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Double ortho meta regiocontrolled functionalisation of tricarbonyl-(η^6-1-*tert*-butoxycarbonyl-2,3-dimethylbenzene)chromium; ^{17}O NMR study of saponification-elimination mechanism

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Abstract

The title compound **1** promotes the attachment of an electrophilic group preferentially to the 2-methyl group while the 3-methyl group reacts slightly. A condensation mechanism of **1** with aldehyde involving a lactonisation step is confirmed by a labelling experiment.

Keywords: ^{17}O NMR; Mechanism; Tricarbonylchromium; Regioselectivity; Benzylic carbanions

1. Introduction

During the past 20 years there has been a great interest in the chemistry and synthetic applications of tricarbonyl(η^6-arene)chromium [1]. Regiospecific and stereospecific functionalisation of extra arenic sites mediated by an organometallic temporary activation technique has been demonstrated. The behaviour of stabilised benzylic anions, generated with potassium *tert*-butoxide in the presence of aldehyde [2] and with *n*BuLi in the presence of alkyl halide [3] has been particularly analysed. Electronic effects in directing the regioselectivity of benzylic attack were found [4]. When two potential benzylic sites of attack (meta and para position with respect to the donor methoxy or dimethylamino substituent) are present in the same molecule only products bearing the hydroxymethyl group at the meta-carbon atom are produced. However, when potential sites are ortho and meta positions with respect to the donor moieties, attack occurs preferentially at the meta position, whereas the ortho position is still reactive but less so. This difference in reactivity opens up the possibility of regioselective introduction of two different electrophiles [5]. The behaviour of tricarbonyl(η^6-arene)chromium bearing an electron-withdrawing substituent was examined. It has been shown that tricarbonyl(η^6-1-*tert*-butoxycarbonyl-3,4-dimethylbenzene)-chromium only produced complexes bearing hydroxymethyl group at the para-carbon atom [6].

2. Results and discussion

With the aim of studying the selectivity of proton abstraction from ortho or meta benzylic sites relative to an electron-withdrawing group, **1** was prepared. We report the results of the reaction of **1** with electrophiles. Upon treatment of **1** with potassium *tert*-butoxide in DMSO and methyl iodide at room temperature, ortho ethyl complex **2a** was obtained (Scheme 1). Similar reaction was observed with CH_3SSCH_3. Astonishingly, the reaction of **1** with methanal or benzaldehyde afforded the unexpected ortho ethylenic acid **3** as a single product in very good yield (97%), instead of the *tert*-butyl ester bearing an hydroxy group (**2** with R = CH_2OH or C_6H_5CHOH).

To identify the location of the electrophile at the ortho or meta benzylic carbon, ^{1}H NMR studies were undertaken. 300 MHz ^{1}H NMR indicated that the vinyl group is in the ortho position with respect to the ester or

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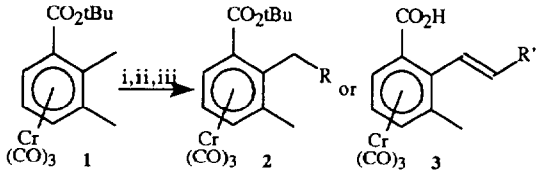


ii = I CH_3	R = CH_3:	**2a** = 82%* (89%)**
ii = $(CH_3 S)_2$	R = S CH_3:	**2b** = 69%* (90%)**
ii = HCHO	R' = H :	**3a** = 97%*
ii = C_6H_5CHO	R' = C_6H_5:	**3b** = 82%* (99%)**

Scheme 1. Reagents and conditions: (i) ^{t}BuOK (1.2–2 equivalents); (ii) electrophile (1.2–2 equivalents) room temperature, 2 h, (iii) H_2O. * Isolated yields, all compounds gave satisfactory ^{1}H NMR and MS data. ** Yield includes recovered starting material.

