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Synthesis of Methyl 1-Aryl-2-oxo-cycloalkanecarboxylates *via* Tricarbonylchromium Complexes Under Mild Conditions

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Dedicated to Prof. Dr. Hans Schick on the Occasion of his 60th Birthday

Arylated alkanone derivatives are important synthons *inter alia* for the preparation of biologically active compounds with miticidal, herbicidal [1], and anticonvulsant activities [2]. Arylmalonic acid esters are used in the synthesis of nonsteroidal antiinflammatory agents [3].

Therefore, much attention has been focused on the synthesis of arylated dicarbonyl compounds and their application as intermediates. The arylation methods most often used for carbanions are nucleophilic displacement reactions, reactions with aryllead triacetate, pentavalent bismuth reagents, and arylations with aryl iodonium salts (cf. reviews [4–6]).

For example, phenylations of carbanions are carried out by reactions with diphenyliodonium salts [7, 8]. The phenylation of enols and enolate anions of ketones, β-diketones and keto esters has been studied using a range of bismuth reagents [9]. Aryllead triacetates have been shown to be efficient electrophilic C-arylating agents for a wide range of soft carbon nucleophiles, such as β-dicarbonyl compounds, nitroalkanes, α-cyano esters and malonitriles [10–13]. Examples of nucleophilic displacements are the phenylation of esters by reaction with bromobenzene in the presence of sodium amide [14]. 2-Nitroaryl triflates undergo efficient nucleophilic substitution by dimethyl malonate anion to yield dimethyl nitroarylmalonates [15].

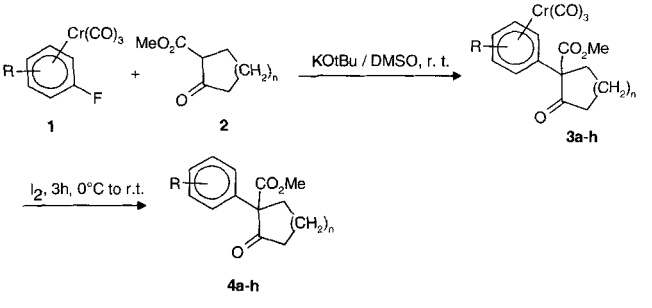
Finally, it is also well known that in fluoro- or chloro-arenetricarbonyl chromium complexes the aromatic ring is activated toward nucleophilic attacks of carbon nucleophiles. When stabilized carbanions ($pK_a<18$) are treated with these complexes the S_NAr-reaction proceeds exclusively as *ipso*-substitution of the haloatom [16, 17].

During the course of our studies on the chemistry of nitroactivated aromatics and related compounds, we could recently show that O/C arylations of cyclic β-diketones succeed with activated fluoroarenes [18]. In continuation of this work, we now report the arylation of methyl 2-oxo-cycloalkanecarboxylates **2** using tricarbonylchromium complexes of fluoroarenes **1** to give compounds **4** *via* **3**.

Results and Discussion

A variety of tricarbonyl(η^6-fluoroarene)chromium(0) complexes **1**, readily prepared from fluoroarenes and hexacarbonylchromium, were added to **2** in the presence of potassium *tert*-butoxide. The tricarbonylchromium complexes of fluorobenzene, 3-and 4-fluorotoluene gave the expected arylation products as contrasted with the sterically hindered complex of 2-fluorotoluene which does not react under these conditions. After stirring at 20 °C for several hours to some days, compounds **3a–h** may be isolated after removing of the KF. In the cases of compounds **3d**, **3e**, the formation of resinous by-products is observed.

The oxidative decomplexation of compounds **3** to give the methyl 1-aryl-2-oxo-cycloalkanecarboxylates **4** proceeds at room temperature in the presence of iodine. The overall yields of pure, isolated racemic products **4** are in the range from 47 to 82% (cf. Table 2). The highest yields were obtained with cycloheptanones **2** (n = 3; yields of **4f–4h**: 71–82%), followed by cyclopentanones **2** (n = 1; yields of **4a–4c**: 64–73%), and cyclohexanones **2** (n=2; yields of **4d**, **4e**: 47–59%).

