cyclization of **10** by action of mercury(II) acetate yields 3-benzyl-1,2,3,4,5,6-hexahydro-1-hydroxy-2,6-methano-3-benzazocine (**11**).

## Introduction

The complexation of arenes with tricarbonylchromium group changes the properties of the aromatic ring and groups attached to it. It provides good possibilities in the use of arenetricarbonylchromium complexes in organic synthesis. The characteristic reaction of (alkylarene)tricarbonylchromium complexes is an easy metallation at a benzylic position owing to the high acidity of the benzylic protons. t-BuOK [4], n-BuLi [5] and $(Me_3Si)_2NNa$ [6] have been used as metallating agents.

## Results and discussion

Here we present in detail the sequence of reactions starting from tetralone-1 that results in the formation of 6,7-benzomorphanes *, which are important, physiologically active compounds. The metallation of the tricarbonylchromium complex of the tetralone-1 dioxolane derivative with sodium amide at the 4 position is a key step in

* We have used the name "6,7-benzomorphanes" as it is used predominantly in the literature. The correct name used by Chemical Abstracts is 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine. A numbering system of atoms and rings associated with this name is shown for compound **14**.

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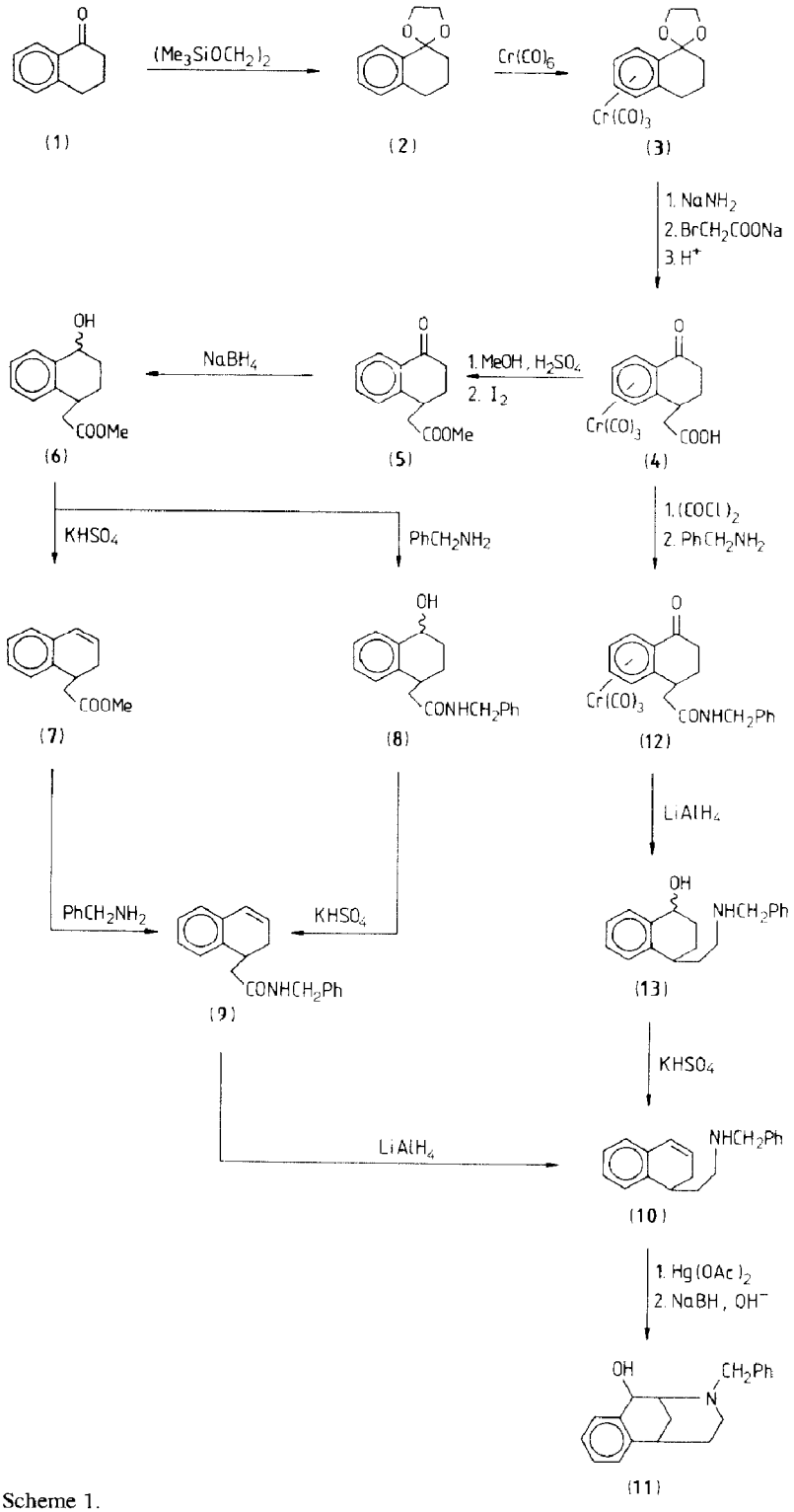
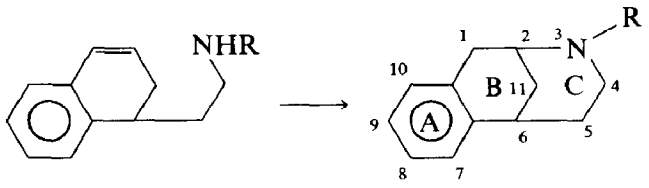

