resultant pasty residue was dissolved in CH_2Cl_2 (12.5 mL) containing CF_3CO_2H (3 mL, ~2 equiv) and the solution set aside at room temperature overnight. After concentration in vacuo and column chromatography (CH_2Cl_2–EtOAc, 1:1), diastereomeric bis-lactone **19a(R,S)** (3.42 g, 71%) was obtained as an oil: TLC ($CHCl_3$–EtOAc, 1:1) R_f 0.26; ^1H NMR ($CDCl_3$) δ 4.76 (ddd, J = 8.2, 5.4, and 2.0 Hz, H-4′$_A$), 4.68–4.52 (m, H-4′$_B$, H-2$_A$, H-4$_B$), 4.27 (q, J = 7.1 Hz, CH_2 ester$_B$), 4.25 (4, J = 7.1 Hz, CH_2 ester$_A$), 3.78 (dd, J = 9.8 and 7.1 Hz, 1 H, H-2′$_A$), 3.72 (t, J = 10.1 Hz, H-2′$_B$), 2.9–2.1 (m, H-2α,β, H-3α,β, H-3′α,β_{A+B}), 1.29 (t, J = 7.1 Hz, CH_3 ester$_{A+B}$); ^{13}C NMR ($CDCl_3$) δ 177.1 (C-1), 172.2 and 171.8 (C-1′), 168.45 and 167.9 (CO ester), 80.6, 79.9, 79.8, and 79.7 (C-4, C-4′), 63.1 (CH_2 ester), 47.2 and 46.8 (C-2′), 29.05, 28.6, and 28.2 (C-2, C-3′), 24.4 (C-3), 14.8 (CH_3 ester).

(*S,S*)-Tetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione (18a). The foregoing product **19a(R,S)** (2.42 g, 0,010 mol), dissolved in *N,N*-dimethylacetamide (30 mL), containing $MgCl_2 \cdot 6H_2O$ (10.15 g, 0.050 mol) and water (3 drops), was heated under reflux (137 °C) with stirring for 7 h. Most of the solvent was distilled in vacuo (80 °C, 0.5 mm), and the residue was treated with water (40 mL). The aqueous phase was exhaustively extracted with $CHCl_3$–EtOAc (1:2, 4 × 75 mL), and the combined extracts were evaporated in vacuo. Column chromatography (EtOAc) of the residue yielded pure, crystalline bis-γ-lactone **18a** (1.33 g, 78%): TLC (EtOAc) R_f 0.33. Analytical material was obtained by recrystallization from ethyl acetate–diisopropyl ether, 2:1: mp 78–79 °C; $[\alpha]^{20}_D$ +82° (*c* 1.78, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.60 (5-peak multiplet, width 16.5 Hz, 2 H, H-4), 2.8–2.5 (m, 4 H, H-2), 2.5–2.15 (m, 4 H, H-3); ^{13}C NMR ($CDCl_3$) δ 177.2 (C-1), 80.8 (C-4), 28.6 (C-2), 24.4 (C-3). Anal. Calcd for $C_8H_{10}O_4$ (MW 170.16): C, 56.47; H, 5.92. Found: C, 56.4; H, 5.8.

(2*R*,2′*S*)-4(*R,S*)-Carbethoxytetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione [19b(R,S)]. Diastereomers **19b(R,S)** were prepared from epoxide **6b** (0.701 g, 0.005 mol) as described for **19a(R,S)** (vide supra) to afford, after chromatography ($CHCl_3$–EtOAc, 1:1, R_f 0.33), a solid 1:1 mixture of diastereomers (0.813 g, 67%): ^1H NMR ($CDCl_3$) δ 4.8–4.6 (m, H-4$_{A,B}$, H-4′$_{A,B}$), 4.28 (q, J = 7.1 Hz, CH_2 ester$_B$), 4.26 (q, J = 7.1 Hz, CH_2 ester$_A$) 3.73 (t, J = 9.9 Hz, H-2′$_B$), 3.7 (dd, J = 9.8 and 5.9 Hz, H-2′$_A$), 2.8–2.0 (m, H-2α,β, H-3α,β, H-3′α,$\beta_{A,B}$), 1.33 (t, J = 7.1 Hz, CH_3 ester$_B$), 1.31 (t, J = 7.1 Hz, CH_3 ester$_A$); ^{13}C NMR ($CDCl_3$) δ 177.0 and 176.85 (C-1), 171.9 (C-1′), 168.2 (CO ester), 80.3, 79.9, and 79.2 (C-4, C-4′), 63.2 (CH_2 ester), 47.1 and 47.0 (C-2′), 28.6, 28.5, 28.4, and 27.7 (C-2 and C-3′), 24.0 and 23.5 (C-3), 14.8 (CH_3 ester).

