

# Preparation of Arene Chromium Tricarbonyl Complexes Using Continuous-Flow Processing: $(\eta^6\text{-C}_6\text{H}_5\text{CH}_3)\text{Cr}(\text{CO})_3$ as an Example

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A continuous-flow approach to the direct synthesis of arene chromium tricarbonyl complexes is presented. By working in flow mode, it is possible to avoid some of the problems of batch synthesis, especially sublimation of the  $\text{Cr}(\text{CO})_6$  starting material and the competitive decomposition of the product during the lengthy reaction times. Heating at 220 °C and operating with a residence time of 10 min through the heated zone allows for the synthesis of  $(\eta^6\text{-C}_6\text{H}_5\text{CH}_3)\text{Cr}(\text{CO})_3$  as an example, along with a selection of other (arene) $\text{Cr}(\text{CO})_3$  complexes.

**Keywords:** chromium, metal carbonyl, aromatic ring, organometallic

## 1. Introduction

Arene chromium tricarbonyl complexes,  $(\text{arene})\text{Cr}(\text{CO})_3$ , have found extensive use in organic synthesis [1, 2]. The coordination of an aromatic ring to the chromium tricarbonyl unit has a profound effect on its reactivity. Due to the electron withdrawing nature of the  $\text{Cr}(\text{CO})_3$  moiety, nucleophilic substitution reactions can be performed on the aromatic ring. The electron-deficient ring is able to stabilize negative charge, allowing both ring and benzylic deprotonation. In addition, the chromium unit effectively blocks one side of the ring and directs incoming reagents to the face opposite the metal. The preparation of chromium arene complexes generally involves heating chromium hexacarbonyl under reflux either in the arene as the solvent or in a high boiling solvent containing the arene (Scheme 1) [3, 4]. Reactions can take in the order of 1–4 days to reach completion and need to be performed under an inert atmosphere. The procedure is complicated by the sublimation of  $\text{Cr}(\text{CO})_6$  as well as the competitive decomposition of the arene chromium product over time. This can be somewhat overcome by heating a 1:1 mixture of arene and  $\text{Cr}(\text{CO})_6$  in a mixture of dibutyl ether and heptane in the presence of a little tetrahydrofuran [5].

Using butyl acetate as an additive, the reaction time can be decreased through the implementation of a special double-condenser apparatus [6]. These  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes have also been prepared in low to moderate yields by broadband UV photolysis of  $\text{Cr}(\text{CO})_6$  in the presence of the arene [7]. To overcome some of the issues associated with their direct synthesis,  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes have also been prepared via an indirect route. This involves either arene exchange with naphthalene chromium tricarbonyl [8] or reaction of the arene with a tricarbonyl chromium complex bearing three labile ligands, such as  $\text{Cr}(\text{CO})_3(\text{NH}_3)_3$  or  $\text{Cr}(\text{CO})_3(\text{MeCN})_3$  [9].

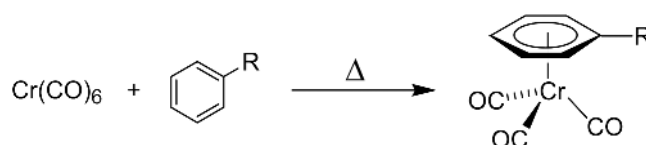
In an attempt to facilitate the direct preparation of  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes, microwave heating has been used. In an open-vessel approach,  $(\text{anisole})\text{Cr}(\text{CO})_3$  could be prepared in 45 % by refluxing a diglyme solution of  $\text{Cr}(\text{CO})_6$  and anisole for 4 h under a blanket of argon [10]. Attempts to prepare the corresponding mesitylene complex were not successful. In a sealed tube,  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes have been prepared by heating  $\text{Cr}(\text{CO})_6$  and the arene at 160 °C for 1 h using either tetrahydrofuran (THF) alone or THF and dibutyl ether as co-solvent [11]. However, this procedure presents significant safety concerns.

Due to the non-polar nature of  $\text{Cr}(\text{CO})_6$  and most arenes, it is difficult to heat the reaction mixture to 160 °C with microwave irradiation. The chromium hexacarbonyl starting material is prone to decomposition to elemental chromium and carbon monoxide gas. Also, the molybdenum analog,  $\text{Mo}(\text{CO})_6$ , has been used as a source of CO in a range of microwave-heated carbonylation reactions for just the same reason [12]. The elemental chromium is deposited on the walls of the glass reaction vessel where it superheats due to its high microwave absorptivity. This leads to melting of the glass vessel. Since the reaction mixture is under pressure because the temperature is above the boiling point of the solvent, the entire contents are ejected through the hole melted in the vessel. Indeed, in our hands, the synthesis of  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes using this sealed vessel approach has been met with vessel failure more times than it has been successful. In an attempt to overcome these problems while at the same time preparing  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes in a direct manner, we turned our attention to continuous-flow processing using conventional heating. We present our results here.

