Removal of All the Protecting Groups from 10. Method A. Compound **10** (6.9 mg, 0.05 mmol) was dissolved in dioxane (0.25 mL) and 0.2 M sodium hydroxide solution (0.25 mL). After being kept at room temperature for 10 min, the solution was neutralized with Dowex 50 W X2 (pyridinium form), and then the resin was filtered and washed with pyridine–water (2:1, v/v, 10 mL). The filtrate and washing were combined, evaporated in vacuo, and coevaporated with toluene (3 × 5 mL). The residue was stirred vigorously in 0.01 M hydrochloric acid solution (20 mL) and adjusted to pH 2.0 by addition of 0.1 M hydrochloric acid solution. After being stirred at room temperature for 24 h, the mixture was treated with pyridine (1 mL) and 0.2 M triethylammonium bicarbonate solution (1 mL). The resulting solution was evaporated in vacuo. The residue was chromatographed on Whatman 3 MM papers with *i*-PrOH–concentrated ammonia–water (7:1:2, v/v/v) to give UpU (83 OD, 91%): R_f 1.9 relative to pU.

Method B. Compound **10** (6.9 mg, 0.05 mmol) was mixed with silver acetate (47 mg, 0.25 mmol) and dissolved in pyridine–water (9:1, v/v, 2 mL). The solution was immediately evaporated in vacuo and the residue was again dissolved in pyridine–water (2:1, v/v, 0.25 mL). The resulting solution was stirred vigorously at room temperature for 24 h. Then the mixture was diluted with pyridine–water (2:1, v/v, 5 mL) and cooled to 0 °C. To the solution was bubbled hydrogen sulfide until a clear supernatant had been obtained. The excess gas was removed by stirring at 0 °C under reduced pressure and silver sulfide was removed by centrifugation. The supernatant was evaporated in vacuo and the residue was coevaporated with toluene (3 × 5 mL). The residue was treated with 0.01 M hydrochloric acid solution (pH 2.0, 20 mL) at room temperature for 24 h. The same workup described before gave UpU (85 OD, 93%).

Enzyme Assays. UpU (20 OD), obtained by method A or method B in the above experiment, was incubated with snake venom phosphodiesterase (20 μg, Boehringer) in 0.05 M Tris-HCl buffer (pH 7.6, 0.3 mL) at 37 °C for 16 h. Analysis by paper chromatography showed that the dimer was completely degraded to give U and pU in the ratio of 1:1.

UpU (10 OD), obtained by method A or method B in the above experiment, was incubated with calf spleen phosphodiesterase (10 μg, Boehringer) in a mixture of 0.01 M pyrophosphate buffer (pH 6.5, 0.1 mL) and 0.05 M ammonium acetate (pH 6.5, 0.2 mL) at 37 °C for 7 h. The dimer was degraded completely, and U and Up were obtained in the ratio of 1:1 in each case.

Registry No. 1, 69304-38-7; 2, 86365-02-8; 3, 86365-03-9; 4, 6773-44-0; 5, 86365-04-0; 6, 86365-05-1; 8, 86365-06-2; 9, 86365-08-4; 10, 86365-09-5; UpU, 2415-43-2.

Nucleophilic Aromatic Substitution of $Cr(CO)_3$-Complexed Dihaloarenes with Thiolates

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The S_NAr nucleophilic displacement of unactivated or slightly activated aryl halides requires rather severe conditions,[1] even if promoted by powerful anionic nucleophiles, both in phase-transfer conditions (PTC)[2] and in dipolar aprotic solvents.[3]

Recently we have shown that $Cr(CO)_3$-activated aryl halides undergo easy and almost quantitative S_NAr nucleophilic substitution with thiolates under mild phase-transfer conditions.[4] We have now synthesized the $Cr(CO)_3$ complexes of the isomeric dichlorobenzenes and studied their reaction with thiolates in Me_2SO or in a PTC solid–liquid system.

Products, reaction conditions, conversion, yields, and product ratios are summarized in Table I. Most of the reactions have been carried out at room temperature; conversion of starting materials as well as the product ratio has been determined by GC analysis. The reported yields refer to isolated and pure products. Dealkylation side products[3] were never observed. From the table it can be inferred that there is no substantial difference of reactivity in the two different reaction conditions, namely, the PTC solid–liquid system or Me_2SO, although in some cases longer reaction times have been observed in PTC particularly with *tert*-butyl thiolate.

Compounds **1a** and **1c** undergo substitution of the first chlorine atom followed by that of the second one in a reaction sequence that can be easily controlled by the amount of added thiolate (1 or 2 mol per mol of substrate).

1b shows a lower selectivity and even in the presence of less than 1 molar equiv of thiolate gives a mixture of the mono- and disubstituted products **2** and **3**, although products **2** are always prevailing.

