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Synthesis of Perhydroisoquinoline Derivatives Mediated by (η^6-arene)Cr(CO)$_3$ Complexes

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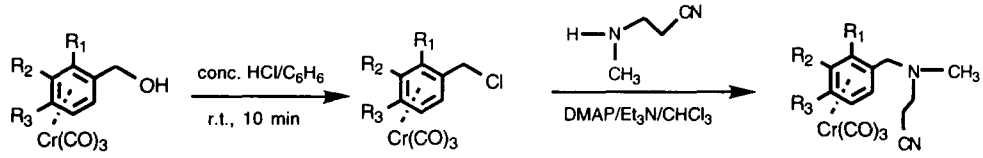
Abstract: Reaction of lithium hexamethyldisilazide (LHMDS) with (η^6-arene)Cr(CO)$_3$ complexes bearing a β-alaninenitrile moiety gives tetrahydroisoquinoline derivatives as the major products after oxidation of the reaction intermediate, whereas protonation of the reaction intermediates produces hexahydroisoquinoline as the major products. © 1997 Elsevier Science Ltd.

(Arene)Cr(CO)$_3$ complexes has been focused in organic synthesis for two decades.[1] The pioneer work in the Semmelhack group had shown that stabilized carbanions added at the (arene)Cr(CO)$_3$ complexes to give (η^5-cyclohexadienyl)Cr(CO)$_3$ anion species, which coupled with acid or oxidized with I_2 produce cyclohexadiene derivatives and nucleophilic substituted arene, respectively.[2] The umpolung reactivity of arenes towards nucleophilic addition opens a new synthetic routes to fairly complicated molecules such as acorenone B.[3] The spiro[4.5]decane ring skeleton of acorenone B was constructed via intramolecular nucleophilic addition of the cyano stabilized carbanion to the arene ligand. Recently, Davies had utilized an electrophilic addition of a benzylic chromiumtricarbonyl cation to 1,2-dimethoxybenzene ring systems in the synthesis of tetrahydroisoquinoline and tetrahydrobenzazepine derivatives.[4] The key step involved the typical electrophilic addition of the benzylic chromiumtricarbonyl cation to the pendant benzene ring. However, there are no reports on the synthesis of heterocyclic ring systems using intramolecular nucleophilic addition to (arene)Cr(CO)$_3$ complexes. Herein we report that addition of N-methyl-β-alaninenitrile to benzylchloride chromiumtricarbonyl complexes followed by intramolecular cyclization and quenching processes provided perhydroisoquinoline derivatives with a cyano group at C-4 position of the ring.[5]

The synthesis of starting complexes are outlined in Scheme 1. Complex **1** was obtained in high yield by refluxing of commercially available benzylic alcohol derivatives with Cr(CO)$_6$ in Bu_2O/THF for 48 h. Reaction of complex **1** with concentrated HCl at 25 °C for 10 min generated benzyl chloride chromiumtricarbonyl complex **2** in good yields (Scheme 1).[6] Treatment of **2** with 1.0 molar equiv of N-

methyl-β-alaninenitrile, 2.0 molar equiv of triethylamine and a catalytic amount of 4-N,N-dimethylaminopyridine in refuxing chloroform for 16 h produced complex **3** in good yields (Scheme 1).

Scheme 1



1

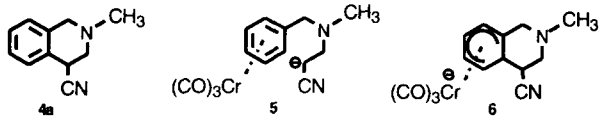
2

a. $R_1=R_2=R_3=$ H,	76%
b. $R_1=CH_3$, $R_2=R_3=$ H	73%
c. $R_2=CH_3$, $R_1=R_3=$ H	71%
d. $R_3=CH_3$, $R_1=R_2=$ H	75%
e. $R_2=OCH_3$, $R_1=R_3=$ H	69%

3

a. $R_1=R_2=R_3=$ H,	85%
b. $R_1=CH_3$, $R_2=R_3=$ H	92%
c. $R_2=CH_3$, $R_1=R_3=$ H	71%
d. $R_3=CH_3$, $R_1=R_2=$ H	69%
e. $R_2=OCH_3$, $R_1=R_3=$ H	73%

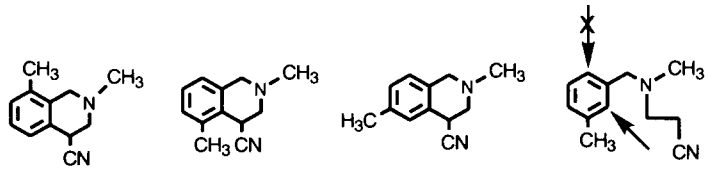
Our intramolecular cyclization started with complex **3a**. Treatment of **3a** with lithium hexamethyldisilazide (LHMDS) in hexamethylphosphoric triamide (HMPA) and tetrahydrofuran (HMPA : THF = 1 : 3) at –78 °C, followed by stirring the reaction mixture at 0 °C for 4h, and then quenched the reaction mixture with excess iodine at 25 °C provided a single product, identified as tetrahydroisoquinoline **4a** in 67% yield after flash column chromatography and short path distillation under reduced pressure.[7]