(Me3SiOCH2)2
Cr(CO)6
(1)
(2)
(3)
1. NaNH2
2. BrCH2COONa
3. H+
NaBH4
1. MeOH, H2SO4
2. I2
(6)
(5)
(4)
KHSO4
PhCH2NH2
1. (COCl)2
2. PhCH2NH2
(7)
(8)
(12)
LiAlH4
PhCH2NH2
KHSO4
(9)
(13)
KHSO4
LiAlH4
(10)
1. Hg(OAc)2
2. NaBH, OH−
(11)

Scheme 1.



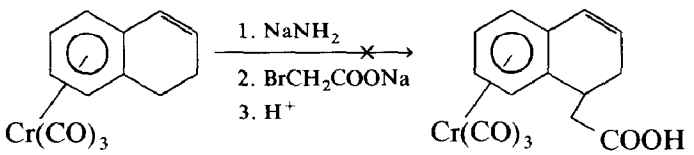

**(14)**

Scheme 2.

the procedure under discussion. Protection by dioxolane is necessary because it eliminates ketone enolisation under action of sodium amide. We used the reaction of **1** with 1,2-bis(trimethylsilyloxy)ethane in the presence of $CF_3SO_3SiMe_3$ (as the catalyst [8]) to prepare 1,3-dioxolane **2** from tetralone-1 (**1**). The reaction of **2** with $Cr(CO)_6$ in dibutyl ether/THF under reflux [9] gives the 1,3-dioxolane complex **3** which is readily metallated at the benzylic position by treatment with sodium amide under the conditions described previously [10]. Subsequent interaction of the sodium derivative, as obtained with $BrCH_2COONa$, after acidic work-up gives complex **4**.

Thus, the complexation with the $Cr(CO)_3$ group permits the direct introduction of a carboxymethyl substituent into the 4 position of tetralone-1, which is of benefit for the synthesis of 6,7-benzomorphanes. A major drawback of the usual methods of 6,7-benzomorphane synthesis—tetralone method and Grewe cyclization—is the low accessibility of the starting materials for the preparation of the substituted tetralones and tetrahydropyridines, which are used in these methods as synthons [7]. The introduction of carboxymethyl substituent into the 4 position of tetralone-1, as described herein, gives the 4-ketoacid **4** suitable for use in the preparation of 6,7-benzomorphanes by a modified tetralone method. This route includes the formation of a benzomorphane C-ring by treatment of the 1,2-dihydronaphthalene $\beta$-aminoethyl derivative with $Hg(OAc)_2$ [11] (Scheme 2).

The ketone carbonyl group in complex **4** must be retained for the formation of the olefin fragment by reduction–dehydratation. None of our attempts to introduce carboxymethyl substituent into benzylic position of the complex **15** by carboxymethylation as described above was successful.




**(15)**

The presence of the carboxymethyl group in complex **4** opens up a number of routes for its transformation into $\beta$-aminoethyl group which is necessary for subsequent cyclization.