With 1,1-dimethylethanethiolate that has been reacted with **1a** and **1b**, we have found in both cases a qualitative but sharp decrease in the reaction rate compared to that found with primary alkyl thiolates, while the products ratio is practically the same as that with primary alkyl thiolates.

The above results show that $Cr(CO)_3$ complexation strongly activates both the halogen atoms to nucleophilic substitution. Nevertheless, their reactivity is still different enough to allow the substitution with two different nucleophiles. For instance, in the case of **1b**, which is the compound of lowest selectivity in the series, the reaction with an equimolar amount of MeS^- followed by the reaction with *n*-BuS^- has led to 1-(butylthio)-3-(methylthio)-benzene in a 58% overall yield of isolated product.

Experimental Section

NMR spectra were recorded on a Varian EM-390 90-MHz spectrometer in $CDCl_3$ solution with Me_4Si as internal standard; IR spectra were measured as films or Nujol mulls on a Perkin-Elmer Model 377 grating spectrophotometer with NaCl cells; GC data were obtained on a Varian Model 3700 gas chromatograph equipped with a 3% Carbowax 20M on Chromosorb W column and were evaluated with a Varian Data System Model 401 by the N % method.

Boiling and melting points are uncorrected.

Compound 1a. *o*-$C_6H_4Cl_2$ (90 mL) and $Cr(CO)_6$ (6 g) were refluxed in dioxane (134 mL) and diglyme (46 mL) for 13 h. Solvents, unreacted $Cr(CO)_6$, and *o*-$C_6H_4Cl_2$ were distilled under vacuum (0.1 mm). The residue was dissolved in Et_2O and filtered on Celite. The solvent was evaporated and the crude product crystallized, mp 101–102 °C (diisopropyl ether/petroleum ether); IR 3020, 1980–1910, 1410, 1110–1040, 640–610 cm^{-1}; ^1H NMR δ 5.12 (m, 2 H), 5.68 (m, 2 H); yield 63%. Anal. Calcd for $C_9H_4Cl_2CrO_3$: C, 38.19; H, 1.41. Found: C, 38.48; H, 1.48.

Compound 1b. The synthesis was performed in the same way as for **1a**, refluxing *m*-$C_6H_4Cl_2$ (84 mL) and $Cr(CO)_6$ (6 g) in dioxane (168 mL): mp 122–124 °C (diisopropyl ether/petroleum ether); IR 3020, 1980–1940, 1420, 1210, 1080, 940 cm^{-1}; ^1H NMR δ 5.1–5.7 m; yield 58%. Anal. Calcd for $C_9H_4Cl_2CrO_3$: C, 38.19; H, 1.41. Found: C, 38.43; H, 1.6.

Compound 1c. The synthesis was performed in the same way as for **1a**, refluxing *p*-$C_6H_4Cl_2$ (10 g) and $Cr(CO)_6$ (6 g) in dioxane (200 mL) for 24 h. After distillation, the residue was taken up with hexane and filtered on Celite. Hexane was evaporated and

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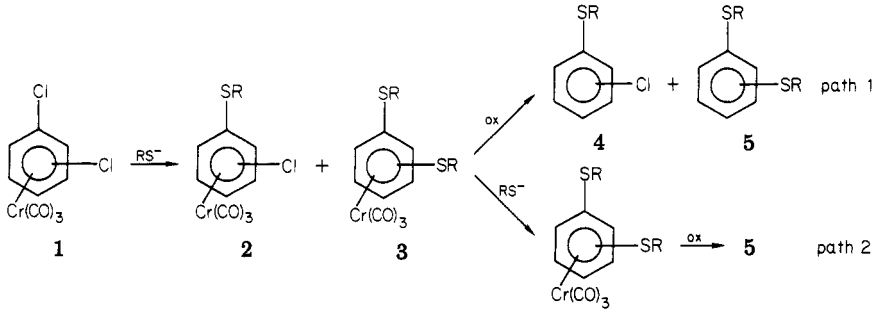
Table I. Reactions of $Cr(CO)_3$-Dichloroarenes with Thiolates



a, 1,2-dichloro; b, 1,3-dichloro; c, 1,4-dichloro

Path 1

		method A[a]					method B[a]			
compd	R	product[b]	time	% convn	yield, %	2:3	time, min	% convn	yield, %	2:3
1a	Me	4	20 min	98	70		15	99		
1a	*n*-Bu	4	20 min	99			10	99		
1a	*t*-Bu	4	1 h	99	97		40	99		
1b	Me	4 + 5	40 min	86		84:16	30	83		79:21
1b	*n*-Bu	4 + 5	5 min	77		70:30	10	77		70:30
1b	*t*-Bu	4 + 5	3 h	82		78:22	10	77.6		72:28
1c	Me	4	15 min	99	65		15	80	74	
1c	*n*-Bu	4	15 min	99			10	78	63	

