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SYNTHESIS OF ^{11}C-LABELED AROMATICS USING ARYL CHROMIUM TRICARBONYL INTERMEDIATES

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Abstract

Stable and ^{11}C-arylnitriles have been synthesized in 10 minutes by treatment of substituted fluoroaryl (R = H, *p*-Me, *o*-Me, *p*-Cl) chromium tricarbonyl complexes with stable and ^{11}C-cyanide in DMSO at 115°-135°. Under the conditions used, decomplexation of the new complex occurs during the substitution reaction liberating the aryl nitrile product without need for the usual oxidative decomplexation step.

Key Words: ^{11}C-aromatics, aryl chromium tricarbonyl complex, aryl nitriles

Introduction

The synthesis of radiopharmaceuticals labeled with short-lived positron emitting isotopes, such as ^{11}C ($t_{1/2}$ = 20 min), requires special organic synthetic techniques. Recently, we and others have explored the use of organometallic derivatives, such as the group XIV organometallics [1], and have now extended this to include the transition metals.

It has recently been shown [2,3,4] that arenechromium tricarbonyl complexes readily undergo nucleophilic displacement reactions on the aromatic ring. This enhanced reactivity to nucleophiles can be attributed to the removal of electron density from the aromatic ring through coordination to chromium [3]. The incorporation of the chromium tricarbonyl moiety into aromatic systems can, in

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most cases, be done more easily and under milder conditions than the synthesis of aromatic *p*-nitro derivatives: the *p*-nitro group having approximately the same magnitude of electron withdrawal as the chromium tricarbonyl moiety. We decided to explore this chemistry further with the aim of labeling aromatics with ^{11}C using ^{11}C-cyanide.

Experimental

General

Chromium Hexacarbonyl was purchased from Pressure Chemical Co. Fluorobenzene, *p*- and *m*-fluorotoluene and 4-chlorofluorobenzene were purchased from Aldrich and were used without further purification. THF was distilled from sodium benzophenone ketyl under nitrogen. Diethyl ether was distilled from calcium hydride or sodium benzophenone ketyl. Dibutyl ether was distilled from sodium under nitrogen while DMSO and hexane were distilled from CaH_2.

All manipulations for the preparation and purification of the aryl chromium tricarbonyl complexes were performed so as to maintain all chemicals under an atmosphere of nitrogen using conventional bench-top techniques for the manipulation of air-sensitive compounds [5].

HPLC analysis was carried out on a Spectrophysics system using a water/acetonitrile (60:40) eluant for the toluene- and chlorobenzene-fluoro derivatives and a water/methanol (1:1) eluant for the fluorobenzene case, with a Waters RCM C-18 column using UV detection at 270 nm. Melting points are uncorrected and were performed in air using a Buchi 510 capillary oil bath melting point apparatus. Mass spectra were recorded with either a Kratos/AEI MS902 or a Kratos/AEI MS50 mass spectrometer. GC-MS was performed using a Delsi Nermag R10-10C quadrupole mass spectrometer interfaced with a Varian Vista 6000 GC or a Kratos MS80 coupled to a Carlo Erba 4160 GC.

$H^{11}CN$ was produced via the catalytic conversion of $^{11}CO_2$. The $^{11}CO_2$ was produced on the TRIUMF CP-42 cyclotron using the $^{14}N(p,\alpha)^{11}C$ reaction at 15 MeV. The $H^{11}CN$ was trapped in a solution of NaOH (0.1 N, 1 ml) to produce $Na^{11}CN$.

Substitution Reactions with Stable Cyanide

The aryl chromium tricarbonyl complex (65 μmol) was dissolved in DMSO (1 mL), then added to a

Reacti-vial containing KCN (32 μmol) under inert atmosphere. The stirred mixture was heated for 10 minutes. After cooling to room temperature, the reaction mixture was diluted with DMSO to a known volume and was analyzed by HPLC to determine the amount of nitrile product formed. Yields are shown in Tables 1 and 3. For the purpose of identification of the organic products by GC-MS, the workup after cooling the reaction mixture was performed as follows. The reaction mixture was diluted with water (3 mL) and extracted with ether (1 × 6 mL, 1 × 3 mL). The combined ether extracts were washed with saturated NaCl (2 × 3 mL). The stirred ether solution was treated with iodine (146 μmol) at 0° for 2 hours to ensure complete decomplexation of both the starting complex as well as the product complex. The treatment was quenched with the addition of aqueous sodium thiosulfate (5 mL, 2.5%) and the ether layer was washed further with sodium thiosulfate (4 mL, 2.5%), then with saturated NaCl (2 × 4 mL) and was dried over $MgSO_4$. The ether solution was analyzed by GC-MS.