acid group. In correlation with the NMR studies of tricarbonyl(η^6-1-*tert*-butoxycarbonyl-2-methylbenzene) chromium (CH_3 ortho: δ = 2.49 ppm) and tricarbonyl(η^6-1-*tert*-butoxycarbonyl-3-methylbenzene)-chromium (CH_3 meta: δ = 2.23 ppm), the δ 2.45 ppm resonance of **1** is assigned to the ortho methyl moiety while the δ 2.20 ppm resonance is assigned to the meta methyl moiety. The remaining shielded singlet of the ^{1}H NMR spectrum of **2a** (2.22 ppm), **2b** (2.15 ppm), **3a** (2.21 ppm) and **3b** (2.28 ppm) is assigned to the remaining meta methyl group. The molecular structure

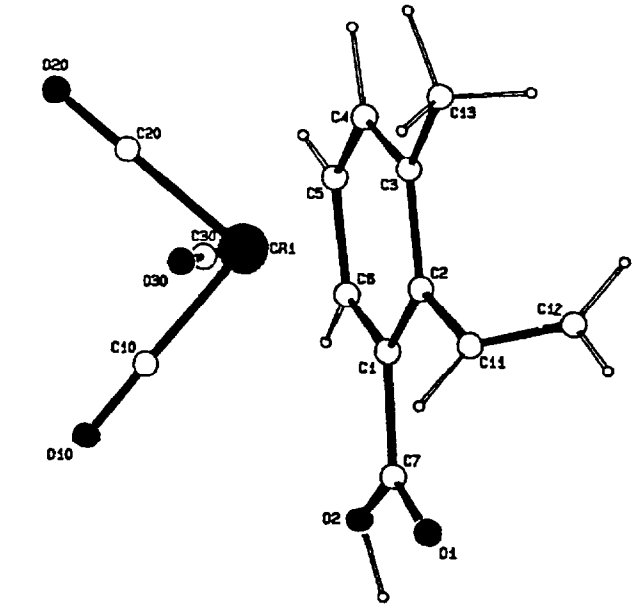
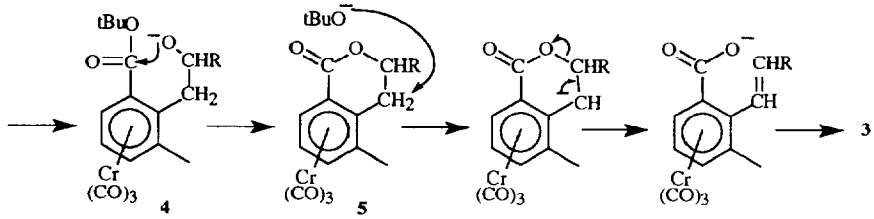


Fig. 1. Molecular structure of complex **3a**. Selected bond lengths (Å): C1–C7 1.490(5), C7–O1 1,228(5), C7–O2 1,306(4), C2–C11 1.498(6), C11–C12 1,313(6), C3–C13 1,507(6): torsion angles (°) C2–C1–C7–O1 0.3(3), C3–C2–C11–C12 61.2(4).

of **3a** and regioselectivity of deprotonation were confirmed by an X-ray crystallographic study (Fig. 1) [7].

It is assumed that the reaction of **1** with aldehyde starts by ortho deprotonation and condensation of the



Scheme 2. Proposed mechanism for the formation of **3**.