## 2. Results and Discussion

Micro- and meso-fluidic flow devices have proven to be powerful enabling technologies in preparative chemistry [13, 14]. It is possible to perform reactions effectively at high temperatures [15] and only a small quantity of material is directly in the reaction zone at any one time. These two characteristics seemed attractive to us for the preparation of  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes. We theorized that we would be able to pass a solution of  $\text{Cr}(\text{CO})_6$  and arene, in an appropriate solvent, through a heated coil for a short period where we could form the desired arene chromium complex. Our initial objective was to determine conditions under which we could achieve this. Using toluene as the arene substrate and THF as the solvent (1:1 v/v), we passed 10 mL of a 0.02 M solution of  $\text{Cr}(\text{CO})_6$  through a 10-mL stainless steel coil heated to 160 °C at a flow rate of 0.5 mL/min, corresponding to a residence time in the heated

**Scheme 1.** Conventional preparation of  $(\text{arene})\text{Cr}(\text{CO})_3$  complexes



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**Table 1.** Optimization of reaction conditions for the preparation of **1a** using flow processing<sup>a</sup>

Entry	Solvent (volume/mL)	Toluene volume/mL	Temperature/°C	Flow rate/mL.min <sup>-1</sup>	Conversion/%
1	THF (5)	5	160	0.5	Trace
2	THF (5)	5	220	0.5	Quantitative <sup>b</sup>
3	THF (9)	1	220	0.5	Quantitative <sup>b</sup>
4	THF (9.9)	0.1	220	0.5	25
5	MTBE (5)/THF (1)	2	220	0.5	Quantitative <sup>b</sup>
6	MTBE (5)/THF (1)	2	220	1.0	Quantitative, 71 <sup>c</sup>

<sup>a</sup> Reactions performed using 10 mL of a 0.02 M solution of Cr(CO)<sub>6</sub>.

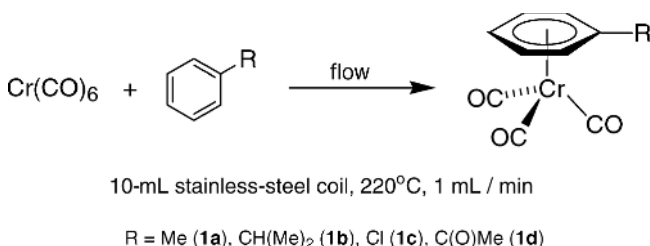
<sup>b</sup> Indicated by complete disappearance of signals in the IR spectrum attributable to Cr(CO)<sub>6</sub>.

<sup>c</sup> Isolated yield.

zone of 20 min. Only a trace of the product was obtained (Table 1, Entry 1). Increasing the temperature of the coil to 220 °C significantly improved the outcome. A 95 % conversion of Cr(CO)<sub>6</sub> to (η<sup>6</sup>-C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>)Cr(CO)<sub>3</sub> (**1a**) was obtained (Entry 2); conversion being measured by comparison of the signals for product with that of starting material in the ν<sub>CO</sub> region of the IR spectrum. The CO that is liberated during the course of the reaction is released as the product mixture exits the back-pressure regulator at the end of the heated coil.

Next, we wanted to probe the effect of varying the quantity of arene used. Performing the reaction using 1 mL of toluene and 9 mL of THF did not affect the outcome (Entry 3). However, decreasing the quantity of arene further did compromise the product conversion (Entry 4). This means that a significant excess of the arene is required. To develop a solvent system that would be suitable for a range of arenes, we trialed the use of methyl tert-butyl ether (MTBE) in conjunction with a small volume of THF, the latter being required as a labile ligand to facilitate product formation. Performing the reaction using a 5:1 ratio of MTBE to THF, we were able to obtain a quantitative conversion to **1a**. We finally revisited the residence time of the reaction mixture in the heated zone and were able to obtain **1a** quantitatively using a flow rate of 1 mL/min, corresponding to a reaction time of 5 min (Entry 6). After work-up and chromatography, we obtained a 71 % isolated yield of **1a**. We find that in the work-up process, we lose some material due to formation of insoluble oxidized chromium complexes. However, the isolated product obtained at the end of the work-up is very pure.

With reaction conditions in hand, we screened a representative selection of arenes as substrates, performing the reactions using 10 mL of a 0.02 M solution of Cr(CO)<sub>6</sub>. We were able to form the desired arene chromium tricarbonyl products in quantitative conversion when using cumene, chlorobenzene and acetophenone (Scheme 2). We also screened anisole and 4-bromoacetophenone but were not able to form arene complexes. In the case of the latter, this is not totally surprising; coordination of aryl bromides generally requires an indirect route [3]. We also wanted to scale-up the reaction to show we could use the flow approach to preparing larger quantities of material. Returning to toluene as the arene, we performed the reaction on the 1-gram scale of Cr(CO)<sub>6</sub> and, after product purification and isolation, obtained a 72 % isolated yield of **1a**.