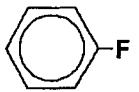
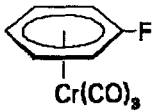
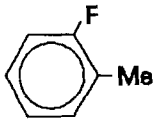
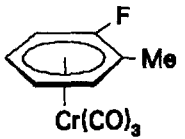
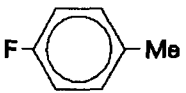
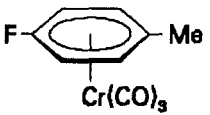
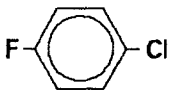
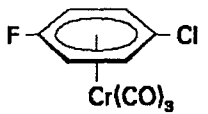
Substitution Reactions with ^{11}CN

After H^{11}CN was bubbled into NaOH (0.1N, 1ml) the solution was evaporated to dryness in a Reacti-vial containing potassium cyanide (32 μmol). A solution of the aryl chromium tricarbonyl complex (65 μmol) in DMSO (1 mL) was added to the dried cyanide and the mixture was heated for 10 minutes. Upon cooling to room temperature, either a portion or the entire reaction mixture was subjected to radio-HPLC purification and the corresponding ^{11}C-nitriles were collected and counted to determine the radiochemical yield. The results are summarized in Table 1.

Table 1: Chemical and Radiochemical Yields

		Yields:		
		Chemical		Radiochemical
COMPLEX	PRODUCT	115°	135°	135°
		33	44	35
		41	33	34
		40	32	31
		35	21	19

Table 2: Preparation of Arene Chromium Tricarbonyl Complexes

ARENE	COMPLEX	REACTION TIME (hr)	YIELD %	m.p. (°C)	lit. m.p. (°C)	[ref]
 (53 mmol)		48	80	117	116–117	[6]
 (53 mmol)		48	89	71–72	73–74	[7]
 (90 mmol)		16.5	89	59–60	61–62	[7]
 (97 mmol)		23	9	62	none found	

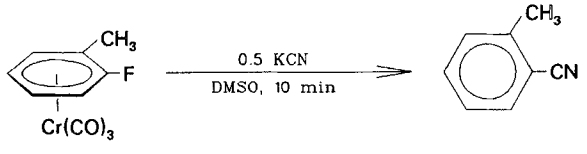
Preparation of Aryl Chromium Tricarbonyl Complexes

Chromium hexacarbonyl and the arene were dissolved in a mixture of Bu_2O/THF (80 mL/10 mL) (Table 2 for experimental details). The mixture was frozen and freeze-pump-thawed for 3 cycles to remove dissolved gasses. The reaction vessel was refilled with nitrogen and heated to reflux for the prescribed time (Table 2). The reaction mixture was cooled and evaporated to dryness *in-vacuo*. The residue was dissolved in diethyl ether and filtered, by canula filtration, into a Schlenk tube. A small amount of hexane was added and the mixture was cooled in the freezer to induce crystallization. After the initial crop of crystals was isolated, two additional crops of crystals were obtained from the mother liquor. Yields are shown in Table 2.

Results and Discussion

The chemical and radiochemical yields for the ^{11}C and stable cyanide substitution reactions are given in Table 1. Under the conditions used, decomplexation also occurs so that the usual oxidative decomplexation step is not necessary. Table 3 shows that the optimum temperature for the cyanide substitution of the *o*-fluorotoluene complex was 105-115°. Reaction times longer that 10 minutes did not improve the yields. Good yields can also be obtained at lower temperatures but much longer

Table 3: Temperature Dependence of Reaction



TEMPERATURE	% YIELD
135	33
125	28
115	41
105	42
95	25

reaction times are required (several hours) and a separate decomplexation step may be necessary. It is interesting to note from Table 1 that at 135° the lowest yield was obtained from the chloro-substituted system which one would have predicted to be the most activated system toward nucleophilic substitution. However, as can be seen in Tables 1 and 3 the yields are very sensitive to the reaction temperature and when this reaction was run at 115° the yield for the chloro-derivative was not significantly lower than the others. We believe that this observation may be due to the thermal stability of the complexes. For example, the fluorobenzene complex gave a higher yield for the substitution reaction at the higher temperature, while the chlorofluorobenzene complex gives a higher yield at the lower temperature. It was clear from working with these complexes that the chloro-derivative was much less stable in solution than was the fluorobenzene complex. As a result decomposition may have preceeded or taken place concurrently with the substitution reaction. In control experiments using the uncomplexed arenes, no product was obtained in all cases under the same labeling conditions.

In the experiments using the stable cyanide, a separate set of reactions were performed so that the organic products could be identified by GC-MS. These reaction mixtures were worked up by liquid-liquid extraction and were decomplexed with iodine. Although the aryl nitrile products were already decomplexed by the reaction conditions, iodine was used to ensure that all of the starting complex and any other complexes were fully decomplexed. It was important to do the decomplexation-extraction procedure since one cannot perform GC-MS on a mixture containing chromium metal. Standard mixtures of the uncomplexed starting arene and product aryl nitrile were also made up in ether and analyzed for direct comparison to the reaction products obtained from the decomplexation-extraction procedure. In all cases these extracted product mixtures were found to be identical to the standard mixtures and that the only components in the ether extractions of the products were the starting arenes and aryl nitrile products.

As a general rule of thumb the more electron rich arene systems form chromium complexes in higher yields than relatively electron deficient ones. Our own yields (Table 2) for the preparation of these complexes seems to be in agreement with this rule since the yield for the chloro-substituted arene complex was much lower that the others.

Given the speed of the displacement reaction, the feasibility of synthesizing a wide variety of chromium tricarbonyl complexes [3], and the ability to convert aromatic nitriles into carbonyl con-

taining compounds, this route should be applicable to the incorporation of ^{11}C into a variety of aromatic radiopharmaceuticals.

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