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Benzylic Organozinc Derivatives of (η^6-Alkylarene)tricarbonylchromium Complexes: Cross-coupling Reactions with Organic Halides

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Treatment of benzylic zinc derivatives of (η^6-alkylarene)tricarbonylchromium complexes with organic halides leads to the corresponding cross-coupling products giving a new method for the introduction of acyl, aryl, heterocyclic and vinyl substituents at the benzylic position of alkyl arenes.

Benzylic functionalization of alkyl arenes is a major problem in organic synthesis because the direct introduction of any substituent at the benzylic position is often impossible. One approach to solving this problem is π-complexation of the arene with an electron-accepting group containing a transition metal atom. This produces a large increase in the CH-acidity of the hydrogen atoms at the benzylic position of the aromatic ligand and allows selective activation of the benzylic CH-bonds *via* α-metallation of the above complex. Reactions of the organometallic intermediate thus obtained subsequently lead to π-arene complexes functionalized at the benzylic position, from which the free ligands can easily be liberated by decomplexation. (η^6-Alkylarene)tricarbonylchromium complexes are very suitable for this procedure.[1,2]

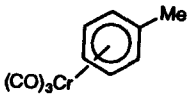
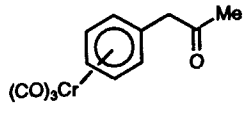
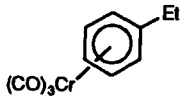
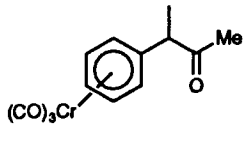
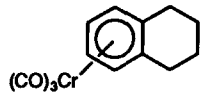
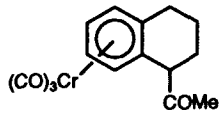
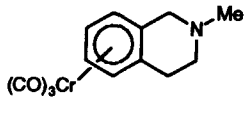
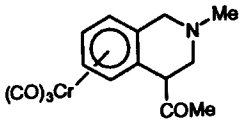
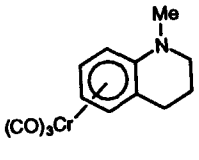
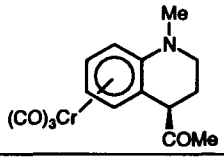
We have previously described methods for the selective metallation of (η^6-Alkylarene)tricarbonylchromium complexes at the benzylic position with sodium amide in liquid ammonia[3] and lithium amides in tetrahydrofuran (THF),[4] together with the use of the sodium and lithium intermediates thus obtained in the preparative introduction of carboxymethyl[3] or carboxylic[5] functions, respectively, at the benzylic position of alkyl arenes.

We describe here the application of benzylic zinc derivatives of (η^6-alkylarene)tricarbonylchromium complexes in cross-coupling reactions with organic halides aimed at benzylic functionalization of alkyl arenes.

Benzylic zinc derivatives of (η^6-alkylarene) tricarbonylchromium complexes obtained from the corresponding lithium derivatives on treatment with zinc chloride[6] are, in contrast to the corresponding lithium complexes, much more thermally stable and alive on refluxing in THF for 1 h. They react readily with acetyl chloride giving the corresponding ketone complexes (Scheme 1). The presence of 0.1 equiv. of $Pd(PPh_3)_4$ as catalyst increases the yields of the products 1.5–2 times. The results are given in Table 1.†

† *Typical experimental procedure.* An (η^6-alkylarene)tricarbonylchromium complex (1.0 mmol) was added to a solution of Et_2NLi (1.5 mmol) in 20 ml THF (prepared from 1.5 mmol of Et_2NH and 1.5 mmol of Bu^nLi). The mixture was stirred at 20 °C for 3–10 min and cooled to −30 °C, at which point a further 1.0 mmol Bu^n Li was added. Stirring was continued for 5 min then $ZnCl_2$ (2.5 mmol) was added. The reaction mixture was warmed to 0 °C and stirred for 20 min, then acetyl chloride (3.0 mmol) and $Pd(PPh_3)_4$ (0.1 mmol) were added and the mixture was stirred again for 2 h at 0 °C. After being quenched with saturated aq. NH_4Cl (1 ml) the mixture was diluted with $CHCl_3$ (30 ml) and filtered through alumina oxide (3 cm). The solvent was evaporated and the residue purified by column chromatography on silica gel (eluent hexane–diethyl ether, 3:1).

Table 1 Cross-coupling reactions of benzylic zinc derivatives of (η^6-alkylarene)tricarbonylchromium complexes with acetyl chloride.