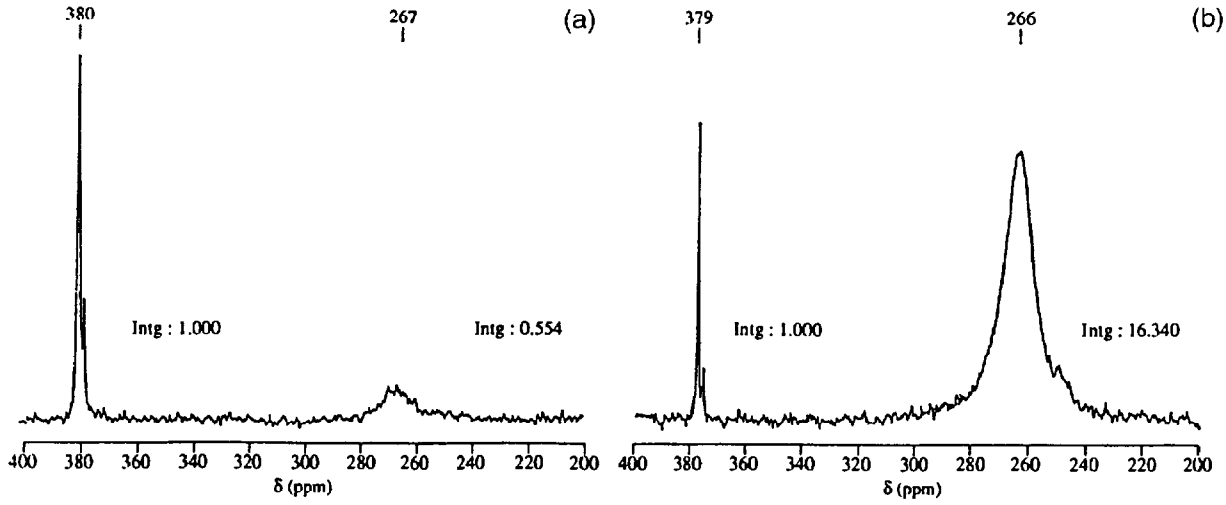
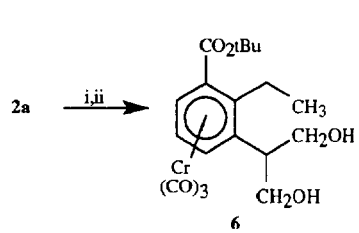


Fig. 2. ^{17}O NMR spectra at 400 MHz of **3b** (a) and **3b*** derived from ^{17}O-enriched benzaldehyde (b).

aldehyde which gives **4** (Scheme 2). The alkoxide **4** attacks the ester function, thus leading to lactone **5** and regenerating *tert*-butoxide. A second basic attack of ortho benzylic proton followed by E_1CB elimination finally gives the product **3**. In this case, the oxygen atom from the aldehyde must be transferred in the carboxylic acid group. Unfortunately, we failed to isolate the lactone **5**. However, the validity of this mechanism was confirmed by a labelling experiment as follows. The ^{17}O NMR spectrum of **3b** exhibited two signals (broad, δ 267 ppm: CO_2H group; sharp δ 380 ppm: $Cr(CO)_3$ group) (Fig. 2(a)). In contrast, the benzaldehyde dimethylacetal was hydrolysed with ^{17}O-enriched water in an acidic medium to give ^{17}O-enriched benzaldehyde ($0.168 \pm 0.017\%$ ^{17}O) [8]. As expected, reaction of **1** with ^{17}O-enriched benzaldehyde afforded ^{17}O-enriched ethylenic acid **3b***. Integration of the CO_2H ^{17}O signal of **3b*** (267 ppm) using the $Cr(CO)_3$ ^{17}O signal (379 ppm) as internal standard showed that the CO_2H group of **3b*** derived from enriched benzaldehyde was labelled with ^{17}O to $0.182 \pm 0.017\%$ (Fig. 2(b)). The fact that ^{17}O was present in the CO_2H group of **3b*** in a similar percentage as in the starting ^{17}O-enriched benzaldehyde is consistent with the existence of a lactone intermediate **5**.

In order to establish the possibility of a second benzylic deprotonation after the first ortho benzylic reaction of **1**, **2a** was treated with potassium *tert*-butoxide in DMSO and excess methanal. In this reaction, the hydroxymethyl groups took place exclusively at the meta position affording diol **6** (71%) (Scheme 3). Interestingly, it appears that benzylic protons of **2a** from 3-methyl are more reactive than those from 2-ethyl. This results from the restriction of approach of base to 2-benzylic protons, so that exclusively 3-benzylic proton attack is observed.

