## Reactivity of Nitroarenes towards Grignard Reagents; General Synthesis of Alkyl-Chloro Compounds in Aromatic Bicyclic Systems

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We have already reported on the conjugate addition of Grignard reagents to nitroarene systems which leads to *ortho*- or *para*-substituted alkyl nitronate adducts. These compounds, when treated *in situ* with strong mineral acids[1], reducing agents[2], or oxidizing agents[3], can be converted, in fair to good yields, into aromatic alkyl-nitroso, -amino, or -nitro derivatives, respectively. The generality of this reaction has been checked for several mono- and bicyclic, hetero- and homocyclic systems.

We now report a further application of this type of reaction which allows conversion of a nitroarene into the corresponding alkyl-chloro derivative. This conversion is achieved by treatment of a nitronate adduct, from a nitroarene and an alkyl Grignard reagent, with an excess of sodium hypochlorite. Thus, a tetrahydrofuran solution of 1-nitronaphthalene (1a; 1 equiv) reacts with two mol of methylmagnesium halide (2) to give nitronates 3a and 5a. Subsequent addition of an excess of aqueous sodium hypochlorite in alkaline/alcohol solution at room temperature, decomposes 3a and 5a to 4a and 6a, respectively.
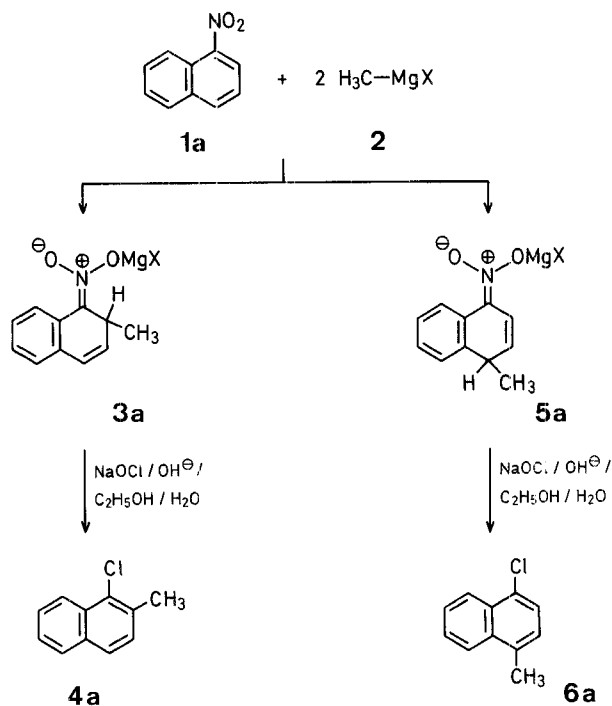
The reaction is similar to that reported[4] for nitrobenzofurazans and related compounds which undergo an alkoxy halo substitution when treated with an aqueous/alcoholic so-

Table 1. Alkyl-chloro-arenes 4 and 6 prepared

Substrate	Product		Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	
1a	4a		60[b]	oil	C₁₁H₉Cl	(176.6)[c]
	6a		20[b]	oil	C₁₁H₉Cl	(176.6)[c]
1b	4b	R = CH₃	84	54–55° (C₂H₅OH)	C₁₂H₁₁ClO	(206.7)
		R = C₆H₅CH₂	78	84–85° (C₂H₅OH)	C₁₈H₁₅ClO	(282.8)
1c	4c	R = CH₃	85	62–63° (C₂H₅OH)	62°[7]	
		R = C₆H₅CH₂CH₂	82	61–63° (C₂H₅OH)	C₁₈H₁₄Cl₂	(301.2)
1d	4d		70	oil	C₁₁H₉Cl	(176.6)
1e	4e		89	85–86° (C₂H₅OH)	C₁₃H₁₁Cl	(202.7)
1f	4f	R = CH₃	73	81–82° (C₂H₅OH)	C₁₀H₈ClN	(177.6)
		R = n-C₄H₉	64	oil	C₁₃H₁₄ClN	(205.7)
1g	4g	R = CH₃	58	54–56° (C₂H₅OH)	C₈H₆ClNS	(183.6)
		R = C₆H₅CH₂	53	77–80° (C₂H₅OH)	C₁₄H₁₀ClNS	(259.7)

[a] The microanalyses were in good agreement with the calculated values (C ±0.21, H ±0.08, N ±0.13, Cl ±0.17).
[b] Determined by quantitative G.L.C. analysis of isomer mixture.
[c] Product identical with sample prepared by independent method[6].