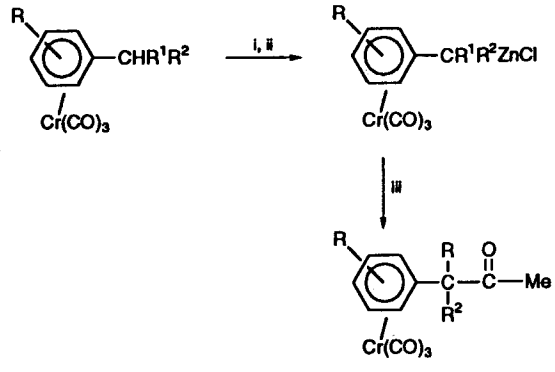
Starting complex	Product[a]	Yield (%)	M.p./°C
		59	56–57
		56	oil
		71	78–79
		75[b]	—
		34	114-115

[a] All products were obtained as chromatographically-pure yellow crystals with satisfactory elemental analyses. Evidence for their formation was provided by ^{1}H NMR spectroscopic data. [b] A mixture of two isomers.

Mendeleev Commun., 1994, 4(2), 53–55

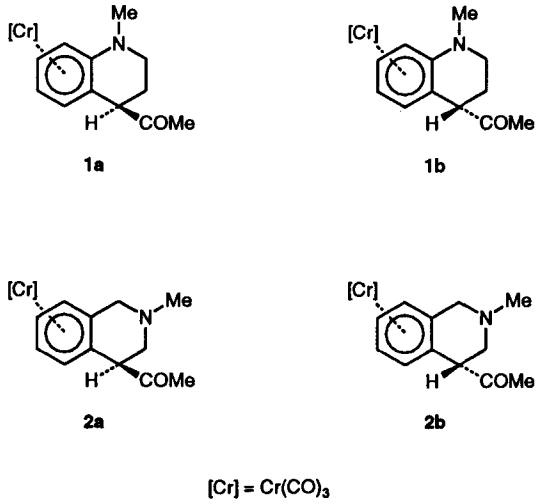
Table 2 Chemical shifts of 4-benzylic and acetyl protons in the ^{1}H NMR spectra of **1a**, **1b**, **2a** and **2b** in $CDCl_3$ and C_6D_6.

Complex	4-Benzylic protons			Acetylic protons		
	δ (ppm)		Δδ (ppm)	δ (ppm)		Δδ (ppm)
	$CDCl_3$	C_6D_6		$CDCl_3$	C_6D_6	
1a	3.56	2.99	0.57	2.26	1.64	0.62
1b	3.54	2.82	0.72	2.46	2.10	0.36
2a	6.65	6.45	0.20	2.14	1.70	0.44
2b	6.50	6.05	0.45	2.14	1.84	0.30



Scheme 1 *Reagents and conditions:* i, n-BuLi, THF, 20 °C, 3–10 min; ii, $ZnCl_2$, 20 °C, 10 min; iii, AcCl, 0.1 equiv. $Pd(PPh_3)_4$, 0 °C, 2 h.

It should be noted that two products were obtained from η^6-(*N*-methyl-1,2,3,4-tetrahydroquinoline)tricarbonylchromium complex on employing the above conditions. These products have been confirmed by ^{1}H NMR spectroscopic data to be the *exo*- and *endo*-isomers of η^6-(4-acetyl-*N*-methyl-1,2,3,4-tetrahydroquinoline)tricarbonylchromium complex (**1a** and **1b**, respectively). The ratio between them has been shown by HLPC to be 60:1. The main product was isolated in a pure form by recrystallization from hexane–diethyl ether (3:1) and identified as the *exo*-isomer (**1a**) by a method based on measurement of the chemical shifts of 4-benzylic and acetyl protons induced in ^{1}H NMR spectra by an aromatic solvent on passing from $CDCl_3$ to C_6D_6 solution (ASIS effect).



^{1}H NMR spectra of **1a** and **1b** in $CDCl_3$ and C_6D_6 were recorded so as to determine their configuration. The chemical shifts of the 4-benzylic and acetyl protons of these compounds are given in Table 2 for each solvent along with the difference (Δδ) between the shifts of the same protons in the two solvents.

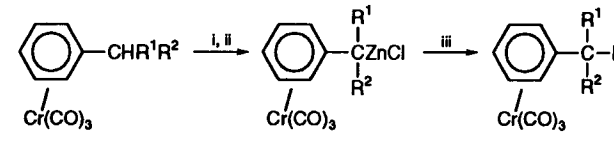
A decrease in the chemical shift of the 4-benzylic proton in **1a** on passing from $CDCl_3$ to C_6D_6 solution is less than that for **1b**.