Complex **4** is readily esterified by methanol in the presence of $H_2SO_4$. After decomplexation with $I_2$ the corresponding methyl ester **5** is isolated. The ketone carbonyl group of the ester **5** was selectively reduced with $NaBH_4$ in isopropyl alcohol to give a mixture of isomeric *cis*- and *trans*-oxyesters **6**. This mixture can be

transformed into *N*-benzylamide of 1-(1,2-dihydronaphthalene)acetic acid (**9**) by two ways. The first involves dehydration of **6** by $KHSO_4$ in boiling benzene to give ester **7**, which is then transformed into the *N*-benzylamide **9** by benzylamine in the presence of $NH_4Cl$. The second is the reversed sequence of above two steps and includes the intermediate formation of oxyamide **8**. The reduction of amide **9** with $LiAlH_4$ in THF gives amine **10**.

The shorter route to amine **10** involves three stages. The reaction of the acid **4** with oxalyl chloride in benzene/acetonitrile solution (70 °C, 6 h) gives the corresponding acyl chloride which yields oxoamide **12** after quenching with an excess of $PhCH_2NH_2$ (mass-spectrum (*m/e*): $M^+$ 429). Note that the tricarbonylchromium group in complex **12** is not eliminated on this stage. All our attempts to use other reagents ($SOCl_2$, $PCl_5$) in place of oxalyl chloride to prepare carboxylic acid chloride destroyed **4** and no **12** was formed. Reduction of **12** with $LiAlH_4$ in THF was accompanied by complete decomplexation to oxoamide **13**, which was transformed into amine **10** by $KHSO_4$ in boiling benzene for 6 h.

The amine **10** was cyclized into benzomorphane **11** by the reaction with $Hg(OAc)_2$ under the conditions described previously [8]. The structure of **11** was confirmed by $^1H$ NMR and mass spectroscopy. The correlation of $^1H$ NMR spectrum signals with the structure of **11** was checked by $^1H$–$^1H$ 2D COSY (Fig. 1). The value of the

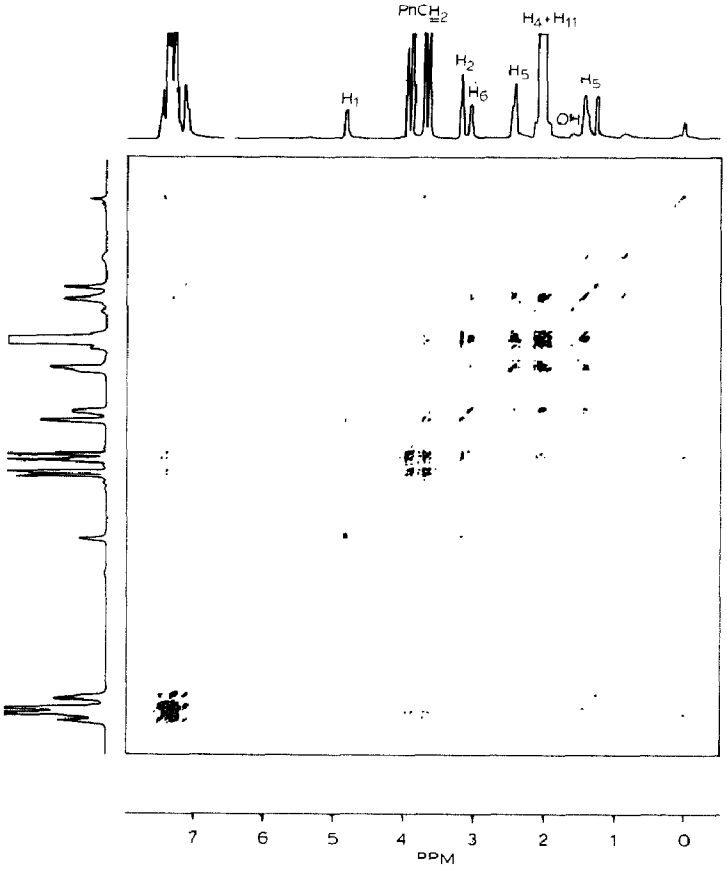



Fig. 1. Correlative $^1H$–$^1H$ 2D COSY spectrum for compound **11**.

$^3J(H^1,H^2)$ coupling constant (1.1 Hz), deduced from the proton homonuclear double resonance spectrum of **11**, corresponds to *trans* positions of the $H^1$ and $H^2$ protons relative to the B-ring of the benzomorphane. As a corollary, the hydroxy group and nitrogen atom in **11** are also *trans* to each other. The differences in the chemical shifts between the diastereotopic *N*-benzyl protons are found to increase significantly on going from **9** and **10** to **11**, which is probably attributable to the large distance between the chiral center at $C^1$ and the *N*-benzyl protons in **9** and **10**. The formation of the cycle when **11** results produces a second asymmetric center at $C^1$ (it is necessary to take into account a change in the numbering system on going from **10** to **11**) which is not so far removed from the diastereotopic protons.

