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Synthesis of 2′-*O*-(1,3-Benzodithiol-2-yl)uridine and Related Compounds as Key Intermediates in Oligoribonucleotide Synthesis

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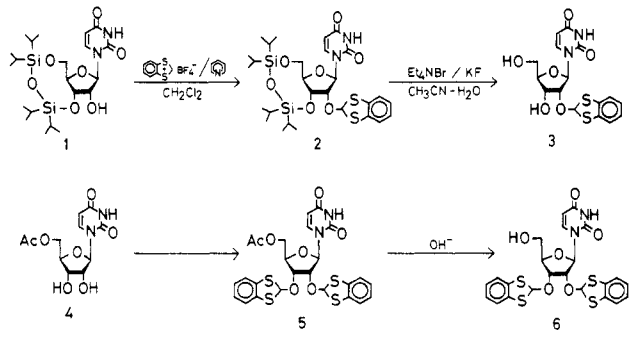
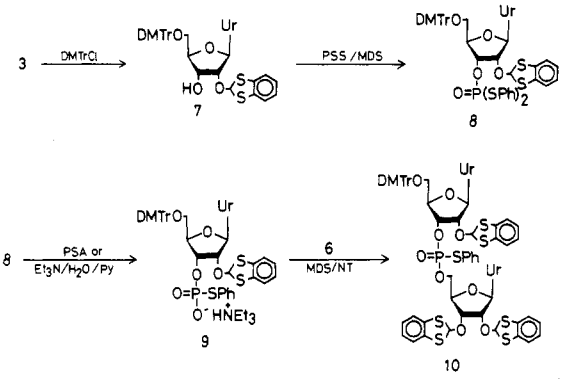
In a previous paper,[1] we reported a new protecting group, 1,3-benzodithiol-2-yl (BDT), designed for nucleoside hydroxyl functions. The BDT group has proved to be readily introduced into primary and secondary hydroxyl groups and removed under mildly acidic conditions. This paper describes the utility of the BDT group as a 2′-hydroxyl protecting group.[2-5] When a cyclic silylated uridine derivative (1)[6] was allowed to react with 1.5 equiv of 1,3-benzodithiolium tetrafluoroborate (BDTF), the 2′-*O*-(1,3-benzodithiol-2-yl)uridine derivative **2** was obtained in 80% yield. In this reaction, the N^3-alkylation occurred competitively with the 2′-O-alkylation. However, the dialkylated product was unstable during chromatography and was decomposed to **2**. In a similar manner, 5′-*O*-acetyluridine (**4**) reacted with BDTF to give the 2′-O-alkylated product **5** in 77% yield. In this case, an unstable N^3-alkylated product was also detected.[7]



Next, we prepared two key intermediates **3** and **6** for the synthesis of oligoribonucleotides from **2** and **5**, respectively. Fluoride ion mediated deprotection[8] of **2** gave **3** in 94% yield. On the other hand, alkaline hydrolysis of **5** afforded **6** in 88% yield. Compound **6** was also obtained in good yield from **4** without purification of **5**.

Next, the synthesis of uridylyl (3′→5′)uridine was examined by using **3** and **6** in order to ascertain their usefulness. The compound **8** was synthesized in high yield by the usual dimethoxytritylation followed by phosphorylation with cyclohexylammonium *S,S*-diphenyl phosphorodithioate (PSS)[9] in the presence of mesitylene-1,3-disulfonyl chloride (MDS).[10] Selective removal of one



phenylthio group was performed in two ways. The first of these was use of phosphinic acid (PSA)-triethylamine-pyridine[1,7,9] as previously described by us. The other involves basic conditions, i.e., triethylamine-water-pyridine.[1] Although the latter method was simple and gave a mixt. of diester **9** and thiophenol upon evaporation, the reaction required 5 h. In contrast with this result, a phenylthio group was removed from **8** within 15 min when a 3.3 M solution of PSA buffered with triethylamine in pyridine was employed. We previously reported that thiophenol, a byproduct of the extractive workup, did not affect the condensation of a diester with a hydroxyl component.[1,11] Therefore, the mixture of the triethylammonium salt of **9** and thiophenol was allowed to react with **6** in the presence of MDS and 3-nitro-1,2,4-triazole (NT). This coupling proceeded smoothly and gave dimer **10** in 76% yield. The dimer **10** was successfully converted to UpU by treatment with 0.2 M NaOH-dioxane or a silver ion catalyzed dephenylthiolation,[9] followed by treatment with 0.01 M HCl (pH 2.0)[12] The unprotected dimer was isolated in more than 91% yields by paper chromatography and analyzed by snake venom and spleen phosphodiesterases, whereupon the correct ratios of the degradation product were obtained.