***meso*-Tetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione (18b).** The diastereomer mixture **19b(R,S)** (0.605 g, 0.0025 mol) was decarboxylated as described for **19a(R,S)** (vide supra). Column chromatography with a gradient elution (CH_2Cl_2–EtOAc, 1:1, to EtOAc) afforded pure **18b** (0.315 g, 75%): TLC ($CHCl_3$–EtOAc, 1:1) R_f 0.39. Recrystallization from ethyl acetate–diisopropyl ether gave analytically pure material: mp 104–105 °C (lit.[25] mp 105 °C); $[\alpha]^{20}_D$ 0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.58 (11-peak multiplet, width 21 Hz, 2 H, H-4), 2.7–2.55 (m, 2 H, H-2), 2.55–2.3 (m, 2 H, H-3α), 2.2–2.0 (m, 2 H, H-3β); ^{13}C NMR ($CDCl_3$) δ 176.9 (C-1), 80.4 (C-4), 28.4 (C-2), 23.3 (C-3).

(2*R*,2′*R*)-4(*R,S*)-Carbethoxytetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione [19c(R,S)]. The epoxy butanolide **6c** (2.56 g, 0.020 mol) was converted into the title compounds in the manner described for the preparation of **19a(R,S)**. The product was a diastereomeric mixture (1:1), 3.24 g (70%), featuring the same R_f value and ^1H and ^{13}C NMR spectra as described for **19a(R,S)**.

(*R,R*′)-Tetrahydro[2,2′-bifuran]-5,5′(2*H*,2′*H*)-dione (18c). Decarboxylation of the diastereomers **19c(R,S)** (2.42 g, 0.010 mol) by the procedure described for the preparation of enantiomer **18a** afforded white, crystalline compound **18c** (1.23 g, 73%): TLC (EtOAc) R_f 0.34; mp 78–79 °C; $[\alpha]^{20}_D$ −81° (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_8H_{10}O_4$ (MW 170.16): C, 56.47; H, 5.92. Found: C, 56.3; H, 6.0.

Cleavage of 2-Quinolinylmethyl Ethers with Copper Salts: Potential Use as a Protecting Group for Alcohols

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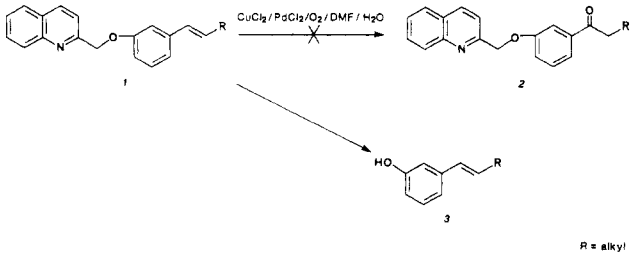
Received February 27, 1990

A variety of 2-quinolinylmethyl ethers were efficiently cleaved by $CuCl_2$ in DMF/H_2O to regenerate the corresponding alcohols. The same cleavage also takes place with the 4-regioisomer. On the other hand, the 2- and 4-pyridinylmethyl analogues were found to be stable under these reaction conditions. A mechanistic scheme for this cleavage is proposed.

In the last decades, the advent of many protecting groups[1] for alcohols have given the synthetic organic chemists important tools in the elaboration of complex molecules. Among these protecting groups, the benzyl group has found much use since it is easily introduced and can be removed under various conditions.[1] Surprisingly, there are only a few reports on the use of the pyridinylmethyl group[2,3] and none to our knowledge on the quinolinylmethyl group, although they are direct analogues of the benzyl group. Both pyridinylmethyl and quinolinylmethyl ethers, like benzyl ethers, can be prepared through the Williamson synthesis.[2,3] The methods published on the deprotection of pyridinylmethyl ethers involve electrolysis[2,3] or hydrogenolysis under acidic conditions.[2]

Scheme I

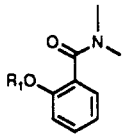
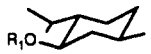
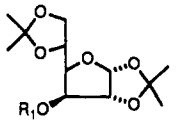
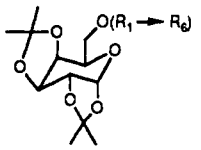


As part of our ongoing LTD_4 antagonists drug program, we became interested in the synthesis of ketones having the general structure **2** (Scheme I). It was envisaged that these ketones could be derived from the available styrenes