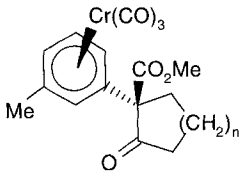


3, 4	a	b	c	d	e	f	g	h
R	H	3-Me	4-Me	H	3-Me	H	3-Me	4-Me
n	1	1	1	2	2	3	3	3

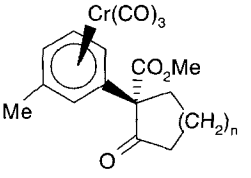
In all cases we exclusively found C-arylation products. The S_NAr reaction proceeds with regiospecific *ipso*-substitution. The complex of fluorobenzene **1** (R = H) shows the highest reactivity towards cycloheptanones and cyclopentanones, respectively.

Examination of the crude products by HPLC indicated that the diastereoisomers *rac*-**3b/3b'** (55:45), *rac*-**3e/e'** (50:50), and *rac*-**3g/3g'** (50:50) were formed (for physical and spectroscopic data cf. Table 1).

The influence of temperature was studied using the synthesis of **3c** as model reaction, monitored by means of TLC. At 20 °C the arylation of methyl 2-oxo-cyclopentanecarboxylate proceeds within 5 days. As expected, at 60 °C the reaction time may be considerably reduced (4 h). But, the decomplexation **3c** → **4c** takes place to a large degree. Thus, the ratio of reaction products **3c**:**4c** has been decreased from 87:13 at 20 °C to 62:38 at 60 °C.



rac-**3b, e, g**



rac-**3b', e', g'**

The structures of the products **3** and **4** were established by mass spectra, IR, ^1H and ^{13}C NMR spectra and elemental analysis. The molecular structure of compound **3d** is shown in Figure 1. These data are in good agreement with the spectroscopic investigations. Moreover, the structural data exhibit that the arylsubstituent is located in the equatorial position of the cyclohexanone ring.

In conclusion, the arylation of stabilized tertiary carbanions succeeds at room temperature using tricarbonylchromium complexes of fluoroarenes to give the corresponding arylated compounds.

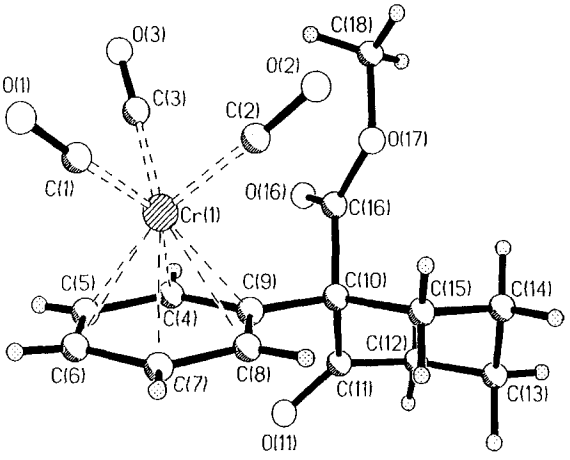


Fig. 1 Molecular structure of tricarbonyl[η^6-(methyl 2-oxo-1-phenyl-cyclohexanecarboxylate)]chromium(0) **3d**.

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Experimental

The fluoroarenes and methyl 2-oxo-cycloalkanecarboxylates were purchased from Aldrich and used without further purification. Compounds **1** were prepared according to ref. [19–21].

Melting points were determined with a Boëtius apparatus and are corrected. ^1H NMR spectra were measured at 300 MHz on a Varian Unity 300 or at 500 MHz on a Varian Unity 500 in DMSO-d_6 with TMS as internal standard. ^{13}C NMR spectra were obtained on a Varian Gemini 300 spectrometer in DMSO-d_6; internal standard: HMDS (δ: 1.9 ppm). Mass spectra were carried out on an Autospec (Fisons). IR spectra were recorded on a Specord 75 (Carl Zeiss, Jena). Elemental analyses were performed on a Elemental Analyzer 1106 (Carlo Erba); chromium was determined by means of ICP-OES using an Optima 3000 XL (Perkin-Elmer). Flash chromatography was carried out using silica gel (Kieselgel 60, 230–400 mesh, Merck).