**Scheme 2.** Synthesis of (arene)Cr(CO)<sub>3</sub> complexes using flow processing

### 3. Conclusion

We report a continuous-flow approach to the direct synthesis of arene chromium tricarbonyl complexes. By working in flow mode, it is possible to avoid some of the problems of batch synthesis, especially sublimation of the Cr(CO)<sub>6</sub> starting material and the competitive decomposition of the product over the lengthy reaction times required. We find that heating at 220 °C results in good yield of the desired (arene)Cr(CO)<sub>3</sub> complexes. This is interesting given that, while higher temperature has previously been shown to shorten reaction times, it increases the risk of decomposition that, once started, can be autocatalytic and compromise product yield [16]. We do not observe this when working in flow. In addition, since the lower boiling (and hence easier to remove) MTBE can be used as a solvent instead of higher boiling solvents such as dibutyl ether, isolation of the product can be facilitated.

### 4. Experimental Section

**4.1. General Experimental.** All reactions were performed under a nitrogen atmosphere unless otherwise noted. Chromium hexacarbonyl was purchased from Aldrich Corporation. A Vapourtec R-series flow reactor was used [17]. The system was equipped with a high-temperature 10-mL volume stainless-steel coil (1-mm internal diameter, 12-m length). The “reagent in” port of the reactor coil was connected to the pump with a 32-cm length of tubing. The “reagent out” port was then directly interfaced with a 500-psi back pressure regulator followed by a 6-cm length of tubing leading to a collection flask. <sup>1</sup>H-NMR spectra were recorded at 298 K on either a Bruker Avance Ultra Shield 300 MHz or Bruker DRX-400 400 MHz spectrometer, using CDCl<sub>3</sub> as the solvent. Signals were referenced to residual non-deuterated chloroform (7.26 ppm) in the deuterated solvent. IR spectra of solid samples were recorded using a Jasco FTIR410 spectrometer employing an attenuated total reflectance module.

**4.2. General Procedure for Synthesis of (Arene)Cr(CO)<sub>3</sub> Complexes: (η<sup>6</sup>-C<sub>6</sub>H<sub>5</sub>CH<sub>3</sub>)Cr(CO)<sub>3</sub>, **1a**.** Chromium hexacarbonyl (1.0 g, 4.5 mmol) was placed into a Schlenk tube, and methyl tert-butyl ether (50 mL) was added. With the gentle application of heat and agitation, the solution was warmed to facilitate the dissolution of the Cr(CO)<sub>6</sub>. After cooling to room temperature, tetrahydrofuran (10 mL) and toluene (20 mL) were added. The Schlenk tube was then sealed with a septum, the air was evacuated, and the tube was backfilled with nitrogen. The evacuate/nitrogen fill process was repeated a total of three times. The “reagent-in” line from the flow unit was then placed into the Schlenk tube, keeping the contents of the tube under an atmosphere of nitrogen. The “solvent-in” line from the flow unit was placed into a bottle containing hexane. The flow system was primed using the equipment manufacturer’s suggested start-up sequence. The stainless-steel coil was flushed with hexane for 5 min at a flow rate of 5 mL/min. The flow rate was then decreased to 1 mL/min, and the coil was heated to 220 °C. Once at the target temperature, the flow was then changed from solvent to reaction mixture by means of a switch on the flow unit. The

reaction mixture was then flowed through the heated coil, product collection commencing 5 min after this switch. Following the entire contents of the Schlenk tube had been loaded into the flow reactor, the flow was changed from reaction mixture back to solvent. Once all the products had exited the heated coil, the flow of hexane solvent was stopped. The contents of the collection vessel were decanted into a round bottom flask, and the organic solvents removed using rotary evaporation, leaving behind the crude yellow crystalline product. The crude product was re-dissolved in a minimal amount of THF (~5 mL), and loaded onto a pad of silica, pre-wetted with a 9:1 hexanes/EtOAc solvent mixture. The pad was rinsed thoroughly with 9:1 hexanes/EtOAc, and the solvent was once again stripped using rotary evaporation, leaving behind pure (toluene)tricarbonylchromium as yellow crystals (0.7092 g, 72 %). IR( $\nu_{\text{CO}}$ ): 1968(s), 1864(vs).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm 5.42 (m, 3 H), 5.16 (m, 2 H), 2.21 (s, 3 H) [18].

( $\eta^6\text{-C}_6\text{H}_5\text{CH}(\text{CH}_3)_2$ )Cr(CO) $_3$ , **1b**: IR( $\nu_{\text{CO}}$ ): 1966(s); 1882(s) [19].