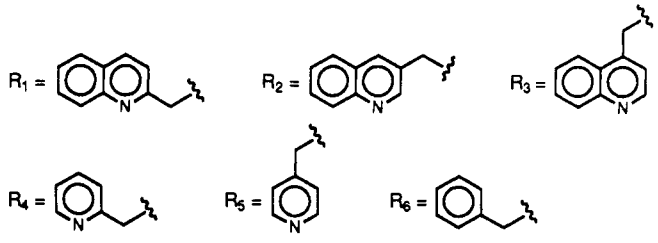
(1) Green, T. W. In *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; Chapter 2.
(2) Rizo, J.; Albericio, F.; Romero, G.; Garcia-Echeverria, C.; Claret, J.; Muller, C.; Giralt, E.; Pedreso, E. *J. Org. Chem.* **1988**, *53*, 5389–5390.
(3) Wieditz, S.; Schafer, H. J. *Acta Chem. Scand.* **1983**, *6*, 475–483.

0022-3263/90/1955-5344$02.50/0

Table I

ether (yield of etherification, %)	alcohol (deprotection yield, %)
$R_1O(CH_2)_{11}CH_3$ **4** (99)[a]	**15** (73)[h]
$R_1O(CH_2)_2C{\equiv}C(CH_2)_4OTHP$ **5** (85)[a]	**16** (<5) and DIOL (64)[h]
 **6** (80)[b]	**17** (74)[i]
 **7** (78)[a]	**18** (71)[i]
 **8** (85)[a]	**19** (65 → 70)[k]
 **9** R_1 (98)[a], **10** R_2 (70)[c], **11** R_3 (71)[d], **12** R_4 (90)[e], **13** R_5 (74)[f], **14** R_6 (89)[g]	**20** (75[h] from **9**) (80%) from **11**) (0% from **10**, **12**, **13**, and **14**)

[a] Alcohol, KH, THF, 0 °C, then 2-(chloromethyl)quinoline 0 °C → room temperature. [b] Phenol, K_2CO_3, DMF, then 2-(chloromethyl)quinoline, 70 °C. [c] As in footnote *a*, then 3-(methanesulfonyloxymethyl)quinoline. [d] As in footnote *a*, then 4-(methanesulfonyloxymethyl)quinoline. [e] As in footnote *a*, then freshly prepared 2-(chloromethyl)pyridine. [f] As in footnote *a*, then freshly prepared 4-(chloromethyl)pyridine. [g] As in footnote *a*, then benzyl chloride. [h] $CuCl_2{\cdot}2H_2O$ 1.5 equiv, DMF–H_2O (4/1), 65 °C, in air, 18 h. [i] $CuCl_2{\cdot}2H_2O$ 1.5 equiv, DMF–H_2O (4/1) 65 °C, in air, 18 h. [j] $CuCl_2{\cdot}2H_2O$ 5 equiv, DMF–H_2O (4/1), 65 °C, in air, 18 h. [k] $CuCl_2{\cdot}2H_2O$ 3 equiv, Et_3N 3 equiv, DMF–H_2O (4/1), 65 °C, in air.

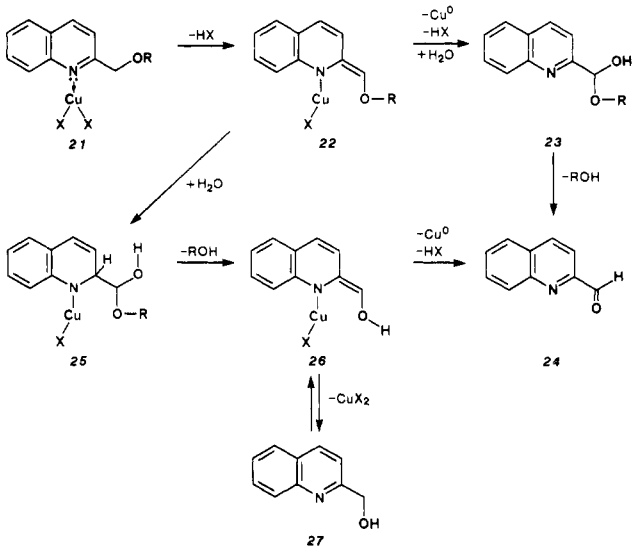


1. To this end, the Wacker reaction[4] was attempted ($PdCl_2/CuCl_2/DMF/H_2O/O_2$, 65 °C) but resulted in the cleavage of the ether bond to produce the phenol **3** rather than the desired ketone. It was reasoned that the cleavage of the ether bond was induced by a complexation of the quinoline nitrogen with the copper.[5] Following this result, a series of 2-quinolinylmethyl ethers were prepared and attempts were made to regenerate the alcohols in order to investigate the generality of the reaction.

