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Competitive Nucleophilic Aromatic Substitution and Palladium-Catalyzed Alkoxycarbonylation of (substituted chloroarene)Cr(CO)3 Complexes

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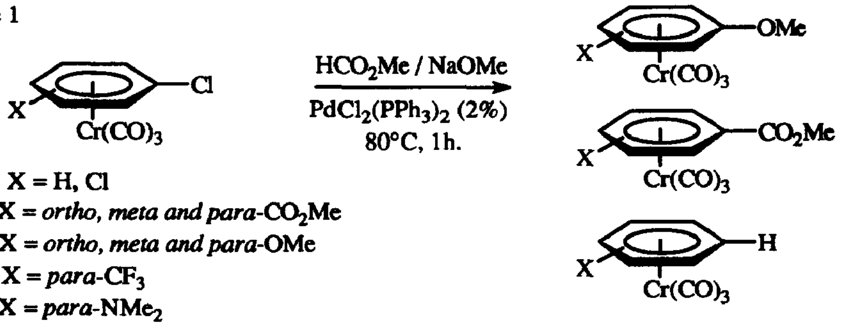
Abstract : *The reaction of $Cr(CO)_3$-complexed chloroarenes with HCO_2CH_3 and $NaOCH_3$ in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ gives esters in good yields provided that the arene is substituted by an electron-donating group, whereas the presence of an electron-withdrawing substituent on the aromatic ring leads to ethers via an ipso nucleophilic aromatic substitution.*

The activation of the C-Cl bond of chloroarenes by coordination of a tricarbonylchromium moiety to the aromatic ring has been extensively studied. In this field, much attention has been devoted to nucleophilic aromatic substitutions, particularly with anionic nucleophiles such as alcoholates, thiolates and amides[1]. Moreover, in recent years, there has been a great interest in carrying out palladium-catalyzed processes on $Cr(CO)_3$-activated aryl chlorides since these substrates easily undergo oxidative addition of the C-Cl bond to zerovalent palladium complexes[2]. In particular, we have shown[3] that tricarbonyl(mono- and dichloroarene)-chromium complexes (**1**) react with alkyl formates and alcoholates in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ to give esters (**3**) (Scheme 1). Unfortunately, in the case of the dichlorobenzene complexes, alkoxycarbonylation competes with nucleophilic aromatic substitution, source of ethers (**2**), and in a minor way with reduction of the C-Cl bond[4] which gives arenes (**4**). Actually, with *ortho* and *para*-dichlorobenzene complexes, the monocarbonylation-monosubstitution product, i.e. methyl methoxybenzoate, was obtained predominantly (66 and 61%, respectively), while the *meta* isomer gave similar proportions of this product (32%) and of 1,3-dimethoxybenzene (35%), i.e. the disubstitution product.

In view to explain these changes in chemoselectivity, we have investigated the reactivity of the different intermediates resulting from either carbonylation (**1C**), or S_NAr substitution (**1S**) of one C-Cl bond of each isomer of dichlorobenzene complexes. The behaviour of chloroarene chromium complexes substituted in the *para* position by a trifluoromethyl (**1F**) or a dimethylamino (**1N**) group was also studied.

Scheme 1



2

3

4

1 X = H, Cl
1C X = *ortho, meta and para*-CO_2Me
1S X = *ortho, meta and para*-OMe
1F X = *para*-CF_3
1N X = *para*-NMe_2

The results obtained from the *ortho, meta* and *para* isomers of $Cr(CO)_3$-complexed methyl chlorobenzoate (**1C**) and chloroanisole (**1S**) are summarized in Table 1[5]. The results were strikingly dependent on the nature of the substituent on the arene ring. Chlorobenzoate complexes (**1C**) gave essentially ether derivatives (**2**) (entries 1-4), whereas under similar reaction conditions chloroanisole complexes (**1S**) underwent palladium-catalyzed methoxycarbonylation and gave in very good yields esters **3** (entries 6-9). In each case, small amounts of reduced products (**4**) were also obtained.

Table 1. Reactivity of (Substituted Chloroarene)$Cr(CO)_3$ Complexes[a]

Entry	**1** X =	Conv.[b] (%)	Dec.[c] (%)	**2** (%)[d]	**3** (%)[d]	**4** (%)[d]
1	2-CO_2Me	100	15	95	traces	5
2	3-CO_2Me	95	33	60	35	5
3	4-CO_2Me	98	20	80	12	8
4[e]	4-CO_2Me	100	nd	98	1	1
5	4-CF_3	96	16	96	traces	4
6	2-OMe	98	26	traces	92	8
7	3-OMe	98	20	20	80	traces
8[f]	3-OMe	95	23	71	25	4
9	4-OMe	98	60	2	95	3
10[g]	4-NMe_2	95	20	traces	63	traces

a) $ArCl[Cr(CO)_3]$ 0.71 mmol, $NaOCH_3$ 1.0 mmol, HCO_2CH_3 46 mmol, $PdCl_2(PPh_3)_2$ 14 µmol, $P(N_2) = 15$ atm, T = 80°C, t = 1h. b) Conversion based on 1. c) Decomposition products (uncomplexed arenes). d) ^1H NMR and GLC selectivities including $Cr(CO)_3$-complexed and uncomplexed arenes. e) $ArCl[Cr(CO)_3]$ 0.39 mmol. f) $NaOCH_3$ 2.0 mmol, $PdCl_2(PPh_3)_2$ 7 µmol. g) See note 6.

