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Mescaline synthesis via tricarbonyl (η^6-1,2,3-trimethoxybenzene)chromium complex

Françoise Rose-Munch, René Chavignon, Jean-Philippe Tranchier, Vanessa Gagliardini, Eric Rose *

Laboratoire de Synthèse Organique et Organométallique, UMR 7611, Université P. et M. Curie, Case 181, 4 place Jussieu Tour 44, 75252 Paris Cedex 05, France

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Abstract

Treatment of tricarbonyl(η^6-1,2,3-trimethoxybenzene)chromium complex **1** with acetonitrile carbanion in THF and then with iodine followed by reduction of the nitrile function gives mescaline. Deprotonation of complex **1** at the C_5 carbon with LiTMP followed by chlorination, bromation or iodation gives 5-chloro, 5-bromo or 5-iodo complexes, useful synthons in organic synthesis for the preparation of 1,2,3-trimethoxy-5-substituted derivatives, precursors of natural products. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Nucleophilic aromatic substitutions; Arene tricarbonyl chromium complexes; Mescaline

1. Introduction

Arenes bound to the electrophilic tricarbonylchromium tripod realize many transformations that are impossible or difficult with the free arene. Indeed, nucleophilic aromatic substitutions as well as lithiation are easier and occur usually with high yield [1]. Our present research is mainly oriented in the mechanism study of the addition of nucleophiles and electrophiles to substituted arene complexes, and herein we report the study of the reactivity of tricarbonyl(η^6-1,2,3-trimethoxybenzene)chromium complex **1** in order to prepare precursors of natural products, namely mescaline (**2**) [2a] and podophyllotoxine (**3**) [3]. In the case of mescaline, several total syntheses of this hallucinogen alkaloid, isolated from the cactus plant Anhalonium Lewinii (Lophophora Williamsii) have been described in the literature [2b–h] but all these procedures were found to be tedious giving low overall yields or using too many steps for a synthetic pathway, except [2g]. Indeed, mescaline was obtained from 2,6-dimethoxy phenol by a Mannich reaction followed by a subsequent quaternization, CN^- nucleophilic substitution, methylation and reduction in 42% overall yield. In connection with our own research field, it was interesting to show that the use of chromium tricarbonyl entity coordinated to trimethoxy-1,2,3 benzene could help in the regioselective C5 functionalization of this arene in order to obtain mescaline in a straightforward and efficient way. In this paper, we will describe in a first part the addition of a stabilized carbanion to the electrophilic complex **1** and in a second part the trapping of tricarbonyl(η^6-1,2,3-trimethoxy 5-lithio benzene)chromium with electrophiles: arene complexes playing the role of electrophiles and nucleophiles, respectively.

2. Experimental

All reactions were carried out under a dry nitrogen atmosphere. The (η^6-arene)tricarbonylchromium complexes were generally stable in air for a long period of time in the solid state. Nevertheless, many derivatives were found to decompose fast in THF solutions on exposure to air. Consequently, all experiments were

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* Corresponding author. Tel.: +33-1-44-276 235; fax: +33-1-44-275 504.

E-mail address: rose@ccr.jussieu.fr (E. Rose)

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always protected from exposure to light and oxygen. Tetrahydrofuran (THF) and di-n-butylether (n-Bu_2O) were dried over sodium benzoketyl under dry nitrogen atmosphere and distilled just before use. Before performing NMR experiments, NMR solvents and tubes were purged with dry nitrogen to remove oxygen. ^1H and ^{13}C NMR spectra were acquired on a Bruker AC 200 and 400 spectrometer and chemical shifts were reported in ppm downfield of Me_4Si. ^1H NMR spectra were referenced against the residual. ^1H impurity of the deuterated solvent (7.25, $CDCl_3$), and ^{13}C NMR spectra were referenced against the ^{13}C resonance of the solvent δ (ppm) (77.2, $CDCl_3$). IR spectra were performed on a Perkin–Elmer 1420. Mass spectra were obtained on a Nermag R30-40 spectrometer, with a direct insert source, using the electronic impact (EI) method. Elemental analyses (reported in % mass) were performed by 'Le Service de Microanalyses de l'Université P. et M. Curie'.

2.1. *Tricarbonyl(η^6-1,2,3-trimethoxybenzene)chromium (**1**)*

This complex was prepared in 96% yield from 1,2,3-trimethoxybenzene and $Cr(CO)_6$, see Ref. [4].