Our study started with the synthesis of 2-quinolinylmethyl ethers (**4**–**9**, Table I) by condensation of the alkoxides generated from the corresponding alcohols **15**–**20** (KH, THF, 0 °C and K_2CO_3/DMF for **17**) on 2-(chloromethyl)quinoline as the free base. These ethers were then submitted to various cleavage conditions, and it was found that the alcohols could be regenerated in moderate to good yields by the use of $CuCl_2{\cdot}2H_2O$ (1.5 equiv) in DMF/H_2O (4/1) at 65 °C for 18 h in air.[6] As a control experiment, the benzyl ether analogue **14** was prepared and subjected to the same conditions. In this case, no alcohol was detected after 18 h. The cleavage of the ether bond therefore appears to be related to the presence of the quinoline nitrogen.

In order to assess if these conditions could be used to regenerate the alcohols from 2-pyridinylmethyl ethers, the ether **12** was prepared and placed under the cleavage conditions described. To our surprise, no alcohol was formed after 18 h at 65 °C in DMF/H_2O and even after several hours at 80°C. It is noteworthy that the cleavage reaction took place just as efficiently with the 4-quinolinylmethyl ether **11**[7] as with the 2-isomer **9**, but under these conditions the 3-quinolinylmethyl ether **10** did not undergo cleavage. From these results and further investigations, a mechanistic scheme was proposed to rationalize this difference in reactivity between 2-quinolinylmethyl and 2-pyridinylmethyl ethers toward $CuCl_2$.

Scheme II



Mechanistic Considerations

In all cases of the 2-quinolinylmethyl ether cleavage mediated by $CuCl_2$, the quinoline part of the molecule was isolated as 2-quinoline-carboxaldehyde (**24**) (Scheme II). However, since only 20–30% of the aldehyde was recovered from the reaction mixture and since 2-(hydroxymethyl)-quinoline (**27**) was found to be partially oxidized to the aldehyde **24** in the presence of $Cucl_2{\cdot}2H_2O$ in air, the suggestion of a mechanistic scheme is hazardous.[8] The

(4) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlemeier, J.; Sabel. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 80–88.

(5) Corey had observed that the hydrolysis of 8-(carbamoyloxy)-quinoline is accelerated by copper salts. See his proposal for the protection of the amino group: Corey E. J.; Dawson, R. C. *J. Am. Chem. Soc.* **1962**, *84*, 4899–4904.

(6) No advantages were found in using other copper salts such as $Cu(OTf)_2$ or $Cu(OTs)_2$ or other solvents such as acetone. Better results are obtained when the reaction are conducted in air rather than under nitrogen.

(7) The reaction with the 4-isomer **11** was only slightly slower than with the 2-isomer **9**.

(8) Several attempts were made to account for the quinoline portion (displacement of a putative quinoline–copper complex by ammonia gas, ethylenediamine, H_2S), and only the aldehyde **24** has been isolated. In the cases where the reactions were conducted under nitrogen only traces of aldehyde were detected. In some of these instances, insoluble materials were isolated, presumably copper complexes, which are currently being characterized.

differences in reactivity between 2-quinolinylmethyl ethers and the 2-pyridinylmethyl ether **12**[9], as well as the stability of the 3-quinolinylmethyl ether, nevertheless give some indication on how the ether cleavage could proceed.

A possible interpretation of these results is depicted in Scheme II. The observed 2- and 4-isomer specificity suggested that a dearomatization could be involved in the process. Once a complex such as **21** is formed (Scheme II), the enamine **22** may be generated and subsequently converted via a reductive elimination and hydration to the hemiacetal **23**,[10] which in turn would hydrolyze to liberate the alcohol and 2-quinolinecarboxaldehyde (**24**). Alternatively, the enamine **22** could be hydrated first to give the hemiacetal **25**, from which the alcohol may be liberated producing the enamine **26**. Subsequently, the enamine **26** could lead to 2-quinolinecarboxaldehyde (**24**) or to 2-(hydroxymethyl)quinoline (**27**). According to this reaction pathway,[11] which is also applicable to the 4-isomer, it is likely that the rate-limiting step of the reaction would be the formation of the enamine **22**. This would nicely rationalize why 2- and 4-pyridinylmethyl ethers are inert to the condition of deprotection used for 2- and 4-quinolinylmethyl ethers, since the former would involve a complete loss of aromaticity.