As a conclusion, the benzylic deprotonation of tricarbonyl(η^6-1-*tert*-butoxycarbonyl-2,3-dimethylbenzene)-chromium occurs preferentially at the ortho position. Structural aspects of products were investigated via NMR and X-ray methodology, and a regiochemical assignment was unambiguously confirmed. The meta position is still reactive, but much less so. This difference in reactivity opens up the possibility of a regioselective introduction of two different electrophiles. In addition, a ^{17}O NMR study of the saponification-elimination reaction is consistent with the formation of a lactone as a transient intermediate.



Scheme 3. Reagents and conditions: (i) ^{t}BuOK (3 equivalents), HCHO (3 equivalents), room temperature, 2 h; (ii) H_2O.

3. Experimental

The ^1H NMR spectra were performed on a Bruker AM 300 instrument in $CDCl_3$ with tetramethylsilane as an internal standard, the ^{17}O spectra on Bruker ASX 400 at 40°C with acetone (solvent) and water as internal standards. Mass spectra were recorded on Ribber 10-10. The microanalysis was performed by the central service of analysis of the CNRS. The melting points were determined with a Kofler instrument. DMSO was preserved on a molecular sieve. Commercial 70–230 mesh Kieselgel 60 (Merck) silica gel was used for chromatography columns.

3.1. Tricarbonyl(η^6-tert-butoxycarbonyl-2,3-dimethylbenzene)chromium (1)

5.3 ml of $SOCl_2$ were added to 2,3-dimethylbenzoic acid (2 g; 13 mmol). The solution was stirred at 80°C for 2 h. $SOCl_2$ was evaporated. The resulting oil was recovered with dried ether and added to ^{t}BuOK (1.5 g; 13.4 mmol) in 50 ml of ^{t}BuOH. The mixture was stirred for 2 h at 35°C. 2×30 ml of diethyl ether were added to extract the ester then the organic layer was washed with 2×60 ml of a saturated aqueous solution of NaCl. The solvent was evaporated and the residue was purified on a chromatography column (silica gel; 90% hexane–30% diethyl ether) to give 1.9 g of ester (70%). A mixture of the ester (1.9 g; 9.2 mmol) and $Cr(CO)_6$ (2.43 g; 11 mmol) in dibutyl ether (dried over sodium and distilled; 15 ml) and THF (dried over sodium and benzophenoneketyl and distilled; 8 ml) was purged under nitrogen for 15 min and refluxed for 68 h. The solution was cooled, then filtered through celite. The solvents were removed and the residue was purified on a chromatography column (silica gel; 70% hexane–30% diethyl ether) and recrystallised from hexane–diethyl ether to give 1.47 g of **1** (47%), m.p. 88°C. ^1H NMR (δ, ppm): 5.87 (1H, dd, J 6.5 and 1.0 Hz, C_6H_3), 5.45 (1H, dd, J 6.5 and 1.0 Hz, C_6H_3), 5.20 (1H, t, J 6.5 Hz, C_6H_3), 2.45 (3H, s, CH_3 ortho), 2.20 (3H, s, CH_3 meta), 1.58 (9H, s, ^{t}Bu). MS (*m/e*): 342 (M^+, 8), 286 ($M^+ - 2CO$, 3), 258 ($M^+ - 3CO$, 16), 202 ($M^+ - 3CO - (CH_3)_2C{=}CH_2$, 100), 52 ($Cr^+$, 66). Anal. Found: C, 56.25; H, 5.50. $C_{16}H_{18}CrO_5$. Calc.: C, 56.14; H, 5.26%.