2.2. *Electrophilic addition*

Lithium-2,2,6,6-tetramethylpiperidide (LiTMP), was prepared by adding n-BuLi (1.6 M in hexane, 1.25 ml, 2 mmol) to tetramethylpiperidine (337 μl, 2 mmol) in THF (10 ml) at −78°C under N_2. After 10 min, a THF solution (10 ml) of complex **1** (304 mg, 1 mmol) at −78°C was transferred via a cannula to the LiTMP solution. After 30 min at −78°C, the solution was transferred at −78°C in an I_2 solution (508 mg, 2 mmol) in THF (10 ml) and stirred for 1 h at r.t. The solution was extracted with ether–H_2O. The organic phase was washed with H_2O and brine. After filtration over $MgSO_4$ and celite pad, the solvents were evaporated under reduced pressure. The yellow residue was purified on a 15–40 μm silica gel chromatography column with a mixture of acetone–petroleum ether giving complexes **7c**, **8c** and **9c** in 65% (280 mg), 17% (73 mg) and 9% (50 mg) yields, respectively.

7c: Tricarbonyl (η^6-5-iodo-1,2,3-trimethoxybenzene)-chromium. Yellow solid. *F* (dec.) = 128°C. *Anal.* Calc. For $C_{12}H_{11}CrIO_6$: C, 33.51; H, 2.57. Found: C, 33.57; H, 2.57%. MS: *m/z* 430 (M^+), 346 ($M^+ - 3CO$), 294 ($M^+ - Cr(CO)_3$). IR (CCl_4, cm^{-1}): ν(CO) 1970, 1905. ^1H NMR ($CDCl_3$): δ 5.14 (2H, s, $H^{4,6}$), 3.84 (6H, s, OCH_3 $C^{1,3}$), 3.82 (3H, s, OCH_3 C^2). ^{13}C NMR ($CDCl_3$): δ 233.18 (Cr–*C*O), 139.17 ($C^{1,3}$), 120.10 (C^2), 78.13 ($C^{4,6}$), 66.37 (O*C*H_3 C^2), 63.08 (C^5), 56.77 (O*C*H_3 $C^{1,3}$).

8c: Tricarbonyl (η^6-4-iodo-1,2,3-trimethoxybenzene)-chromium. Yellow solid. *F* (dec.) = 136°C. *Anal.* Calc. for $C_{12}H_{11}CrIO_6$: C, 33.51; H, 2.57. Found: C, 33.46; H, 2.62%. MS: *m/z* 430 (M^+), 346 ($M^+ - 3CO$), 294 ($M^+ - Cr(CO)_3$). IR (CCl_4, cm^{-1}): ν(CO) 1965, 1885. ^1H NMR ($CDCl_3$): δ 5.72 (1H, d, $J = 7$, H^5), 4.73 (1H, d, $J = 7$, H^6), 3.95–3.75 (9H, 3s, OCH_3 $C^{1,2,3}$). ^{13}C NMR ($CDCl_3$): δ 232.72 (Cr–*C*O), 138.01, 123.83, 110.0 ($C^{1,2,3}$), 96.97 (C^5), 71.79 (C^6), 65.76, 62.48, 56.56 (O*C*H_3 $C^{1,2,3}$), 47.99 (C^4).

9c: Tricarbonyl (η^6-4,6-diiodo-1,2,3-trimethoxybenzene)chromium. Yellow oil. *Anal.* Calc. for $C_{12}H_{10}CrI_2O_6$: C, 25.92; H, 1.81. Found: C, 25.86; H, 1.85%. IR (CCl_4, cm^{-1}): ν(CO) 1965, 1890. ^1H NMR ($CDCl_3$): δ 5.93 (s, H^5), 3.94 (s, OCH_3 C^2), 3.89 (s, OCH_3 $C^{1,3}$).

Using the same experimental procedure with *N*-bromosuccinimide NBS (356 mg, 2 mmol), complex **7b** was obtained (8%, 30 mg) and 12% (36 mg) of complex **1** was recovered (separated by chromatography column).

7b: Tricarbonyl (η^6-5-bromo-1,2,3-trimethoxybenzene)chromium. Yellow oil. *Anal.* Calc. For $C_{12}H_{11}BrCrO_6$: C, 37.62; H, 2.89. Found: C, 37.51; H, 2.89%. MS: ^{79}Br *m/z* 382 (M^+), 298 ($M^+ - 3CO$), 246 ($M^+ - Cr(CO)_3$). ^{81}Br *m/z* 384 (M^+), 300 ($M^+ - 3CO$), 248 ($M^+ - Cr(CO)_3$). IR (CCl_4, cm^{-1}): ν(CO) 1970, 1905. ^1H NMR ($CDCl_3$): δ 5.11 (2H, s, $H^{4,6}$), 3.84 (6H, s, OCH_3 $C^{1,3}$), 3.82 (3H, s, OCH_3 C^2). ^{13}C NMR ($CDCl_3$): δ 232.93 (Cr–*C*O), 138.66 ($C^{1,3}$), 119.55, 97.16 ($C^{2,5}$), 73.26 ($C^{4,6}$), 66.45 (O*C*H_3 C^2), 56.74 (O*C*H_3 $C^{1,3}$).