In summary, it has been demonstrated that 2- and 4-quinolinylmethyl ethers are cleaved by copper salts to regenerate the corresponding alcohol. Therefore, in some circumstances, 2- and 4-quinolinylmethyl groups can be used as an alternative to the benzyl protecting group. These quinolinylmethyl groups could be used on molecules that have functionalities sensitive to hydrogenolysis or dissolving metal reduction. We also believe that the deprotection conditions developed herein could be useful for other synthetic applications.

Experimental Section

NMR spectra were recorded on a Bruker AM 250 (250 MHz) spectrometer. Numbers in the spectral assignments refer to carbohydrate numbering system. 2-(Chloromethyl)quinoline hydrochloride, 3- and 4-quinoline carboxyaldehyde, and 2- and 4-picolyl chloride hydrochloride were purchased from Aldrich Chemical Co.

Typical Procedure for the Preparation of 2-Quinolinylmethyl Ethers (4, 5, 7–9), 2-Pyridinylmethyl Ether (12), and 4-Pyridinylmethyl Ether (13). 1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(2-quinolinylmethyl)-α-D-galactopyranose (9). To a suspension of KH (35% in oil) (1.14 g, 10.0 mmol) in THF (7.2 mL) at 0 °C under nitrogen was added diacetonide D-galactose (2.00 g, 7.70 mmol) in THF (3.6 mL). 2-(Chloromethyl)quinoline free base (2.05 g, 11.5 mmol) was then added to the reaction mixture. The resulting mixture was stirred at 0 °C for ≈10 min and allowed to warm up to room temperature. After TLC (40% ethyl acetate in hexane) showed completion of the reaction (≈$^1/_2$ h), a 25% ammonium acetate (40 mL)–ethyl acetate extractive workup was performed. Flash chromatography (20% ethyl acetate in hexane) of the crude mixture afforded the desired ether (3.03 g, 7.50 mmol, 98%) as a yellow oil: $[\alpha]^{22}_D$ −66.1° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, acetone-d_6) δ 1.29, 1.31, 1.34, and 1.48 (4 s, 12 H, 2 $(CH_3)_2C$), 3.72 (2 AB, 2 H, $J_{6,6}$ = 10.2 Hz, H-6 and H-6′), 4.08 (dt, 1 H, $J_{5,6}$ = 5.3 Hz, H-5), 4.31–4.36 (m, 2 H, H-2 and H-4), 4.63 (dd, 1 H, $J_{3,2}$ = 8.0, $J_{3,4}$ = 2.3 Hz, H-3) 4.80 (AB, 1 H, *J* = 15.8 Hz, CH_2O), 5.48 (d, 1 H, $J_{1,2}$ = 5.0 Hz, H-1), 7.55, 7.66, 7.71, 7.95, and 8.13 (6 H, aromatic); high-resolution mass spectrum, *m/z* calculated for $C_{22}H_{28}NO_6$ $(M + H)^+$ 402.1916, found 402.1913.

1,2:5,6-Bis-*O*-(1-methylethylidene)-3-*O*-(2-quinolinylmethyl)-α-D-glucofuranose (8): $[\alpha]^{22}_D$ −33.2° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, acetone-d_6) δ 1.41, 1.30, 1.33, and 1.41 (4 s, 12 H, 2 $(CH_3)_3C$), 3.90 (dd, 1 H, *J* = 5.8 and 8.7 Hz, H-6), 4.05–4.17 (m, 3 H, H-6, H-3, and H-4), 4.41 (m, 1 H, H-5), 4.84 (d, 1 H, $J_{2,1}$ = 3.6 Hz, H-2), 4.93 (AB, 2 H, *J* = 13.2 Hz, CH_2O), 5.92 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 7.56, 7.70, 7.96, and 8.36 (6 H, aromatic). Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65,84; H, 6,73; N, 3.49. Found: C, 65,51; H, 7.90; N, 3.47.

1-(2-Quinolinylmethoxy)dodecane (4): ^1H NMR (250 MHz, acetone-d_6) δ 0.83 (t, 3 H, *J* = 8.2 Hz), 1.21–1.55 (m, 20 H), 1.65 (quintet, 2 H, *J* = 8.2 Hz), 3.58 (*t*, 2 H, *J* = 8.2 Hz, OCH_2), 4.76 (s, 2 H, CH_2O), 7.53, 7.63, 7.71, 7.95, and 8.33 (6 H, aromatic). Anal. Calcd for $C_{22}H_{33}NO$: C, 80.73; H, 10.09; N, 4.28. Found: C, 80.42; H, 10.00; N, 4.42.