Path 2

		method A					method B			
compd	R	product[b]	time	*T*,[c] °C	% convn	yield, %	time	*T*,[c] °C	% convn	yield, %
1a	Me	5	15 min	rt	99	91	10 min	rt	99	94
1a	*n*-Bu	5	40 min	rt	99	91	15 min	rt	98	85
1a	*t*-Bu	5	4 h	45	96	61	2 h	45	98	63
1b	Me	5	10 min	rt	84	80	10 min	rt	77	63
1b	*n*-Bu	5	5 min	rt	98		10 min	rt	87	62
1b	*t*-Bu	5	5 h	rt	95	66	1 h	rt	94	60
1c	Me	5	20 min	rt	99		15 min	rt	98	81
1c	*n*-Bu	5	15 min	rt	91	58	10 min	rt	91	

[a] Reactions were carried out at room temperature. [b] Spectroscopic and analytical data are consistent with assigned structures. [c] rt = room temperature.

the crude product crystallized, mp 86–87 °C (lit.[5] 88 °C).

Compounds 4 and 5. Method A. General Procedure. To a vigorously stirred mixture of 500 mg (1.77 mmol) of 1a–c, 212 mg (5.31 mmol) of ground NaOH, and 2.71 mg (0.49 mmol) of tetraoctylammonium bromide (TOAB) in 30 mL of benzene was added a solution of 1.77 mmol of thiolate in 1 mL of benzene at room temperature under nitrogen. The reaction progress was monitored by TLC. When the substrates **1a–c** had disappeared, the reaction mixture was worked up either along path 1 or path 2 (see below).

Path 1. The solvent was removed under reduced pressure and the residue extracted with a small amount of ether. Decomplexation was performed by treatment with iodine (2.7 mmol) at 0 °C (2–3 h), and the products were purified by distillation.

Path 2. To the reaction mixture was added an additional 1.77 mmol of thiolate; after reaction completion (TLC), the mixture was worked up as described for path 1.

Compounds 4 and 5. Method B. General Procedure. To a stirred mixture of 500 mg (1.77 mmol) of **1a–c** and 212 mg (5.31 mmol) of ground NaOH in 5 mL of Me_2SO, was added a solution of 1.77 mmol of thiolate in 1 mL of Me_2SO at room temperature under nitrogen. The reaction progress was monitored by TLC. When the substrates **1a–c** had disappeared, the reaction mixture was worked up either along path 1 or path 2, as follows.

Path 1. The Me_2SO solution was diluted with water (about 10 mL) and extracted with 10 × 2 mL of ether, and the products were then decomplexed as described above.

Path 2. To the reaction mixture was added an additional 1.77 mmol of thiolate. After reaction completion (TLC), the mixture was worked up as described for path 1.

1-(Butylthio)-3-(methylthio)benzene. The reaction was carried out along method A (path 1), starting with 0.4 g of **1b** and an equivalent amount of MeSH. After 40 min, decomplexation of the products in a small sample, follwed by GC analysis, revealed 72% 3-(methylthio)chlorobenzene, 14% of 1,3-bis(methylthio)-benzene, and 14% dichlorobenzene. *n*-BuSH (1.7 mmol) was then added to the reaction mixture; after 40 min, workup was performed in the usual way and 230 mg of the crude products were obtained. The GC analysis revealed the presence of 10% di-*n*-butyl disulfide, 72% 1-(butylthio)-3-(methylthio)benzene, 14% 1,3-bis(methylthio)benzene, and 4% dichlorobenzene.

1,2-Bis(*tert*-butylthio)benzene: bp 105–107 °C (1 mm); ^1H NMR δ 1.4 (s, 18 H, Me_6), 7.3 (m, 2 H, aromatics), 7.7 (m, 2 H, aromatics). Anal. Calcd for $C_{14}H_{22}S_2$: C, 66.10; H, 8.73. Found: C, 66.46; H, 8.71.

1,3-Bis(*tert*-butylthio)benzene: bp 115–117 °C (1 mm); ^1H NMR δ 1.2 (s, 18 H, Me_6), 7.1–7.7 (m, 4 H, aromatics). Anal. Calcd for $C_{14}H_{22}S_2$: C, 66.10; H, 8.73. Found C, 66.24; H, 8.70.