Using the same experimental procedure with *N*-chlorosuccinimide (NCS) (267 mg, 2 mmol), complexes **7a** and **8a** were obtained in 37% (125 mg) and 4% (14 mg) respective yield; 17% (52 mg) of complex **1** was recovered (separated by chromatography column).

7a: Tricarbonyl (η^6-5-chloro,1,2,3-trimethoxybenzene)chromium. Yellow oil. *Anal.* Calc. For $C_{12}H_{11}ClCrO_6$: C, 42.56; H, 3.27. Found: C, 42.36; H, 3.20%. MS: ^{35}Cl *m/z* 338 (M^+), 254 ($M^+ - 3CO$), 202 ($M^+ - Cr(CO)_3$). ^{37}Cl *m/z* 340 (M^+), 256 ($M^+ - 3CO$), 204 ($M^+ - Cr(CO)_3$). IR (CCl_4, cm^{-1}): ν(CO) 1970, 1905. ^1H NMR ($CDCl_3$): δ 5.04 (2H, s, $H^{4,6}$), 3.86 (6H, s, OCH_3 $C^{1,3}$), 3.81 (3H, s, OCH_3 C^2). ^{13}C NMR ($CDCl_3$): δ 233.02 (Cr–*C*O), 138.16 ($C^{1,3}$), 119.55, 110.91 ($C^{2,5}$), 70.99 ($C^{4,6}$), 66.63 (O*C*H_3 C^2), 56.82 (O*C*H_3 $C^{1,3}$).

8a: Tricarbonyl (η^6-4-chloro,1,2,3-trimethoxybenzene)chromium. Yellow oil. *Anal.* Calc. For $C_{12}H_{11}ClCrO_6$: C, 42.56; H, 3.27. Found: C, 42.45; H, 3.19%. IR (CCl_4, cm^{-1}): ν(CO) 1965, 1890. ^1H NMR ($CDCl_3$): δ 5.55 (1H, d, $J = 7$, H^5), 4.86 (1H, d, $J = 7$, H^6), 4.0–3.75 (9H, 3s, OCH_3 $C^{1,2,3}$).

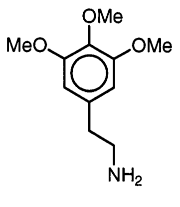
2.3. *Nucleophilic aromatic substitution*

n-BuLi (1.5 M in hexane, 1.6 ml, 2.4 mmol) was added to diisopropylamine (336 μl, 2.4 mmol) in THF

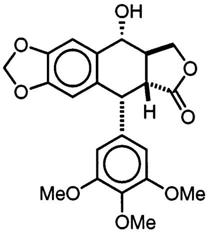
(4 ml) at − 78°C under N_2. After 10 min, CH_3CN (126 μl, 2.4 mmol) was added and the solution stirred for 15 min at − 40°C and then, HMPA (1.74 ml, 10 mmol) was added at − 78°C. A THF (8 ml) solution of complex **1** (608 mg, 2 mmol) at − 78°C was transferred via a cannula to the $LiCH_2CN$ solution. After 2 h at − 78°C, the solution was transferred at − 78°C in an I_2 solution (2 g, 8 mmol) in THF (20 ml) and stirred for 10 min at − 78°C and then at r.t. overnight. The solution was extracted with ether–$Na_2S_2O_4$. The organic phase was washed with $Na_2S_2O_4$ saturated solution till the aqueous phase was uncoloured. After filtration over Na_2SO_4 and celite pad, the solvents were evaporated under reduced pressure. The residue was purified on a 15–40 μm silica gel chromatography column with a mixture of ether–petroleum ether giving a white compound **5** (86%, 363 mg).