(1*R*-(1α-2β,5α))-2-(((5-Methyl-2-(1-methylethyl)cyclohexyl)oxy)methyl)quinoline (7): $[\alpha]^{22}_D$ −82.6° (*c* 0.8, acetone); ^1H NMR (250 MHz, acetone-d_6) δ 0.73 and 0.74 (d, 3 H, *J* = 7.4 Hz, CH_3), 0.88, 0.91, and 0.94 (t, 6 H, *J* = 7.0 Hz, 2 CH_3), 0.84–1.06 (m, 3 H), 1.27–1.36 (m, 2 H), 1.60–1.70 (m, 2 H), 2.26–2.38 (m, 2 H), 3.32 (dt, 1 H *J* = 4.1 and 10.5 Hz, CHO), 4.77 (AB, 2 H, *J* = 13.1 Hz, OCH_2), 7.55, 7.65, 7.69, 7.91, 7.98, and 8.30 (6 H, aromatic); high-resolution mass spectrum, *m/z* calculated for $C_{20}H_{28}NO$ $(M + H)^+$ 298.2172, found 298.2171.

1-(2-Quinolinylmethoxy)-7-[(2-tetrahydropyranyl)oxy]-3-heptyne (5): ^1H MR (250 MHz, acetone-d_6) δ 1.38–1.83 (m, 5 H), 1.20 (m, 2 H), 1.50 (m, 2 H), 3.25–3.50 (m, 2 H), 3.61–3.83 (m, 4 H), 4.53 (br t, 1 H), 4.76 (s, 2 H, OCH_2), 7.55, 7.68, 7.75, 7.96, and 8.33 (6 H, aromatic). Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.20; H, 7.90; N, 3.81. Found: C, 74.87; H, 7.99; N, 3.85.

1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(4-pyridinylmethyl)-α-D-galactopyranose (13): ^1H NMR (250 MHz, acetone-d_6) δ 1.30, 1.33, and 1.43 (3 s, 12 H, 2 $(CH_3)_2C$), 3.55 and 3.71 (2 m, 2 H, H-6 and H-6′), 4.05 (br t, 1 H, *J* = 7.5 Hz, H-5), 4.33 (m, 2 H, H-2 and H-4), 4.58 (m, 3 H, H-3 and OCH_2), 5.48 (d, 1 H, $J_{1,2}$ = 5.3 Hz, H-1), 7.33 and 8.53 (4 H, aromatic); high-resolution mass spectrum, *m/z* calculated for $C_{18}H_{26}NO_6$ $(M + H)^+$ 352.1760, found 352.1759.

1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(2-pyridinylmethyl)-α-D-galactopyranose (12): ^1H NMR (250 MHz, acetone-d_6) δ 1.31, 1.35, and 1.48 (3 s, 12 H, 2 $(CH_3)_2C$), 3.63 (2 AB, 2 H, $J_{6,6}$ = 10.8 Hz, H-6 and H-6′), 4.05 (m, 1 H, H-5), 4.33 (m, 2 H, H-2 and H-4), 4.58 (m, 3 H, H-3 and OCH_2), 5.45 (d, 1 H, $J_{1,2}$ − 7.0 Hz, H-1), 7.23, 7.48, 7.76, and 8.45 (4 H, aromatic). Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.54; H, 7.12; N, 3.99. Found: C, 61.36; H, 6.81; N, 3.68.

***N,N*-Dimethyl-2-(2-quinolinylmethoxy)benzamide (6).** To a solution of the phenol **17** (500 mg, 3.03 mmol) in DMF (3.0 mL) was added the 2-(chloromethyl)quinoline (647 mg, 3.60 mmol) followed by K_2CO_3 (969 mg, 7.02 mmol). The resulting mixture was then stirred under nitrogen at 70 °C until TLC (50% ethyl acetate in hexane) showed completion of the reaction. A 25% ammonium acetate–ethyl acetate extractive work up was performed. Flash chromatography (50% ethyl acetate in hexane) of the crude mixture afforded the title compound **6** (736 mg, 80%): mp 104 °C (ether); ^1H NMR (250 MHz, $CDCl_3$) δ 1,88 and 2.13 (2 s, 6 H, 2 CH_3), 5.41 (s, 2 H, OCH_2), 6.95, 7.25, 7.53, 7.65, 7.73, 7.80, 8.08, and 8.20 (10 H, aromatic); high-resolution mass spectrum, *m/z* calculated for $C_{19}H_{19}N_2O_2(M + H)^+$ 307.1446, found 307.1448.