These results suggest that the BDT group can be used as a useful protecting group of the 2′-hydroxyl and 2′,3′-cis-diol functions.

Since the BDT group has a stability similar[1] to that of the 4-methoxytetrahydropyran-4-yl group[4,7] under acidic conditions, chain elongation of oligoribonucleotides will be realized by employing the levulinyl[13] and fluoren-9-ylmethoxycarbonyl[14] groups, recently reported by van

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(7) It is interesting that compound **5**, protected with the two BDT groups, could be obtained since we have failed to obtain 5′-*O*-acetyl-2′,3′-di-*O*-(4-methoxytetrahydropyran-4-yl)uridine by the pyranylation of **4** under usual conditions (Reese, C. B.; Saffhill, R.; Sulston, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 3366, and see also ref 4). The successful introduction of the BDT groups into the cis diol of **4** may be attributed to the avoidance of 2′,3′-cyclic acetal formation by employing almost neutral rather than acidic conditions in the case of the pyranylation.
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Boom and Chattopadhyaya, as the 5'-hydroxyl-protecting group.

Further studies are now under investigation in this direction.

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. ^1H NMR spectra were recorded on a JNM-PS-100 spectrometer using Me_4Si as the internal standard. CH_2Cl_2 was dried over P_4O_{10} overnight, distilled over K_2CO_3, and stored over 3A molecular sieves. Pyridine was distilled first from *p*-toluenesulfonyl chloride, redistilled from calcium hydride, and stored over 3A molecular sieves.

3-Nitro-1,2,4-triazole was kindly supplied by Dojin Chemical Co. Ltd. (Kumamoto).

2'-*O*-(1,3-Benzodithiol-2-yl)-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine (2). To a suspension of **1**[6] (6.33 g, 13 mmol) and BDTF[14] (4.68 g, 19.5 mmol) in dry CH_2Cl_2 (65 mL) was added dry pyridine (3.15 mL, 39 mmol). The mixture immediately became homogeneous and a precipitate gradually appeared. After being stirred at room temperature for 3 h, the mixture was quenced by addition of water (3.25 mL) and the solution was stirred for 30 min. The mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, filtered, and evaporated in vacuo. Then, the residue was coevaporated with toluene several times, dissolved in hexane–CH_2Cl_2 (5:1, v/v, 100 mL), and applied to a column of silica gel (Waco gel C-200, 100 g). Elution with hexane–CH_2Cl_2 (1:1, v/v) containing 0.5% pyridine gave fractions containing the dialkylated product and **2**, which resulted from decomposition of the former on the column. Elution with CH_2Cl_2 containing 0.5% pyridine gave **2** (6.21 g). The mixture obtained in the early fractions was again chromatographed twice on a column of silica gel (50 g and 10 g, respectively) to give **2** (0.39 g). The total yield of **2** was 6.6 g (6.21 g). For **2**: R_f 0.79 (CH_2Cl_2–MeOH, 9:1, v/v); H^1 NMR ($CDCl_3$) δ 1.03 (m, 12, CH_3), 1.62 (m, 4, CHSi), 4.00 (m, 2, 5'-H), 4.14 (m, 1, 4'-H), 4.29 (m, 2, 2',3'-H), 5.71 (d, J = 8 Hz, 1, 6-H), 5.74 (s, 1, 1'-H), 6.92 (s, 1, SCHS), 7.11 (m, 2, Ar H), 7.34 (m, 2, Ar H), 7.75 (d, J = 8 Hz, 1, 5-H), 9.84 (br s, 1, NH).

Anal. Calcd for $C_{28}H_{42}N_2O_7S_2Si_2$: C, 52.63; H 6.63; N, 4.38. Found: C, 52.63; H, 6.80; N, 4.34.