5: 3,4,5-trimethoxyphenylacetonitrile. White solid. M.p. = 76°C. *Anal.* Calc. for $C_{11}H_{13}NO_3$: C, 63.71; H, 6.27. Found: C, 63.59; H, 6.35%. IR (CCl_4, cm^{-1}): ν(CN) 2240. ^1H NMR ($CDCl_3$): δ 6.51 (2H, s, $H^{4,6}$), 3.85 (6H, s, OCH_3 $C^{1,3}$), 3.82 (3H, s, OCH_3 C^2), 3.69 (2H, s, CH_2CN). ^{13}C NMR ($CDCl_3$): δ 153.62 ($C^{1,3}$), 137.66 (C^2), 125.29 (C^5), 117.80 (CN), 104.98 ($C^{4,6}$), 60.83 (OCH_3 C^2), 56.13 (OCH_3 $C^{1,3}$), 23.74 (CH_2CN).

2: mescaline. $LiAlH_4$ (4 mmol, 152 mg) was added to a dry THF solution (10 ml) of the nitrile **5** (252 mg, 1.2 mmol). The reaction was refluxed for 2 h. Excess hydride was decomposed with AcOEt and the reaction was filtered and evaporated under reduced pressure. By adding a calculated amount of HCl in MeOH, the resulting mescaline hydrochloride was recrystallized in isopropanol. M.p. 181°C (80%). Lit. [2h]: 180–181°C.



2 mescaline

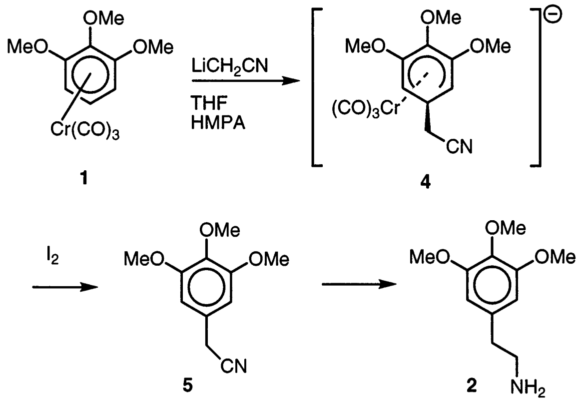


3 podophyllotoxine

3. Results and discussion

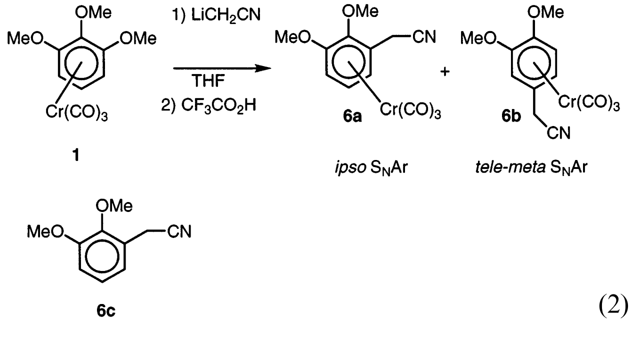
3.1. Reactivity of tricarbonyl (η^6-1,2,3-trimethoxybenzene)chromium with acetonitrile carbanion

Treatment of the tricarbonyl (η^6-1,2,3-trimethoxybenzene)chromium complex **1** [4] with $LiCH_2CN$ in THF and HMPA gave the anionic (η^5-cyclohexadienyl) **4** which was oxidised into **5** with I_2 (Eq. (1)). 3,4,5-trimethoxyphenylacetonitrile **5** was recovered in 86% yield after silica gel chromatography column and precipitation in a mixture of petroleum ether and ether. If the reaction was performed without HMPA, the yield did not exceed 25%; furthermore, some dimethoxy derivative **6c** corresponding to an *ipso* substitution of the nucleophile to a carbon bearing an external methoxy group was obtained as a minor compound. The best yield of nitrile **5** was obtained by using five equivalents of HMPA [5].

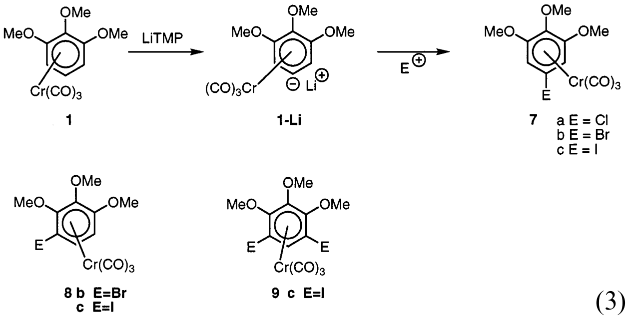


(1)

It is worthy to point out the influence of HMPA: indeed, in the presence of this cosolvent, the addition of a stabilized carbanion is irreversible [5], avoiding the rearrangement of the η^5-cyclohexadienyl intermediate **4** into **6a** via an *ipso* addition at the carbon bearing a methoxy group. We observed previously [4a] that treating a solution of **1** with $LiCH_2CN$ in THF and then with CF_3CO_2H, at low temperature, lead to a mixture of two regioisomers **6a** and **6b** in 22 and 42% yields, respectively (Eq. (2)). The formation of these complexes involved respectively an *ipso* and a *tele-meta* [1f,1g,4c] nucleophilic aromatic substitution (Eq. (2)).