Preparation of 3-(((Methylsulfonyl)oxy)methyl)quinoline. To a solution of 3-quinolinecarboxaldehyde (3.00 g, 19.1 mmol) in absolute ethanol (100 mL) at 0 °C was slowly added $NaBH_4$ (799 mg, 21.2 mmol) under nitrogen. After no aldehyde was detected by TLC (50% ethyl acetate in hexane), a 25% solution of ammonium acetate–ethyl acetate extractive workup was performed. Flash chromatography (30% ethyl acetae in hexane) of the crude mixture afforded the desired alcohol (3.01 g, 99%). A solution of this alcohol (500 mg, 3.14 mmol) in THF (15.0 mL) at −78 °C was then treated with Et_3N (960 μL, 6.91 mmol) and MsCl (291 μL, 3.77 mmol). The resulting mixture was stirred at −78 °C for 10 min and then allowed to warm to 25 °C. After TLC

(9) The 4-pyridinylmethyl ether **13** was also found to be stable to the cleavage conditions.

(10) The cleavage reaction of substrate **9** with 0.5 equiv of $CuCl_2$ in air or with 1.05 equiv under nitrogen was carried out almost to completion (by TLC). On the other hand, when the reaction was conducted with 0.5 equiv of $CuCl_2$ under N_2, the cleavage did not go to completion. These results combined with the finding that only traces of aldehyde were detected in the reaction performed under nitrogen suggest that an inert copper complex is formed under nitrogen (ref 8).

(11) The cleavage reaction, under air, was not inhibited by BHT (1.5 equiv), therefore a radical chain mechanism is unlikely.

(70% ethyl acetate in hexane) showed no alcohol left, a 25% ammonium acetate, ethyl acetate extractive workup was performed. Flash chromatography (70% ethyl acetate in hexane) gave the mesylate compound (580 mg, 78%), which was stored at −78 °C until used: ^{1}H NMR (250 MHz, acetone-d_6) δ 3.23 (3 H, OSO_2Me), 5.33 (s, 2 H, OCH_2), 7.66, 7.83, 8.05, 8.06, 8.43, and 9.00 (6 H, aromatic); high-resolution mass spectrum, m/z calculated for $C_{11}H_{12}NO_3S$ $(M + H)^+$ 238.0538, found 238.0538.

4-(((Methylsulfonyl)oxy)methyl)quinoline: ^{1}H NMR (250 MHz, acetone-d_6) δ 3.23 (s, 3 H, SO_2Me), 5.83 (s, 2 H, OCH_2), 7.63, 7.70, 7.83, 8.12, and 8.96 (6 H, aromatic); high-resolution mass spectrum, m/z calculated for $C_{11}H_{12}NO_3S$ $(M + H)^+$ 238.0538, found 238.0538.

1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(3-quinolinylmethyl)-α-D-galactopyranose (10). To a suspension of KH (35% in oil) (40 mg, 0.350 mmol) in THF (350 mL) at 0 °C was added to a solution of diacetonide To this mixture was added a solution of 3-(((methylsulfonyl)oxy)methyl)quinoline (100 mg, 0.40 mmol) in THF (250 μL). The temperature was then raised to room temperature to give a dark solution afer few hours. A 25% ammonium acetate–ethyl acetate extractive workup was performed. Flash chromatography (50% ethyl acetate in hexane) of the crude mixture afforded the desired ether **10** (90 mg, 80%) as an oil: $[\alpha]^{22}_D$ −61.8° (*c* 1.6, acetone); ^{1}H NMR (250 MHz, acetone-d_6) δ 1.30, 1.31, 1.36, and 1.48 (4 s, 12 H, 2 $(CH_3)_2C$), 4.60 and 4.75 (2 m, 2 H, H-6 and H-6'), 4.06 (5, 1 H, J = 5.4 Hz, H-5), 4.31 (m, 2 H, H-2 and H-4), 4.63 (dd, 1 H, $J_{3,2}$ = 8.0 Hz, $J_{2,3}$ = 2.3 Hz, H-3), 4.78 (AB, 2 H, J = 12.4 Hz, OCH_2), 5.50 (d, 1 H, $J_{1,2}$ = 6.0 Hz), 7.58, 7.63, 7.95, 8.03, 8.23, and 8.91 (6 H, aromatic); high-resolution mass spectrum, m/z calculated for $C_{22}H_{28}NO_6$(M + H)$^+$ 402.1917, found 402.1917.