It has to be noticed that the better selectivities, either into the S_NAr or into the carbonylation product, were obtained from the *ortho* and *para* complexes. The latter yielded more carbonylation product than their *ortho* analogues. This is probably due to a steric effect of the *ortho* substituent which limits the oxidative addition of the C-Cl bond to the bulky $Pd(CO)_n(PPh_3)_m$ zerovalent complex. Anyway, the *ortho* and *para* complexes yielded almost one product, whereas the two *meta* compounds (*m*-**1C** and *m*-**1S**) gave significant amounts of the corresponding side product (35% and 20%, respectively).

The conjunction of this observation with the fact that the methoxycarbonyl moiety is electron-withdrawing in contrast with the methoxy group which is electron-donating, has led us to think that the reactivity of (substituted chlorobenzene)chromium complexes may be controlled by the electronic effects induced by the substituent. In order to check this hypothesis, we have carried out some experiments with chloroarene complexes substituted by other groups. The introduction of the very electron-withdrawing trifluoromethyl group in the *para* position (complex **1F**) resulted in the selective formation of the corresponding ether, with only traces of the ester (entry 5). On the contrary, when the reaction was carried out with a strong electron-donating substituent on the aromatic ring, i.e. from *para*-dimethylamino-chlorobenzene (**1N**), there was no S_NAr substitution at all and the ester was obtained as the main product[6] (entry 10). By introducing the Hammet σ value[7] that sum up the total electronic effects (resonance plus field) of the substituent, a correlation can be obtained with the S_NAr / carbonylation products ratio, i.e. **2** / **3** (Table 2).

Table 2. Hammet Correlation of the Reactivity of (Substituted Chloroarene)$Cr(CO)_3$ Complexes

Group	4-NMe_2	4-OMe	4-Me[3]	4-H[3]	3-OMe	3-CO_2Me	4-CO_2Me	4-CF_3
σ	- 0.63	- 0.28	- 0.14	0	0.10	0.35	0.44	0.53
2 / 3	< 0.01	0.02	0.10	0.32	0.25	1.7	6.7	> 200

As seen from Table 2, electron-withdrawing substituents activate the substrate towards nucleophilic aromatic substitution, whereas electron-donating groups clearly favour alkoxycarbonylation. The beneficial effect of increasing electron density of the aromatic ring during palladium-catalyzed carbonylation reactions of free chloroarenes has recently been reported[8], and is in full agreement with our observed selectivities in alkoxycarbonylation. Although it is known that oxidative addition of aromatic halides to zerovalent palladium complexes is greatly favoured by reducing the electron density on the aromatic ring[9], especially by indroducing the $Cr(CO)_3$ group[10], these results show that the comparison which is classically made between this elementary step and a nucleophilic substitution is not completely satisfactory[11]. It is also highly probable that the substituents on the aromatic ring modify the rate of the CO insertion[12], and consequently the substitution / methoxycarbonylation ratio.

The **2** / **3** ratio was also greatly affected by changing the initial proportions of the reactants (entries 4 and 8). This effect was more pronounced for the *meta*-chloroanisole complex for which a total inversion of the selectivity was observed (entries 7 and 8). Even though these last experiments prompt us the necessity of comparing carefully the results obtained from monochloroarene complexes (present paper) and those obtained from the isomers of $Cr(CO)_3$-complexed dichlorobenzene[3] (*vide supra*), it is however quite probable that the first step in this latter case is mainly the nucleophilic aromatic substitution. Two lines of argument support this hypothesis: first, diesters were not detected at all from any of the dichlorobenzene complexes while *meta* and *para*-chlorobenzoate complexes (**1C**) yielded significant amounts of the corresponding alkoxycarbonylation products (35% and 12%, respectively); furthermore, the σ values for the chloro group ($\sigma_p = 0.24$; $\sigma_m = 0.37$)[7] indicate a global reduction of the electron density on the aromatic ring that favours the S_NAr substitution.

In conclusion, we have shown that under competitive reaction conditions, the substitution / methoxycarbonylation ratio depends upon the electronic effects induced both by the $Cr(CO)_3$ moiety and the substituents of the complexed arenes.

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6. The formation of a yet unidentified product, probably a polymer resulting of a homo-coupling reaction of the tricarbonyl(chloroarene)chromium complex with its NMe_2 moiety, accounts for the balance. This reaction is currently under investigation.

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12. Some compilation of results seems to indicate that the CO insertion into the Pd-C bond is favoured by electron-donating substituents, whereas the presence of electron-withdrawing groups would disfavour this elementary step; see references 9a and 11, p 370. Furthermore, whereas $Cr(CO)_3$ is known to be an electron-withdrawing moiety, it has been demonstrated that it does not greatly affect the CO insertion; see reference 10. We thank the reviewer for helpful discussion to this purpose.

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