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lution of sodium hypochlorite. Nevertheless, the mechanism suggested by these authors to explain the action of hypochlorite ion on the σ-anionic adduct, that is, a synchronous attack of the chlorine of the hypochlorite ion on the carbon bearing the nitro group and of the oxygen on the hydrogen attached to the sp³ carbon atom with consequent expulsion of nitrite ion and hydroxide ion, cannot fit the results obtained by us in the case of 1-nitronaphthalene, as far as the formation of 6a from 5a is concerned.

Alternatively, the action of hypochlorite ion on the nitronate adduct can be very likely explained in terms of an initial chlorination at the carbon atom bearing the nitronate function, followed by immediate elimination of a molecule of HNO_2 promoted by the strongly basic medium, and contemporaneous re-aromatization of the system to give the alkyl-chloro derivative.

The method is of wide applicability for bicyclic systems as demonstrated by yields obtained in reactions with the benzothiazoles, naphthalenes, and quinolines reported in Table 1. Unfortunately the reaction fails with benzene derivatives. In fact, from treatment of p-chloro- and p-methoxynitrobenzenes under the conditions described above, only intractable tars were obtained.

Furthermore, in reactions with 2-nitronaphthalene, 6-nitroquinoline, and 6-nitrobenzothiazole, small amounts of the corresponding oxidation compounds (1-alkyl-2-nitronaph-

Table 2. ¹H-N.M.R. Data for Products 4 and 6

Compound	¹H-N.M.R. (CDCl₃/TMS) δ [ppm]
4a	2.66 (s, 3H, CH₃); 7.20–7.96 + 8.36–8.50 (2m, 6H$_{arom}$)
6a	2.72 (s, 3H, CH₃); 7.28–8.10 + 8.35–8.40 (2m, 6H$_{arom}$)
4b (R=CH₃)	2.56 (s, 3H, CH₃); 4.00 (s, 3H, OCH₃); 6.70 (s, 1H, H-3); 7.36–7.70 + 8.18–8.32 (2m, 4H$_{arom}$)
4b (R=C₆H₅CH₂)	3.92 (s, 3H, OCH₃); 4.34 (s, 2H, CH₂); 6.66 (s, 1H, H-3); 7.14–7.36 (m, 5H$_{arom}$); 7.40–7.72 + 8.20–8.40 (2m, 4H$_{arom}$)
4c (R=CH₃)	2.55 (s, 3H, CH₃); 7.45 (s, 1H, H-3); 7.50–7.74 + 8.15–8.40 (2m, 4H$_{arom}$)
4c (R=C₆H₅CH₂CH₂)	2.84–3.34 (m, 4H, CH₂CH₂); 7.10–7.40 (m, 5H$_{arom}$); 7.42 (s, 1H, H-3); 7.50–7.80 + 8.20–8.50 (m, 4H$_{arom}$)
4d	2.80 (s, 3H, CH₃); 7.42–8.15 (m, 6H$_{arom}$)
4e	2.56 (s, 3H, CH₃); 3.36 (s, 4H, CH₂CH₂); 7.14 (s, 1H, H-3); 7.20–7.94 (m, 3H$_{arom}$)
4f (R=CH₃)	2.70 (s, 3H, CH₃); 7.40 (dd, 1H, H-3, $J_{H-3,H-2}$=4.25 Hz, $J_{H-3,H-4}$=8.60 Hz); 7.62 (d, 1H, H-7, $J_{H-7,H-8}$=9.25 Hz); 7.90 (dd, 1H, H-8, $J_{H-8,H-4}$=0.85 Hz); 8.30 (m, 1H, H-4, $J_{H-4,H-2}$=1.75 Hz); 8.88 (dd, 1H, H-2)
4f (R=n-C₄H₉)	0.92 (s, 3H, CH₃); 1.48 (m, 4H, CH₂CH₂); 3.10 (t, 2H, CH₂); 7.40 (dd, 1H, H-3, $J_{H-3,H-2}$=4.25 Hz, $J_{H-3,H-4}$=8.60 Hz); 7.62 (d, 1H, H-7, $J_{H-7,H-8}$=9.25 Hz); 7.90 (dd, 1H, H-8, $J_{H-8,H-4}$=0.85 Hz); 8.30 (m, 1H, H-4, $J_{H-4,H-2}$=1.75 Hz); 8.88 (dd, 1H, H-2)
4g (R=CH₃)	2.65 (s, 3H, CH₃); 7.51 (d, 1H, H-4, $J_{H-4,H-5}$=9.5 Hz); 7.92 (d, 1H, H-5); 8.97 (s, 1H, H-2)
4g (R=C₆H₅CH₂)	4.42 (s, 2H, CH₂); 7.27 (m, 5H$_{arom}$); 7.59 (d, 1H, H-4, $J_{H-4,H-5}$=9.5 Hz); 7.96 (d, 1H, H-5); 8.93 (s, 1H, H-2)