The corresponding changes in the chemical shifts for the acyl protons show the opposite tendency. This proves that the 4-benzylic proton occupies a more sterically hindered *endo*-position in **1a** and that the acetyl group has an *exo*-orientation (see ref. 7).

Acylation of η^6-(*N*-methyl-1,2,3,4-tetrahydroisoquinoline)-tricarbonylchromium complex with acetyl chloride also leads to two isomeric acetyl derivatives (**2a** and **2b**) in the ratio 12:1. The structure of these complexes was elucidated by ^{1}H NMR spectroscopy as described above (see Table 2), but all our attempts to separate the isomers failed. The structures of other acylated chromium complexes containing bicyclic ligands have not been studied in detail.

We explain the formation of two acylated products in the cases described above in terms of a two-stage process involving the formation of the corresponding *exo*-isomers in the first place followed by rearrangement into the *endo*-products *via* the enol form. A possible coordination of the ketone functions with the chromium atoms in the *endo*-isomers would facilitate this process.

We have found that benzylic zinc derivatives of (η^6-alkylarene)tricarbonylchromium complexes undergo reactions with aryl, heterocyclic and vinyl halides giving the corresponding cross-coupling products (Scheme 2, Table 3).‡



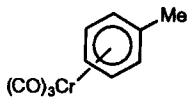
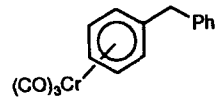
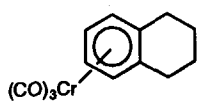
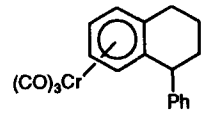
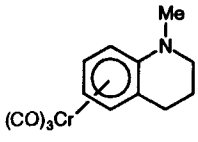
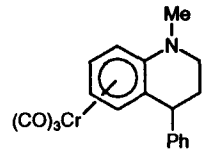
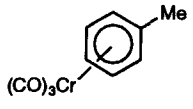
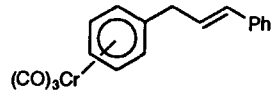
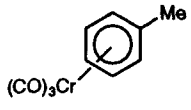
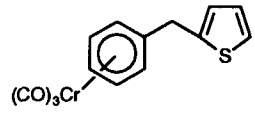
Scheme 2 *Reagents and conditions:* i, n-BuLi, THF, 20 °C, 3–10 min; ii, $ZnCl_2$, 20 °C, 10 min; iii, RHal, 10% $Pd(PPh_3)_4$, heat, 1 h.

Thus, the use of zinc derivatives of (η^6-alkylarene)-tricarbonylchromium complexes in cross-coupling reactions allows the substitution of alkyl arenes at the benzylic position by acyl, aryl, heterocyclic and vinyl groups.

This work was carried out with the support of the Russian Foundation of Fundamental Research (project number 93–03–4403).

‡ *Typical experimental procedure.* An (η^6-alkylarene) tricarbonylchromium complex (1.0 mmol) was added to a solution of Et_2NLi (1.5 mmol) in 20 ml THF (prepared from 1.5 mmol of Et_2NH and 1.5 mmol of Bu^nLi) and the mixture was stirred at 20 °C for 3–10 min. The solution was cooled to −30 °C and a further 1.0 mmol Bu^n Li was added. The mixture was stirred for 5 min then $ZnCl_2$ (2.5 mmol) was added. The mixture was allowed to warm to 20 °C and added dropwise to a boiling solution of RHal (10 mmol) and $Pd(PPh_3)_4$ (0.1 mmol) in 10 ml THF over 1 h. After an additional reflux for 1 h and cooling to room temperature, saturated aq. NH_4Cl (1.0 ml) was added. The mixture was diluted with $CHCl_3$ (30 ml) and filtered through alumina oxide (3 cm). The solvent was evaporated and the residue purified by column chromatography on silica gel (eluent hexane–diethyl ether, 3:1).

Table 3 Cross-coupling reactions of benzylic zinc derivatives of (η^6-alkylarene)tricarbonylchromium complexes with organic halides.

Starting complex	RHal	Product[a]	Yield (%)	M.p./°C
	PhI		66	
	PhI		37	119–121
	PhI		27	137–138
	Ph—CH=CHBr		44	116–117.5
			13	92-93

[a] All products were obtained as chromatographically-pure yellow crystals with satisfactory elemental analyses. Evidence for their formation was provided by ^{1}H NMR spectroscopic data.

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