## Experimental

The reactions were performed under dry argon in dry solvents. $^1H$ NMR spectra were recorded on a Bruker WP-200 SV (200 MHz for $^1H$) instrument in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were recorded on an AEI-MS-30 instrument. Microanalysis data are listed in Table 1.

*1',2',3',4'-Tetrahydro-spiro(1,3-dioxolane-2,1'-naphthalene) (2).* $CF_3SO_3SiMe_3$ (0.84 ml) was added to a solution of 1,2-bis(trimethylsilyloxy)ethane (91.0 g; 0.44 mmol) and **1** (63.6 g; 0.44 mmol) in 100 ml of $CH_2Cl_2$ at −78°C. The reaction mixture was stirred for 35–40 h at −78°C (the reaction was monitored by GLC; $CF_3SO_3SiMe_3$ (1–2 ml) or $CH_2Cl_2$ (50 ml) should be added to the mixture if precipitation takes place). Pyridine (25 ml) at −78°C was slowly added then water was added, and a saturated solution of $NaHCO_3$ and ether. The aqueous layer was separated off and extracted with ether. The extract and the organic layer were combined, the solvent was evaporated and the residue was distilled to give 87.0 g (58%) of **2**, b.p. 118–124°C/3 torr.

*Tricarbonyl-η⁶-[1',2',3',4'-tetrahydro-spiro(1,3-dioxolane-2,1'-naphthalene)]chromium (3).* A mixture of **2** (3.39 g; 17.84 mmol) and $Cr(CO)_6$ (23.55 g; 107.05 mmol) in dibutyl ether (100 ml) and THF (20 ml) was refluxed for 28 h. The

Table 1

Microanalytical data of the compounds prepared

| Compound | Formula | Anal. (found (calc.) (%)) | | | |
|---|---|---|---|---|---|
| | | C | H | N | Cr |
| **3** | $C_{15}H_{14}CrO_5$ | 55.08 (55.22) | 4.27 (4.33) | – | 15.62 (15.94) |
| **4** | $C_{15}H_{12}CrO_6$ | 52.83 (52.94) | 3.39 (3.53) | – | 15.50 (15.29) |
| 2,4-Dinitrophenyl-hydrazone (**5**) | $C_{19}H_{18}N_4O_6$ | 57.50 (57.29) | 4.60 (4.55) | 14.02 (14.06) | – |
| 4-Nitrobenzoate (**6**) | $C_{20}H_{19}NO_6$ | 65.00 (65.03) | 5.15 (5.18) | 3.71 (3.79) | – |
| **9** | $C_{19}H_{19}NO$ | 82.02 (82.28) | 6.98 (6.90) | 4.90 (5.05) | – |
| **11** | $C_{19}H_{21}NO$ | 81.60 (81.68) | 7.85 (7.58) | 4.96 (5.01) | – |

solution was cooled and then filtered through $Al_2O_3$ (5 cm). The solvent was removed and the residue was recrystallized from benzene/heptane to give 4.30 g (74%) of **3**, m.p. 122.5–124°C. MS (*m/e*): 326 ($M^+$).

*Tricarbonyl-η⁶-[1-(1,2,3,4-tetrahydro-4-oxonaphthalene)acetic acid]chromium (**4**).* To a suspension of $NaNH_2$ (prepared from 0.70 g of sodium) in liquid $NH_3$ (120 ml) were added THF (25 ml) and **3** (8.40 g; 25.8 mmol) at −70°C. The mixture was stirred for 1 h at −70°C and then for 30 min at −50°C. $BrCH_2COONa$ (4.90 g; 30.4 mmol) was added, most of the $NH_3$ was evaporated off, and $NH_4Cl$ (1 g), water and NaOH (10% aqueous solution) were added. The alkaline solution was extracted with ether and acidified with HCl (10%) on cooling. The product was extracted with ether; the ether was removed to give 5.65 g (64%) of **4**, m.p. 202–205°C. MS (*m/e*): 340 ($M^+$).