3.2. Tricarbonyl(η^6-tert-butoxycarbonyl-2-ethyl-3-methylbenzene)chromium (2a)

A solution of **1** (342 mg; 1 mmol) and ^{t}BuOK (336 mg; 3 mmol) in 4 ml of DMSO was stirred at room

temperature for 1 min then ICH_3 (1.25 ml; 20 mmol) was added. After 2 h the solution was hydrolysed with 4 ml of 1 N HCL, then extracted with 3 × 20 ml of diethyl ether. The organic layer was washed with 2 × 60 ml of a saturated aqueous solution of NaCl and dried over Na_2SO_4. The solvent was evaporated. The chromatography column of the residue (silica gel: 70% hexane–30% diethyl ether) generates 291 mg of the yellow oil **2a** (82%). ^1H NMR (δ, ppm): 5.82 (1H, d, J 6.5 Hz, C_6H_3), 5.40 (1H, d, J 6.5 Hz, C_6H_3), 5.25 (1H, t, J 6.5 Hz, C_6H_3), 3.05 (1H, qd, J 14.0 and 7.5 Hz, diastereotopic CH_2 ortho), 2.55 (1H, qd, J 14.0 and 7.5 Hz, diastereotopic CH_2 ortho), 2.22 (3H, s, CH_3 meta), 1.57 (9H, s, ^{t}Bu), 1.23 (3H, dd, J 7.5 and 7.5 Hz, CH_3). MS (m/e): 356 (M^+, 7), 300 ($M^+ - 2CO$, 2), 272 ($M^+ - 3CO$, 14), 216 ($M^+ - 3CO - (CH_3)_2C=CH_2$, 100), 170 ($M^+ - 3CO - (CH_3)_2C=CH_2 - COOH$, 27), 52 ($Cr^+$, 80). Anal. Found: C, 57.40; H, 5.82. $C_{17}H_{20}CrO_5$. Calc.: C, 57.30; H, 5.66%.

3.3. Tricarbonyl(η^6-tert-butoxycarbonyl-3-methyl-2-(2-thiapropyl)benzene)chromium (2b)

A solution of **1** (342 mg; 1 mmol) and ^{t}BuOK (448 mg; 4 mmol) in 4 ml of DMSO was stirred at room temperature for 1 min then CH_3SSCH_3 (360 μl; 4 mmol) was added. After 2 h the solution was hydrolysed with 5 ml of 1 N HCl, then extracted with 3 × 20 ml of diethyl ether. The organic layer was washed with 2 × 60 ml of a saturated aqueous solution of NaCl and dried over Na_2SO_4. The solvent was evaporated. The chromatography column of the residue (silica gel; 70% hexane–30% diethyl ether) generates the yellow oil **2b** (0.69 mmol; 69%). ^1H NMR (δ, ppm): 5.85 (1H, d, J 6.0 Hz, C_6H_3), 5.40 (1H, d, J 6.0 Hz, C_6H_3), 5.29 (1H, t, J 6.0 Hz, C_6H_3), 4.57 (1H, d, J 13.0 Hz, diastereotopic CH_2 ortho), 3.50 (1H, d, J 13.0 Hz, diastereotopic CH_2 ortho), 2.29 (3H, s, SCH_3), 2.15 (3H, s, CH_3 meta), 1.58 (9H, s, ^{t}Bu). MS (m/e): 388 (M^+, 2), 332 ($M^+ - 2CO$, 28), 304 ($M^+ - 3CO$, 17), 252 ($M^+ - Cr(CO)_3$, 15), 248 ($M^+ - 3CO - (CH_3)_2=CH_2$, 100), 196 ($M^+ - Cr(CO)_3 - (CH_3)_2=CH_2$, 27), 149 ($M^+ - Cr(CO)_3 - (CH_3)_2=CH_2 - SCH_3$, 29), 57 ($^tBu^+$, 38), 52 ($Cr^+$, 92). Anal. Found: C, 53.26; H, 5.67. $C_{17}H_{20}CrO_5S$. Calc.: C, 52.57; H, 5.19%.