thalene, 5-alkyl-6-nitroquinoline, and 7-alkyl-6-nitrobenzothiazole)[5] have been obtained as by-products. Nevertheless, their presence in the crude reaction mixture does not cause difficulties in the purification of the desired chloro derivatives.

It is interesting to remark that the present results represent the first example of the application of a conjugate addition reaction of RMgX to nitroarenes and to the quinoline system. In fact, 6-nitroquinoline could not be used in the synthesis of both nitro-[3] and nitroso-alkyl derivatives[1]. It is now clear that the previous unsatisfactory results have to be attributed to the inapplicability of the decomposition methods thus far used to the above mentioned system.

Alkyl-chloro-arenes 4a–g, 6a; General Procedure:

A solution of the alkylmagnesium chloride 2 (20 mmol) in tetrahydrofuran (30 ml) is added dropwise at room temperature under nitrogen to a stirred solution of the nitroarene 1 (10 mmol) in the same solvent (50 ml). The mixture is stirred for a few minutes and then added dropwise to a freshly prepared solution of sodium hypochlorite (40 mmol) and potassium hydroxide (40 mmol) in a mixture (80 ml) of ethanol/water (1:1, v/v). The mixture is stirred for ~10 min and then extracted with dichloromethane (3 × 50 ml), the organic layer is filtered, washed with water (3 × 100 ml), dried with magnesium sulphate, and evaporated at reduced pressure. The crude alkyl-chloro-arene was purified by chromatography on a short silica gel column using an appropriate mixture of cyclohexane/ethyl acetate as eluent.

In the reaction of 1a with 2 the two formed isomers could not be quantitatively separated by column chromatography. The values reported in Table 1 refer to yields calculated by quantitative G.L.C. analysis on a mixture of both isomers. Their characterization was made on small amounts of pure isomers obtained by quantitative G.L.C. separation.

6-Chloro-5-methylquinoline (4f; R=CH₃):

A solution of methylmagnesium chloride (2; X=Cl; 20 mmol) in tetrahydrofuran (20 ml) is added dropwise at ~20°C under nitrogen to a stirred solution of 1f (1.86 g, 10 mmol) in the same solvent (50 ml). The mixture is stirred for ~10 min and then added dropwise to a vigorously stirred solution of sodium hypochlorite and potassium hydroxide [freshly prepared by adding 40 ml of 8% aqueous sodium hypochlorite to a solution of potassium hydroxide (2.16 g) in 40 ml of ethanol]. The mixture is stirred for ~10 min and then extracted with dichloromethane (3 × 50 ml). The organic layer is filtered, washed with water (3 × 100 ml), dried, and evaporated at reduced pressure. The crude residue is submitted to chromatographic separation on a silica gel column. Elution with cyclohexane/ethyl acetate (4:1, v/v) gives pure 6-chloro-5-methylquinoline; yield: 0.75 g (73%). Further elution with cyclohexane/ethyl acetate (1:1, v/v) gives 5-methyl-6-nitroquinoline; yield: 0.12 g.

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