*1-(1,2,3,4-Tetrahydro-4-oxonaphthalene)acetic acid methyl ester (**5**).* A solution of **4** (4.00 g; 11.8 mmol) in MeOH (20 ml) and $CCl_4$ (200 ml) was refluxed in the presence of $H_2SO_4$ (0.5 ml) for 4 h. The mixture was cooled and washed with 1 M NaOH and then with water. The organic layer was separated and the solvent was removed. The residue was dissolved in 50% aqueous acetonitrile (50 ml) and the mixture was stirred for 45 min at room temperature with an excess of iodine. Unchanged iodine was removed by the addition of $Na_2S_2O_3$. The products were extracted with ether; the solvent was removed to give 1.97 g (82%) of **5** as oil. MS (*m/e*): 218 ($M^+$). $^1H$ NMR spectrum ($\delta$, ppm): 3.78 (3H, $OCH_3$). 2,4-Dinitrophenyl hydrazone **5**: m.p. 136–137°C, MS (*m/e*): 398 ($M^+$).

*1-(1,2,3,4-Tetrahydro-4-hydroxy-naphthalene)acetic acid methyl ester (**6**).* To a solution of $NaBH_4$ (1.31 g; 34.4 mmol) in isopropyl alcohol (100 ml) was added a solution of **5** (1.50 g; 6.88 mmol) in isopropyl alcohol (25 ml). The mixture was left to stand overnight, then treated with water and then HCl (3%). The products were extracted with ether, washed with water, and dried over $Na_2SO_4$. The solvent was removed to yield 1.01 g (67%) of **6** (a mixture of *cis*- and *trans*-isomers) as an oil. 4-Nitrobenzoate **6**: MS (*m/e*): 369 ($M^+$).

*1-(1,2-Dihydronaphthalene)acetic acid methyl ester (**9**).* A mixture of **7** (0.24 g; 1.18 mmol) was heated at 130°C with benzylamine (1.5 ml) in the presence of $NH_4Cl$ (0.025 g; 0.47 mmol) for 17 h. The mixture was cooled, diluted with water and treated with HCl (10%). The products were extracted with chloroform, and the solvent was removed. Column chromatography of the residue ($SiO_2$, $CHCl_3$) yielded 0.25 g (76%) of **9**, m.p. 123.5–124.5°C (benzene/hexane). $^1H$ NMR ($\delta$, ppm): 4.32 and 4.35 (1H and 1H, $PhCH_2$, AB-system), 5.70 (1H, NH), 5.88 (1H, $H^3$), 6.42 (1H, $H^4$), $^3J_{3,4} = 9.55$ Hz.

*1-(N-Benzyl-2-aminoethyl)-1,2-dihydronaphthalene (**10**).* A solution of **9** (0.33 g; 1.19 mmol) in THF (25 ml) was added dropwise to a suspension of excess $LiAlH_4$ in THF (20 ml). The mixture was refluxed for 18 h, hydrolysed with water and treated with HCl (10%). The acidic layer was separated off and the organic layer was washed with water. The acidic solution and the water extract were combined, treated with solid NaOH, and the products were extracted with ether. The extract was dried over NaOH. Removed of the solvent yielded 0.21 g (67%) of **10**. MS (*m/e*): 263 ($M^+$). $^1H$ NMR ($\delta$, ppm): 3.72 (2H, $PhCH_2$), 5.88 (1H, $H^3$), 6.41 (1H, $H^4$).

*3-Benzyl-1,2,3,4,5,6-hexahydro-1-hydroxy-2,6-methano-3-benzazocine (**11**).* To a solution of **10** (0.21 g; 0.80 mmol) in THF (35 ml) was added $Hg(OAc)_2$ (0.26 g;

0.80 mmol). Water (15 ml) was added after 10 min stirring at 20 °C and the mixture was stirred for 75 h. KOH (10% solution, 15 ml) and $NaBH_4$ (0.30 g) were added and the mixture was stirred for 1 h. The solution was filtered, the products were extracted with ether and washed with HCl (10% solution, $3 \times 30$ ml). The acidic extracts were treated with 1 *M* NaOH till alkaline, and the products were extracted with ether. The ether solution was dried over NaOH, the solvent was removed. Column chromatography of the residue over silica gel (chloroform/methanol, 20 : 1) yielded 0.09 g (45%) of **11**, m.p. 139–141 °C (hexane), MS (*m/e*): 279 ($M^+$).

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