5'-*O*-Acetyl-2',3'-di-*O*-(1,3-benzodithiol-2-yl)uridine (5). To a suspension of **4**[15] (573 mg, 2 mmol) and BDTF[14] (2.31 g, 9.6 mmol) in dry CH_2Cl_2 (8.0 mL) was added dry pyridine (1.13 mL, 19.2 mmol). After being stirred for 19 h, the mixture was quenched with triethylamine (0.13 mL, 0.96 mmol). The same workup as described in the previous experiment gave **5** (906 mg, 77%): R_f 0.70 (CH_2Cl_2–MeOH, 9:1, v/v); H^1 NMR ($CDCl_3$) δ 1.88 (s, 1, C(O)CH_3), 4.00–4.40 (m, 5, 2',3',4',5'-H), 5.68 (d, J = 8 Hz, 1, 5-H), 5.84 (d, J = 3.2 Hz, 1, 1'-H), 6.91 and 7.03 (s, 2, SCHS), 7.10–7.60 (m, 9, Ar H and 6-H), 9.24 (br s, 1, NH).

Anal. Calcd for $C_{25}H_{22}N_2O_7S_4$: C, 50.83; H, 3.75; N, 4.74. Found: C, 50.98, H, 3.86; N, 4.66.

2'-*O*-(1,3-Benzothiol-2-yl)uridine (3). To a mixture of **2** (6.73 g, 10.5 mmol), potassium fluoride (3.55 g, 63.2 mmol), and tetraethylammonium bromide (13.3 g, 63.2 mmol) were added acetonitrile (116 mL) and water (3.16 mL). The resulting suspension was stirred at 60 °C for 1 h. After being cooled to room temperature, the mixture was transferred to a separatory funnel with water (200 mL) and CH_2Cl_2–pyridine (9:1, v/v, 200 mL). The organic layer was collected and the aqueous layer was further extracted with CH_2Cl_2–pyridine (5:1, v/v, 4 × 60 mL). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The residue was triturated with CH_2Cl_2 (20 mL), and the resulting solid was filtered, washed with CH_2Cl_2 (4 × 10 mL), and dried in a dessicator to give **3** (4.03 g, 94%): mp 136–137 °C; R_f 0.45 (CH_2Cl_2–MeOH, 9:1, v/v); ^1H NMR ($CDCl_3$–CD_3OD, 1:1, v/v) δ 3.70 (m, 2, 5'-H), 4.02 (m, 1, 4'-H), 4.23 (m, 2, 2',3'-H), 5.70 (d, J = 8.3 Hz, 1, 5-H), 6.02 (d, J = 5.2 Hz, 1, 1'-H), 7.20 (m, 2, Ar H), 7.41 (m, Ar H), 7.75 (d, J = 8.3 Hz, 1, 6-H).

Anal. Calcd for $C_{16}H_{16}N_2O_6S_2 \cdot 0.5H_2O$: C, 47.40; H, 4.23; N, 6.91. Found: C, 47.23; H, 3.97; N, 6.82.

2',3'-Di-*O*-(1,3-benzothiol-2-yl)uridine (6). To a solution of **5** (591 mg, 1 mmol) in dioxane (20 mL) were added with stirring 0.2 M sodium hydroxide solution (20 mL) and pyridine (10 mL). After being stirred at room temperature for 20 min, the mixture was neutralized with a mixture of 0.5 M hydrochloric acid (10 mL) and pyridine (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The residual solid was triturated with CH_2Cl_2, collected by filtration, washed with CH_2Cl_2 (50 mL), and dried over P_4O_{10} in dessicator to give **6** (513 mg, 88%): mp 164–166 °C; R_f 0.51 (CH_2Cl_2–MeOH, 9:1, v/v); ^1H NMR ($CDCl_3$–Me_2SO-d_6, 4:1, v/v) δ 3.54 (m, 2, 5'-H), 4.02 (m, 1, 4'-H), 4.32 (m, 2, 2',3'-H), 4.86 (br s, 1, OH), 5.59 (d, J = 8.4 Hz, 1, 5-H), 5.93 (d, J = 4 Hz, 1, 1'-H), 6.88 and 7.00 (s, 2, SCHS), 7.04–7.56 (m, 8 Ar H), 7.81 (d, J = 8.4 Hz, 1, 6-H).

Anal. Calcd for $C_{23}H_{20}N_2O_6S_4$: C, 50.35; H, 3.67; N, 5.10. Found: C, 50.01; H, 3.50; N, 5.10.