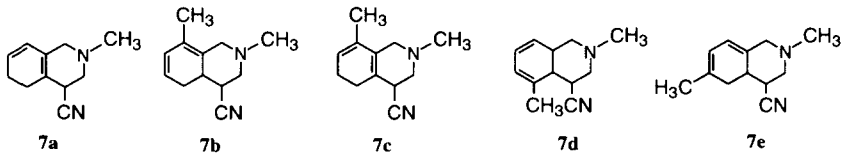
4a **5** **6**

The formation of **4a** agrees closely with the mechanism proposed for the formation of 1-cyanotetrahydronaphthalene derivative via intramolecular cyclization of arene-chromium complex bearing an carbon side chain.[3a-c] Deprotonation of **3a** using LHMDS at –78 °C gave the cyano stabilized carbanion **5**. The carbanion **5** may add at the *ortho* position of the arene ligand to generate (η^5-cyclohexadienyl)$Cr(CO)_3$ anionic complex **6**, which oxidized by I_2 to generate tetrahydroisoquinoline derivative **4a**. It is important to mention that the stabilized carbanion, such as **5** does not undergo β-elimination of the amino group under the reaction conditions. Moreover, complexes with an additional methyl group at *ortho, meta, or para* position of the arene ligand, for example complexes **3b–d**, also underwent intramolecular cyclization to yield tetrahydroisoquinoline derivatives **4b–d**, respectively, as

the single product isolated in each case and in moderate yields (yields: **4b** : 56%, **4c** : 19%, **4d** : 41%). It is worth to mention that tetrahydroisoquinoline derivatives **4c** were derived from nucleophilic addition at more hindered *ortho* position (C-2) of the amino side chain. None of the addition at C-6 (*para* to the methyl substituent) was found. The more active *ortho* position (and not *para)* of the toluene ligand towards addition of a cyano stabilized carbanion is consistent with those reported in the literature.[2d-f] However, intramolecular cyclization of the starting complex with a methoxy group at the arene ligand, for example complex **3e**, failed to give cyclized products. Dettachment of the metal center was the major process of the reaction. The electron donating effect of the methoxy group at the arene ring may decrease the electrophilicity of the arene ligand towards nucleophilic attack.

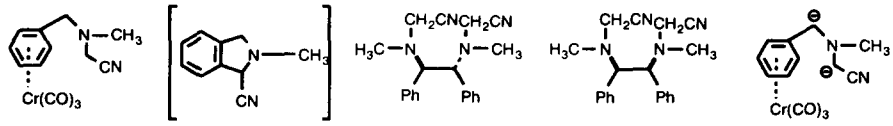


As expected, anionic intermediate **6** can also be quenched with trifluoroacetic acid to give hexahydroisoquinoline derivatives. Thus, treatment of **3a** with LHMDS at 0 °C followed by protonation of the (η^5-cyclohexadienyl)$Cr(CO)_3$ anion intermediate, such as **6** , provided hexahydroisoquinoline derivative **7a** in 23% yield as a single isomer after purification by flash column chromatography and distillation under reduced pressure. The formation of **7a** may result from initial protonation of the anionic intermediate **6** followed by reductive elimination of the hydride species and double bond migration. Under the same reaction conditions, intramolecular cyclization/protonation of complex **3b** produced hexahydroisoquinoline isomerss **7b** and **7c** in a 2:3 ratio and in 40% total yield as a mixture of isomers. Attempts to separate the mixture of **7b** and **7c** using various analytical methods were not successful. Whereas intramolecular cyclization of complexes **3c** and **3d** produced hexahydroisoquinoline isomers **7d** (24%) and **7e** (45%), respectively as a single isomer isolated in each case.



Attempted intramolecular cyclization of the arenechromiumtricarbonyl complex containing a methylaminoacetonitrile moiety, for example complex **8**, failed to give the desired isoindole derivative **9**. Decomplexation of the metal center occurred upon iodonation of the reaction mixture. However, increasing the amount of LHMDS to 2.4 molar equiv resulted in formation of benzylic homo coupling products **10a** and **10b** in a 6:5 ratio and in 64% total yield. The structure of **10a** was further confirmed

by X-ray diffraction analysis. The formation of **10a** and **10b** may derive from benzylic homo coupling of the benzylic **11**.



8 **9** not formed **10a** **10b** **11**

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7. The spectral data for **4a**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (m, 1 H), 7.26 (m, 2 H), 7.09 (m, 1 H), 4.14 (dd, *J* = 7.1, 4.9 Hz, 1 H), 3.62 (d, *J* = 15.6 Hz, 1 H), 3.58 (d, *J* = 15.6 Hz, 1 H), 3.01 (dd, *J*= 11.3, 4.9 Hz, 1H), 2.90 (dd, *J* = 11.3, 7.1 Hz, 1 H), 2.51 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.4 MHz): δ 134.5, 128.4, 128.1, 127.5, 127.1, 126.9, 120.3, 57.1, 54.9, 45.5, 31.3; IR (CH_2Cl_2): 3052 (m), 2949 (m), 2226 (m), 1667 (s), 1630 (m), 1453 (m) cm^{-1}.

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