( $\eta^6\text{-C}_6\text{H}_5\text{Cl}$ )Cr(CO) $_3$ , **1c**: IR( $\nu_{\text{CO}}$ ): 1982(s); 1897(s) [4].

( $\eta^6\text{-C}_6\text{H}_5\text{C}(\text{O})\text{CH}_3$ )Cr(CO) $_3$ , **1d**: IR( $\nu_{\text{CO}}$ ): 1962(s); 1884(s) [20].

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## References

1. For a recent review, see: Rosillo, M.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2007**, *36*, 1589–1604.

2. For an excellent collection of examples, see: *Transition Metal Arene  $\pi$ -Complexes in Organic Synthesis and Catalysis (Topics in Organometallic Chemistry 7)*, Kündig, E. P., Ed.; Springer: Berlin, 2004.

3. For a review, see: Kündig, E. P. *Top. Organomet. Chem.* **2004**, *7*, 3–20.

4. For a general procedure, see: Mahaffy, C. A. L.; Pauson, P. L. *Inorg. Synth.* **1990**, *28*, 136–140.

5. Horstermann, D.; Schmalz, H.-G.; Kociok-Kohn, G. *Tetrahedron* **1999**, *55*, 6905–6916.

6. Hudecek, M.; Toma, S. J. *Organomet. Chem.* **1991**, *406*, 147–151.

7. Kostermans, G. B. M.; Bobeldijk, M.; Kwakman, P. J.; De Wolf, W. H.; Bickelhaupt, F. J. *Organomet. Chem.* **1989**, *363*, 291–296.

8. See for example: Kündig, E. P.; Perret, C.; Spichiger, S.; Bernardinelli, G. *J. Organomet. Chem.* **1985**, *286*, 183–200.

9. See for example: (a) Goti, A.; Semmelhack, M. F. *J. Organomet. Chem.* **1994**, *470*, C4–C7; (b) Öfele, K.; Dotzauer, E. *J. Organomet. Chem.* **1971**, *30*, 211–220; (c) Tweddell, J.; Hoic, D. A.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 8286–8287.

10. Ardon, M.; Hogarth, G.; Oscrift, D. T. W. *J. Organomet. Chem.* **2004**, *689*, 2429–2435.

11. Lee, Y. T.; Choi, S. Y.; Lee, S. I.; Chung, Y. K.; Kang, T. J. *Tetrahedron Lett* **2006**, *47*, 6569–6572.

12. See for example: Kaiser, N. F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109–111; (b) Wannberg, J.; Larhed, M. *J. Org. Chem.*, **2003**, *68*, 5750–5753; (c) Georgsson, J.; Hallberg, A.; Larhed, M. *J. Comb. Chem.*, **2003**, *5*, 350–352; (d) Herrero, M. A.; Wannberg, J.; Larhed, M. *Synlett* **2004**, 2335–2338.

13. For books on the subject, see: (a) Wiles, C.; Watts, P. *Micro Reaction Technology in Organic Synthesis*; CRC Press: Boca Raton, **2011**; (b) Luis, S. V.; Garcia-Verdugo, E., Eds. *Chemical Reactions and Processes under Flow Conditions*; Royal Society of Chemistry: Cambridge, **2010**.

14. For recent reviews, see: (a) Wiles, C.; Watts, P. *Chem. Comm.* **2011**, *47*, 6512–6535; (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Comm.* **2011**, *47*, 4583–4592; (c) Razzaq, T.; Kappe, C. O. *Chem. Asian J.* **2010**, *5*, 1274–1289; (d) Mark, D.; Haerberle, S.; Roth, G.; von Stetten, F.; Zengerle, R. *Chem. Soc. Rev.* **2010**, *39*, 1153–1182.

15. See for example: Cantillo, D.; Sheibani, H.; Kappe C. O. *J. Org. Chem.* **2012**, *77*, 2463–2473.

16. Deubzer, B.; Fischer, E. O.; Fritz, H. P.; Kreiter, C. G.; Kriebitzsch, N.; Simmons, H. D.; Willeford, B. R. *Chem. Ber.* **1967**, *100*, 3084–3096.

17. <http://www.vapourtec.co.uk>

18. Djukic, J.-P.; Rose-Munch, F.; Rose, E.; Simon, F.; Dromzee, Y. *Organometallics* **1995**, *14*, 2027–2038.

19. Jackson, W. R.; Jennings, W. B.; Rennison, S. C.; Spratt, R. J. *Chem. Soc. B* **1969**, 1214–1221.

20. Clark, G. R.; Metzler, M. R.; Whitaker, G.; Woodgate, P. D. *J. Organomet. Chem.* **1996**, *513*, 109–134.