***S,S*-Diphenyl 2'-*O*-(1,3-Benzothiol-2-yl)-5'-*O*-(4,4'-dimethoxytrityl)uridine 3'-Phosphorodithioate (8).** To a solution of **3** (198 mg, 0.5 mmol) in dry pyridine (5 mL) was added 4,4'-dimethoxytrityl chloride (186 mg, 0.55 mmol). The solution was kept at room temperature. After 4 h and 6 h, additional amounts of 4,4'-dimethoxytrityl chloride (34 mg, 0.1 mmol) were added, resp. The mixture was stirred for 9 h, when the reaction was completed. To the mixture was added a solution of PSS (267 mg, 0.7 mmol) and MDS (222 mg, 0.7 mmol) in dry pyridine (2 mL), which had been stirred for 15 min. The resulting mixture was concentrated in vacuo to ca. 3 mL and stirred for 1 h. Then the mixture was extracted with CH_2Cl_2 (50 mL) and washed with 5% $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL). The CH_2Cl_2 extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The residue containing traces of pyridine was dissolved in CH_2Cl_2–hexane (5:1, v/v, 20 mL) and applied to a column of silic gel (20 g). elution with CH_2Cl_2 containing 1% pyridine gave **8** (342 mg, 71%): R_f 0.80 (CH_2Cl_2–MeOH, 9:1, v/v); ^1H NMR ($CDCl_3$) δ 3.30 (m, 2, 5'-H), 3.80 (s, 6, OCH_3), 4.06 (m, 1, 4'-H), 4.46 (t, J = 6 Hz, 1, 2'-H), 5.18 (m, 1, 3'-H), 5.37 (d, J = 8 Hz, 1, 5-H), 6.09 (d, J = 6 Hz, 1, 1'-H), 6.86 (d, J = 9.2 Hz, 4, Ar H), 6.90–7.75 (m, 24, Ar H and 6-H), 7.07 (s, 1, SCHS), 9.16 (br s, 1, NH).

Anal. Calcd for $C_{49}H_{43}N_4O_9S_4P$: C, 61.11; H, 4.50; N, 2.91. Found: C, 61.15; H, 4.63; N, 2.89.

Synthesis of 10. Method A. Compound **8** (347 mg, 0.36 mmol) was dissolved in a mixture of triethylamine–pyridine–water (1:2:1, v/v/v, 14.4 mL) and the solution was kept at room temperature. The reaction was monitored on TLC. After 5 h, TLC showed that **8** was completely converted to the diester **9** [R_f 0.15 (CH_2Cl_2–MeOH, 9:1, v/v)]. Evaportion of the solvents in vacuo gave a mixture of **9** and thiophenol. This was mixed with **6** (165 mg, 0.3 mmol) and 3-nitro-1,2,4-triazole (123 mg, 1.08 mmol). The resulting mixture was coevaporated with dry pyridine (3 × 5 mL) and dissolved in dry pyridine (2 mL). MDS (343 mg, 1.08 mmol) was added and the mixture was stirred for 20 min. Ice (0.5 g) was added. After the usual workup, chromatography on a column of silica gel (12 g) with CH_2Cl_2–MeOH (99:1, v/v) containing 1% pyridine gave **10** (322 mg, 76%): R_f of 0.62 (CH_2Cl_2–MeOH, 9:1, v/v).

Method B. Compound **8** (212 mg, 0.22 mmol) was dissolved in a mixture of 5 M phosphinic acid in pyridine (2.2 mL) and triethylamine (1.1 mL, 7.86 mmol). The mixture was kept at room temperature for 15 min, when the deprotection of one phenylthio group from **8** was complete. Then the mixture was diluted with CH_2Cl_2 (30 mL) and washed with water (20 mL) and 0.2 M triethylammonium bicarbonate (3 × 20 mL). Each washing was extracted with CH_2Cl_2 (20 mL) in another separatory funnel. The two CH_2Cl_2 extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The resulting residue was mixed with **6** (117 mg, 0.2 mmol) and 3-nitro-1,2,4-triazole (46 mg, 0.4 mmol) and coevaporated with dry pyridine (3 × 5 mL). The mixture was dissolved in dry pyridine (5 mL) and MDS (127 mg, 0.4 mmol). After the mixture was stirred for 1 h, the same workup as described before gave **10** (219 mg, 80%).

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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.

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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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