3.4. Tricarbonyl(η^6-3-methyl-2-vinylbenzoic acid)chromium (3a)

A mixture of **1** (342 mg: 1 mmol), ^{t}BuOK (336 mg: 3 mmol) and HCHO (90 mg; 3 mmol) in 4 ml of DMSO was stirred for 2 h. 4 ml of 1 N HCl, were added and the product was extracted with 3 × 20 ml of diethyl ether. The ether extracts were combined and the acid was extracted by salification with 5 × 10 ml of 0.5 N NaOH. The alkaline solution was acidified with 1 N HCl and extracted with 3 × 20 ml of diethyl ether. The solution was washed with 2 × 60 ml of a saturated aqueous solution of NaCl and dried over Na_2SO_4. The solvent was removed and the residue was recrystallised with CH_2Cl_2–hexane–diethyl ether to give 289 mg of **3a** (97%), m.p. = 152–153°C. ^1H NMR (δ, ppm): 6.82 (1H, dd, J 17.5 and 11.0 Hz, $CH=CH_2$), 6.01 (1H, d, J 6.0 Hz, C_6H_3), 5.62 (1H, d, J 11.0 Hz, $CH=CH_2$), 5.52 (1H, d, J 6.0 Hz, C_6H_3), 5.35 (1H, d, J 17.5 Hz, $CH=CH_2$), 5.30 (1H, t, J 6.0 Hz, C_6H_3), 2.21 (3H, s, CH_3 meta). MS (m/e): 298 (M^+, 8), 242 ($M^+ - 2CO$, 1), 214 ($M^+ - 3CO$, 90), 162 ($M^+ - Cr(CO)_3$, 26), 52 (Cr^+, 100). Anal. Found: C, 52.48; H, 3.84. $C_{13}H_{10}CrO_5$. Calc.: C, 52.35; H, 3.36%.

3.5. Tricarbonyl(η^6-3-methyl-2-(E-2-phenylvinylbenzoic acid)chromium (3b)

A solution containing **1** (342 mg; 1 mmol) and ^{t}BuOK (150 mg; 1.3 mmol) in 4 ml of DMSO was stirred for 1 min at room temperature: PhCHO (200 μl; 2 mmol) was added. After 2 h, the work-up was carried out as above. 240 mg of **3b** were obtained (oil; 64%). ^1H NMR (DMSO D_6, δ, ppm): 7.41 (5H, m, C_6H_5), 7.21 (1H, d, J 16.5 Hz, CH=CH), 6.61 (1H, d, J 16.5 Hz, CH=CH), 6.03, (1H, d, J 5.5 Hz, C_6H_3), 5.55 (1H, d, J 5.5 Hz, C_6H_3), 5.32 (1H, t, J 5.5 Hz, C_6H_3), 2.28 (3H, s, CH_3 meta). ^{17}O NMR (δ, ppm): 380 (3O, s, $Cr(CO)_3$): 267 (2O, m, COOH). MS (m/e): 374 (M^+, 1), 290 ($M^+ - 3CO$, 4), 238 ($M^+ - Cr(CO)_3$, 19), 193 ($M^+ - Cr(CO)_3$-COOH, 7), 105 (100), 52 (Cr^+, 33). Anal. Found: C, 60.73; H, 4.30. $C_{19}H_{14}CrO_5$. Calc.: C, 60.96; H, 3.74%).

3.6. ^{17}O-enriched benzaldehyde

A solution of 1 ml of 10% enriched ^{17}O water, 350 μl of HCl 37% and 2.5 ml of dimethylacetalbenzaldehyde were stirred for 30 min. The product was extracted with 3 × 30 ml of diethyl ether. The organic layers were combined, washed with a saturated aqueous solution of NaCl. The ether was evaporated and the residue was distilled under reduced pressure to give 1.7 g of 0.168 ± 0.017% ^{17}O enriched PhCHO, b.p. 90°C (45 mm). ^{17}O NMR (δ, ppm): 567 (s, CHO).

3.7. ^{17}O-enriched tricarbonyl(η^6-3-methyl-2-(E-2-phenylvinylbenzoic acid)chromium (3b*)

The reaction carried out as for **3b** generates 300 mg of 0.182 ± 0.017% ^{17}O enriched **3b*** (80%). ^{17}O NMR (δ, ppm): 379 (integration: 1.000, s, $Cr(CO)_3$); 266 (integration: 16.340, m, COOH).