Methyl 1-Aryl-2-oxo-cycloalkanecarboxylates (4a–h) General Procedures

Arylation Step (**1**+**2** → **3**)

To a solution of potassium *tert*-butoxide (1.12 g, 0.01 mol) in abs. DMSO (4 mL), 0.01 mol of compound **2** is added dropwise. After 15 min 0.01 mol of the appropriated tricarbonyl(η^6-fluoroarene)chromium(0) **1** is added, the mixture stirred at r.t. in a plugged flask under exclusion of light for some hours to several days (cf. Table 1). The beginning of reaction is indicated by the precipitation of KF.

After completion (monitored by TLC), ethyl acetate (75 mL) is added, the organic layer is washed with brine (3×75 mL), dried over Na_2SO_4, and the solvent removed under reduced pressure to afford the crude products **3.** Compound **3a** is recrystallized from ethyl acetate, compounds **3c**, **3d**, and **3f** are recrystallized from diethyl ether. Compounds **3d** and **3e** have to be prepurified by flash-chromatography (eluent: toluene/ethyl acetate 20:1). Due to easy oxidation by air, the liquid complexes **3b**, **3e**, **3g** (diastereomeric mixtures) and **3h** are only characterized as crude product.

Decomplexation Step (**3** → **4**)

under vigorous stirring and cooling with ice-water, a solution of iodine (3.8 g, 0.015 mol) in diethyl ether (25 mL) is added to the ethyl acetate solution of **3** from the arylation step within 30 min and stirring continued for 2.5 h at *r.t.*.

The compounds **3d** and **3e**, purified by flash-chromatography, are dissolved in 75 mL of ethyl acetate and decomplexed with an equimolar amount of iodine as described above. Then the organic layer is washed successively with water (1×100 mL, 2×50 mL), aqueous sodium bisulfite (5%, 2×25 mL), and again with water (2×25 mL). The organic phase is then dried over

Table 1. Selected Physical and Spectroscopic Data of Tricarbonyl(η^6-arene)chromium(0) Complexes (**3a–h**)