(2)



(3)

So, these data shed light on the role of the cosolvent HMPA: in THF without HMPA, the nucleophile $LiCH_2CN$ reacted on the carbons C3 and C5 whereas in THF with HMPA, the nucleophile irreversibly attacked the C5 carbon.

Thus, regioselectivity of the addition of the carbanion to complex **1** can be related to the major conformation of the tripod $Cr(CO)_3$ in solution eclipsing the C1 and C3 carbons bearing the methoxy groups [4a]. Knowing that a stabilized carbanion prefers to react at low temperature with a carbon eclipsed by a Cr–CO bond [4b,5a], it was expected that substitution on the C5 carbon would be privileged. This is also in good agreement with a small shielding δ(H5:free arene)–δ(H5:complex) of the H5 proton of complex **1**. Indeed, this difference of chemical shift is $6.98-5.42=1.56$ ppm for the eclipsed proton H5, whereas, this difference is larger in the case of the non eclipsed protons H4 and H6: $6.57-4.75=1.82$ ppm in solution in $CDCl_3$.

Hydrogenation of the nitrile **5** using a literature procedure [2g] gave mescaline in 80% yield and in 66% overall yield starting from 1,2,3-trimethoxybenzene in three steps.

3.2. Reactivity of tricarbonyl (η^6-1,2,3-trimethoxy-5-lithiobenzene)chromium with electrophiles

Lithiation of tricarbonyl(alkoxy–arene) chromium is well documented in the literature. n-Butyl–lithium has been used for the majority of deprotonation studies, which have shown a good *ortho*-selectivity [6]. The regioselectivity of the deprotonation is dependent on the reaction conditions and on the nature of the electrophiles used in the trapping step. The use of a sterically demanding base such as lithium-2,2,6,6-tetramethyl piperidide (LiTMP) allowed to change this regio selectivity [7]. Indeed in a preliminary communication [7b], we showed that treatment of complex **1** with LiTMP, (two equivalents) gave a *meta* selectivity with respect to the 1,3-methoxy groups affording the lithium salt **1-Li**. The use of only one equivalent of LiTMP gave poor results and the regioselectivity was modified. If the reaction mixture was treated with I_2, NBS and NCS the major product was the halogeno complex **7** (Table 1) (Eq. (3)). Indeed, in the case of *N*-chloro-succinimide, 37% of complex **7a** was obtained besides a small amount of the 4-isomer **8a** (4%). Using *N*-bromo-succinimide, the reaction did not give satisfactory results and only 8% of complex **7b** was isolated. Oxidation of the chromium probably occured. Fortunately, with I_2, the yield of the 5-iodo derivative **7c** reached 65% [8a]. Another example of such iodation has been mentioned in the literature [8b]. The other isomer **8c** was also obtained in 17% yield with the di-iodo derivative **9c** in 9% yield. These 5-halogeno complexes are of interest because they could be the precursors of interesting natural products such as podophyllotoxine (**3**) [3]. Indeed 1,2,3-trimethoxy-5-bromo benzene has been used recently as a synthon in the synthesis of a precursor of this type of alkaloids [9].

Table 1
Trapping of the lithium derivative of **1**

Entry	Electrophile	**7**	**8**	**9**	Total yield%
1	NCS [c]	37	4		41 [a]
2	NBS [c]	8			8 [b]
3	I_2 [c]	65	17	9	91

[a] 17% of complex **1** is recovered.

[b] 12% of complex **1** is recovered.

[c] Two equivalents.

4. Conclusion

We have shown that the highly regioselective addition of acetonitrile carbanion to tricarbonyl (η^6-1,2,3-trimethoxybenzene)chromium (**1**) provided a rapid access to mescaline after reduction of the nitrile function in a 66% overall yield in three steps starting from 1,2,3-trimethoxybenzene. Furthermore, regioselective deprotonation of complex **1** and electrophilic addition of suitable halogens lead to 5-chloro, bromo or iodo trimethoxybenzene derivatives, interesting precursors for the synthesis of natural products.

Acknowledgements

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