1,2:3,4-Bis-*O*-(1-methylethylidene)-6-*O*-(4-quinolinylmethyl)-α-D-galactopyranose (11): $[\alpha]^{22}_D$ −65.6° (*c* 1, acetone); ^{1}H NMR (250 MHz, acetone-d_6) δ 1.32, 1.33, 1.38, and 1.48 (4 s, 12 H, 2 $(CH_3)_2C$), 3.80 (AB, 2 H, $J_{6,6}$ = 10.4 Hz, H-6 and H-6'), 4.11 (5, 1 H, J = 8.3 Hz, H-5) 4.28–4.38 (m, 2 H, H-2 and H-4), 4.63 (dd, 1 H, J = 3.1 and 8.2 Hz, H-3), 5.11 (AB, 2 H, J = 12.8 Hz, CH_2), 7.55, 7.60, 7.71, 8.05, 8.13, and 8.85 (6 H, aromatic); high-resolution mass spectrum, m/z calculated for $C_{22}H_{28}NO_6$ (M + H)$^+$ 402.1917, found 402.1917.

Typical Procedure for the Cleavage of 2-Quinolinylmethyl Ethers by $CuCl_2 \cdot 2H_2O$. Regeneration of 1,2:3,4-Di-*O*-isopropylidene-D-galactopyranose (20) from the Ether 9. To the ether **9** (3.5 g, 8.7 mmol) in DMF (22.0 mL) was added water (5.4 mL). To the resulting homogeneous mixture was then added $CuCl_2 \cdot 2H_2O$ (2.24 g, 13.0 mmol), and the resulting dark green solution was stirred at 65 °C in a flask closed by a septum through which a gauge no. 20 needle was introduced. After 18 h, the brown mixture was then poured in an aqueous solution of 25% ammonium acetate (100 mL), and then ethyl acetate (100 mL) was added. The organic phase was washed three times with aqueous 25% ammonium acetate (50 mL). The colored organic phase was then dried with Na_2SO_4 and evaporated under reduced pressure. Flash chromatography (30% to 50% ethyl acetate in hexane) of the residue afforded the desired alcohol **20** (1.7 g, 75%) showing a light brown coloration. To the alcohol dissolved in MeOH (40 mL) was added charcoal until a colorless solution was obtained, and after filtration on Celite, 1.5 g (70%) of pure alcohol **20** was isolated.

Acknowledgment. We wish to thank Marc Labelle for helpful suggestions in the preparation of this manuscript.

Supplementary Material Available: ^{1} NMR spectra for **6**, **7**, **9**–**13**, 3- and 4-(((methylsulfonyl)oxy)methyl)quinoline (9 pages). Ordering information given on any current masthead page.

Regiochemical Effects Associated with Nucleophilic Aromatic Substitutions by Bidentate Sulfur Nucleophiles

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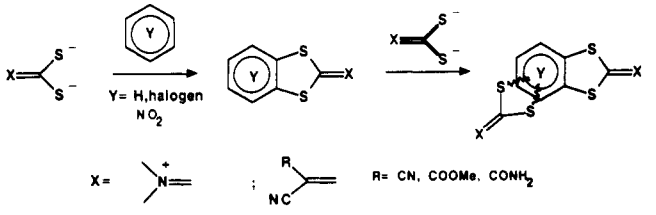
Received March 12, 1990

Aromatic nucleophic substitutions using 2,2-bis(methylthio)ethene 1,1-dithiolate **1** have been investigated. A possible control of the regiochemistry of the compounds resulting from the multiple substitution reactions by this ambident nucleophile have been examined. Starting from hexafluorobenzene, **2a**, containing two para fluorines, is obtained. When 2,3,4-trichloro-1,5-dinitrobenzene is reacted with **1**, leading to **8**, the observed regiochemistry of the two bidentate entering groups is completely modified. The regiochemical aspects of these processes are discussed.

The scope, mechanism, and synthetic utility of the nucleophilic aromatic substitution by thiolate anions RS^- have been extensively studied.[1–3] With rings containing more than one leaving group, an important well-documented[4] aspect concerns the orientations of these reactions. These effects determine the regiochemistry of (i) the compounds from multiple substitutions by a given thiolate anion and (ii) the isomeric thioethers from different thiolates used in consecutive substitutions. Several studies concerning these regiochemical problems have been reported;[5–7] they include the modifications of (i) the nature and the ring arrangements of the leaving groups[5,6] and (ii) the reactivity of the attacking nucleophile and/or the mechanism of the reaction.[7]

Scheme I



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0022-3263/90/1955-5347$02.50/0