3.8. Tricarbonyl(η^6-tert-butoxycarbonyl 2-ethyl-3-(2-hydroxy-1-hydroxymethylethyl)benzene)chromium (6)

A mixture of **2a** (205 mg; 0.6 mmol), ^{t}BuOK (112 mg; 1 mmol) and HCHO (35 mg; 1.2 mmol) in 4 ml of DMSO was stirred for 2 h. 2 ml of 1 N HCl were added and the product was extracted with 3 × 20 ml of diethyl ether. The ether extracts were combined and washed with 2 × 60 ml of a saturated aqueous solution of NaCl and dried over Na_2SO_4. The solvent was evaporated. The chromatography column of the residue (silica gel; diethyl ether) generates 177 mg of the yellow oil **6** (71%). ^{1}H NMR (δ, ppm): 6.07 (1H, d, J 6.5 Hz, C_6H_3), 5.74 (1H, d, J 6.5 Hz, C_6H_3), 5.14 (1H, t, J 6.5 Hz, C_6H_3), 4.05–3.75 (4H, m, 2 × CH_2O), 3.09 (1H, qd, J 14.0 and 7.5 Hz, diastereotopic CH_2 ortho), 2.61 (1H, qd, J 14.0 and 7.5 Hz, diastereotopic CH_2 ortho), 1.57 (9H, s, ^{t}Bu), 3.03 (1H, m, CH meta), 1.29 (3H, t, J 7.5 Hz, CH_3). MS (m/e): 416 (M^+, 19), 332 ($M^+ - 3CO$, 66), 280 ($M^+ - Cr(CO)_3$, 1), 276 ($M^+ - 3CO - (CH_3)2C{=}CH_2$, 59), 246 ($M^+ - 3CO - (CH_3)_2C{=}CH_2 - HCHO$, 51), 91 ($C_6H_5CH_2^+$, 52), 77 ($C_6H_5^+$, 42), 57 ($^tBu^+$, 100), 52 ($Cr^+$, 58). Anal. Found: C, 56.29; H, 6.30. $C_{19}H_{24}OCrO_7$. Calc.: C, 54.81; H, 5.81%.

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[7] Crystal data for **3a**: $C_{13}H_{10}O_5Cr$, $M_r = 297.2$, triclinic, space group $P\bar{1}$, $a = 6.966(4)$, $b = 8.993(4)$, $c = 10.932(4)$ Å, $\alpha = 96.03(15)$, $\beta = 104.12(16)$, $\gamma = 104.84(16)°$, $V = 632(4)$ Å^3, $Z = 2$, $D_c = 1.57$ g cm^{-3}. Data were collected with a Phillips PW 1100 diffractometer, maximum 2θ 74°, using Mo Kα radiation, $\lambda = 0.71069$ Å, μ(Mo Kα) = 8.61 cm^{-1}, $T = 293$ K, crystal dimensions 0.4 × 0.5 × 0.5 mm, 4992 reflections were measured, 2094 were considered observed, ($I/\sigma(I) \geq 3.0$) and used in refinement; they were corrected for Lorentz and polarisation effects, but not for absorption and extinction effects. The Cr, C and O atoms were located from Patterson synthesis. Except for the methyl group, all H atoms peaks were located on a difference Fourier synthesis; the methyl group was treated as a rigid unit with its original orientation taken from the strongest H-atom peak on the difference Fourier synthesis. Only H_2 was refined, other H-atoms riding at 1.08 Å. Final refinement was on F by least squares methods refining 175 parameters. Final $WR = 0.0474$, with weight $w = 1/(\sigma^2(F) + 0.00116F^2)$. Maximum shift/error in final cycle 0.03. Computing with SHELX-S86 (Sheldrick, 1985) for Patterson synthesis and SHEL-X76 (Sheldrick, 1976) for refinement, on a Micro-VAX II. Scattering factors in the analytical form and anomalous dispersion factors were taken from International Tables (1974). Atomic co-ordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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