Registry No. **1a**, 70140-19-1; **1b**, 86409-61-2; **1c**, 86409-62-3; **2b** (R = Me), 86409-63-4; **2b** (R = *n*-Bu), 86409-64-5; **2b** (R = *t*-Bu), 86409-65-6; **3b** (R = Me), 86409-66-7; **3b** (R = *n*-Bu), 86409-67-8; **3b** (R = *t*-Bu), 86409-68-9; **4a** (R = Me), 17733-22-1; **4a** (R = *n*-Bu), 84051-20-7; **4a** (R = *t*-Bu), 84051-21-8; **4b** (R = Me), 4867-37-2; **4b** (R = *n*-Bu), 84051-22-9; **4b** (R = *t*-Bu), 49833-56-9; **4c** (R = Me), 123-09-1; **4c** (R = *n*-Bu), 16155-34-3;

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Direct One-Pot Synthesis of Terminal Olefins and Deuterio Olefins from Carboxylic Acid Chlorides

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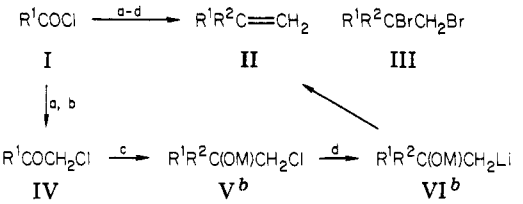
Recently we have reported a regioselective method to obtain olefins and deuterio olefins from α-chloro carbonyl compounds, Grignard reagents or lithium aluminum hydride or deuteride, and lithium.[1] These results prompted us to use the Nierenstein chloromethylation reaction[2] in a one-pot tandem process with the above-described method to obtain terminal olefins and deuterio olefins using carboxylic acid chlorides as starting materials.

The reaction of a carboxylic acid chloride (I) with diazomethane in ether (1:2 molar ratio) at −20 °C and further addition of an ethereal solution of hydrogen chloride (1:1.5 molar ratio) leads to an α-chloromethyl ketone (**IV**);[2] after removal of the excess of hydrogen chloride the chloro ketone was successively treated in situ with a mixture of a Grignard reagent/magnesium bromide at −40 °C and lithium powder (1:3 molar ratio) at −40 to +20 °C. After hydrolysis with aqueous hydrochloric acid the corresponding disubstituted terminal olefin (II1–II30) was obtained (see Scheme I and Table I, entries 1–30). Reaction of the initially generated chloro ketone IV[2] with a Grignard reagent leads to a chlorinated alkoxide, V (M = MgBr),[1,3] which by further lithiation yields a β-substituted organolithium compound, VI (M = MgBr);[4] the spontaneous β elimination of this intermediate VI affords the corresponding olefin II.

In order to improve the reaction yield, we studied different reaction conditions. (a) While the best results were obtained when the addition of the Grignard reagent was carried out in ether, in the lithiation step tetrahydrofuran had to be added to the reaction mixture; otherwise, the reaction times were longer. When the lithiation was carried out in diglyme (Table I, entries 35 and 41), the yields do not vary substantially. (b) When anhydrous magnesium bromide was added with the Grignard reagent (1:1 molar ratio) the yield was highly increased; without this salt yields were lower than 10%. (c) Best yields were obtained when an excess of the organomagnesium (1:2 molar ratio) was used. (d) A stoichiometric amount of lithium (1:2 molar ratio) was used when R^2 = Ph (Table I, entries 6, 11, 17, and 23) in order to avoid the reduction of the resulting conjugated double bond by excess metal.[1]

Scheme I[a]



[a] (a) CH_2N_2, Et_2O; (b) HCl, Et_2O; (c) $R^2MgBr/MgBr_2$ or $LiAlH_4/AlCl_3$ or $LiAlD_4/AlCl_3$; (d) Li. [b] M = MgBr or $Al(OR)_2$.

The method was extended to the preparation of monosubstituted olefins and deuterio olefins (II with R^2 = H or D) by using $LiAlH_4/AlCl_3$ or $LiAlD_4/AlCl_3$[1] as the nucleophile instead of the Grignard reagent R^2MgBr in the addition to the α-chloro ketone IV. The procedure was carried out under reaction conditions similar to those described above, and the reaction involves the same former intermediates V and VI with M = Al $(OR)_2$ (see Scheme I). The low molecular weight olefins were isolated and identified as the *vic*-dibromo derivatives III which were obtained by addition of bromine to the olefin at the end of the reaction sequence (Table I, entries 31–34 and 38–40).

The procedure described herein is, in our opinion, a method of choice for the preparation of terminal olefins and deuterio olefins.[7]

Experimental Section

General Methods. For general experimental information see ref 1. Diazomethane[25] and anhydrous magnesium bromide[26] were prepared by literature methods. The ether solution of hydrogen chloride was prepared by passing HCl gas through anhydrous ether and was used as a ca. 4 N solution. The products previously described (see notes in Table I) were identified by comparison of NMR and IR spectra with those of authentic samples. All new compounds exhibited satisfactory spectral and analytical data (see supplementary material).

Synthesis of Terminal Olefins and Deuterio Olefins II from Carboxylic Acid Chlorides I. Isolation as *vic*-Dibromo Derivatives III. General Procedure. To a previosly evacuated 250-mL two-necked flask containing a solution of diazomethane (40 mmol) in ether was added a solution of the carboxylic acid

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