Prod.	Reaction Time (d)	Molecular Formula [a] (Mol. wt.)	*m.p.* (°C) (solven	IR (KBr) cm^{-1}) $CO)_3$	^{1}H NMR δ [c]) (DMSO-d_6)	^{13}C NMR δ [d]) (DMSO-d_6)	MS *m/z* (%)
3a	0.75	$C_{16}H_{14}CrO_6$ (354.3)	130–132 (AcOEt)	1970, 1885 1875	5.56–5.62 (m, 2H), 5.77–5.83 (m,2H), 6.06–6.10 (m, 1H)	60.96, 92.65, 92.85, 95.87, 96.25, 106.20, 233.19	EI (70eV): 354 (1) $[M]^{+\cdot}$, 270 (100) $[M\text{-}3CO]^{+\cdot}$
3b	2	$C_{17}H_{16}CrO_6$ (368.3)	diast. mix. 55:45 [b]) yellow oil		5.60–5.85 (m, 3H), 5.98–6.04 (m, 1H); signals are broadened bad resolution	60.78/61.02, 92.83/93.12, 94.57/94.63, 95.27/95.46, 95.60/95.64, 108.47/108.53, 109.39/109.99, 233.59	CI (NH_3): 386 (100) $[M+NH_4]^+$, 369 (3) $[M+H]^+$
3c	5	$C_{17}H_{16}CrO_6$ (368.3)	124–126 (Et_2O)	1955, 1885, 1860	5.54–6.18 (m, 4H)	60.76, 92.91, 93.08, 96.87, 97.28, 103.31, 112.67, 233.96	CI (NH_3): 386 (100) $[M+NH_4]^+$, 369(3) $[M+H]^+$
3d	3	$C_{17}H_{16}CrO_6$ (368.3)	124 (dec.) (Et_2O)	1960, 1880 1860,	5.44–5.61 (m, 3H), 5.89–5.94 (m,2H)	64.12, 90.34, 90.47, 97.39, 97.82, 98.52, 107.55, 233.78	LSIMS (3-$NO_2C_6H_4CH_2OH$): 312 (57) $[M\text{-}2CO]^{+\cdot}$, 284 (100) $[M\text{-}3CO]^{+\cdot}$
3e	7	$C_{18}H_{18}CrO_6$ (382.3)	diast. mix. 50:50 [b]) yellow oil		5.39–5.43 (m, 1H), 5.57–5.60 (m, 1H), 5.74–5.88 (m, 2H)	64.22/64.35, 91.73/92.00, 94.66/95.49, 97.28, 97.51/97.92, 106.81/107.07, 109.25/109.28, 233.72/233.76	CI (NH_3): 400 (100) $[M+NH_4]^+$, 383 (6) $[M+H]^+$
3f	0.75	$C_{18}H_{18}CrO_6$ (382.3)	134 (dec.) (Et_2O)	1955, 1895, 1860	5.40–5.49 (m, 2H), 5.72–5.77 (m, 2H), 5.89–5.93 (m, 1H)	65.21, 90.49, 90.54, 96.92, 97.76, 98.05, 107.46, 233.21	CI(NH_3): 400 (100) $[M+NH_4]^+$, 383 (8) $[M+H]^+$
3g	1	$C_{19}H_{20}CrO_6$ (396.3)	diast. mix. 50:50 [b]) yellow oil		5.55–6.04 (m, 4H); signals are broadened bad resolution	65.40/65.46, 91.85/91.89, 94.43/95.41, 96.66/97.49, 97.59/97.89, 106.89/107.12, 109.37/109.59, 233.58	LSIMS (Magic Bullet): 397 (12) $[M+H]^+$, 340 (37) $[M\text{-}2CO]^{+\cdot}$, 312 (48) $[M\text{-}3CO]^{+\cdot}$
3h	1	$C_{19}H_{20}CrO_6$ (396.3)	yellow oil	1965, 1895 1855 (neat)	5.39–5.46 (m, 2H), 5.80–5.87 (m, 2H)	64.93, 91.43, 91.49, 97.47, 98.46, 105.23, 113.52, 234.00	CI (NH_3): 414 (100) $[M+NH_4]^+$, 397 (5) $[M+H]^+$

[a]) Satisfactory microanalyses (with exception of **3b**, **3e**, **3g**, **3h** which were characterized as crude products): C ± 0.15, H ± 0.07, Cr ± 0.13. [b]) Determined by HPLC. [c])Selected values: CH_{arom}. [d]) Selected values: C_{quart}, C_{arom}, $Cr(CO)_3$.

Table 2. Prepared Methyl 1-Aryl-2-oxo-cycloalkanecarboxylates (**4**)

Prod.	Yield [a] (%)	Molecular Formula [b] (Mol. wt)	*b.p.*/mbar (°C) [c] or *m.p.* (°C) (solvent)	^{1}H NMR (DMSO-d_6) δ [f]	^{13}C NMR (DMSO-d_6) δ [g]	MS *m/z* (%)
4a	73	$C_{13}H_{14}O_3$ (218.2)	110–130/0.2	7.24–7.31 (m, 5H)	64.69, 127.34 (2 C-atoms), 128.26, 136.28, 170.86, 211.59	EI (70eV): 218 (100) $[M]^{+\cdot}$
4b	66	$C_{14}H_{16}O_3$ (232.3)	120–135/0.1	7.09–7.12 (m, 3H), 7.21–7.26 (m, 1H)	64.71, 124.47, 127.87,128.08, 128.22, 136.23, 137.46, 170.96, 211.75	CI(NH_3): 250(100) $[M+NH_4]^+$, 233 (8) $[M+H]^+$
4c	64	$C_{14}H_{16}O_3$ (232.3)	130–145/0.17	7.15–7.23 (m, 4H)	64.40, 127.40, 129.05, 133.32, 136.84 171.26, 212.11	CI(NH_3): 250(100) $[M+NH_4]^+$, 233 (7) $[M+H]^+$
4d	59	$C_{14}H_{16}O_3$ (232.3)	120–140/0.2 72–79 (methanol)	7.09–7.11 (m, 2H), 7.23–7.30 (m, 3H)	66.12, 127.26, 127.62, 128.14 136.98, 171.30 205.74	EI(70eV): 232 (100) $[M]^{+\cdot}$
4e	47	$C_{15}H_{18}O_3$ (246.3)	130–150/0.1 [d]	6.93–6.97 (m, 2H) 7.07–7.12 (m, 1H), 7.22–7.26 (m, 1H)	66.21, 125.01, 128.18, 128.29, 128.37, 137.22, 137.53, 171.75, 206.31	CI(NH_3): 264(100) $[M+NH_4]^+$, 247 (42) $[M+H]^+$
4f	82	$C_{15}H_{18}O_3$ (246.3)	140–160/0.4 67–71 (methanol)	7.13–7.18 (m, 2H), 7.26–7.39 (m, 3H)	67.70,127.22, 127.38, 128.27, 138.89, 172.00, 208.09	CI(NH_3): 264(100) $[M+NH_4]^+$ 247 (67) $[M+H]^+$
4g	71	$C_{16}H_{20}O_3$ (260.3)	61–64 (methanol) [e]	6.93–6.97 (m, 2H), 7.09–7.11 (m, 1H), 7.21–7.26 (m, 1H)	67.70, 124.53, 127.85, 127.93, 128.17, 137.45, 138.96, 172.09, 208.24	EI(70eV): 260 (100) $[M]^{+\cdot}$
4h	73	$C_{16}H_{20}O_3$ (260.3)	160–180/0.1 65–70 (methanol)	7.04 (d, 2H; J = 8.20 Hz), 7.17 (d, 2H; J = 8.10 Hz)	67.45, 127.42, 129.03, 136.08, 136.64, 172.38, 208.50	CI(NH_3): 278(100) $[M+NH_4]^+$ 261 (41) $[M+H]^+$

[a] Overall Yields of pure, isolated products. [b] Satisfactory microanalyses: C ± 0.21, H ± 0.13. [c] *B.p.* were determined using an air-bath. [d] After flash-chromatography, toluene/ethyl acaetate 5:1. [e] After flash-chromatography, toluene/ethyl acaetate 10:1. [f] Selected values: CH_{arom}. [g] Selected values: C_{quart}, C_{arom}, CO_{ester}, CO_{ketone}.

Na_2SO_4 and concentrated to give the crude products **4**, which are purified by Kugelrohr distillation, by recrystallization or by flash-chromatography (cf. Table 2).

X-Ray Structure Determination of Tricarbonyl[η^6-(methyl 2-oxo-1-phenyl-cyclohexanecarboxylate)]chromium (0) 3d

The structure was investigated on an ENRAF-NONIUS CAD4 diffractometer at r.t. employing graphite-monochromatized MoKα radiation (λ = 0.71069 Å) and $\omega/2\theta$ scan. The data were corrected for Lorentz and polarization effects. The structure was solved with direct methods (SHELXS-86 [22]) and anisotropic refinement (SHELXL-93 [23]) of the non-hydrogen atoms [1].

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[1] Lists of structure factors, anisotropic parameters, atom coordinates and table of bond distances and angles may be obtained through the Fachinformationszentrum Kalsruhe GmbH, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-405902, the authors and the bibliographical data.