°C (5.5 mm) [lit.[14] bp 93–96 °C (20 mm)]; ^{1}H NMR ($CDCl_3$) δ 0.67–2.88 (m, 7 H), 3.00–3.37 (m, 1 H), 4.04–4.31 (m, 1 H), 5.50–5.94 (m, 2 H).

***endo*-8-Bicyclo[3.3.0]-2-octenyl tosylate (17)** was prepared from **16** in the same manner as described for **11**: ^{1}H NMR ($CDCl_3$) δ 1.29–2.89 (m, 7 H, s, 3 H), 3.04–3.36 (m, 1 H), 4.69–5.00 (m, 1 H), 5.36–5.83 (m, 2 H), 7.55 (dd, 4 H).

***exo*-Bicyclo[3.3.0]-2-octen-8-ol (18)** was prepared as described by Fujita,[10] except that the acetate was not isolated. The tosylate **17** was allowed to react with tetraethylammonium acetate tetrahydrate in acetone for 24 h to yield *exo*-bicyclo[3.3.0]-2-octen-8-yl acetate. The acetate was then saponified in a solution of potassium hydroxide and methanol to yield **17**. From 3.7 g of **16** was obtained 1.6 g (43%) of **18**: bp 66–70 °C (3 mm); ^{1}H NMR ($CDCl_3$) δ 1.03–3.00 (m, 10 H), 3.89–3.97 (m, 1 H), 5.30–5.60 (m, 2 H).

***exo*-8-Bicyclo[3.3.0]-2-octenyl tosylate (19)** was prepared from **18** in the same manner as described for **11**: ^{1}H NMR ($CDCl_3$) δ 1.17–2.98 (m, 7 H), 2.41 (s, 3 H), 3.07–3.33 (m, 1 H), 4.57–4.92 (m, 1 H), 5.25–5.72 (m, 2 H), 7.52 (dd, 4 H).

General Procedure for Acetolysis Reactions. The tosylate and 2 equiv of anhydrous sodium acetate were dissolved in anhydrous glacial acetic acid, and nitrogen was bubbled through the solution for 5 min. The container was sealed, immersed in a thermostated oil bath at 95 ± 0.5 °C for 18 h, and then cooled in an ice bath. Ether and water were added to the solution, and the excess acetic acid was removed by washing with saturated sodium carbonate solution. The ethereal layer was washed with water and then dried over potassium carbonate. The products were analyzed by gas chromatography. Samples for structural analysis were obtained by preparative gas chromatography. The stereoisomeric 7-substituted acetates had identical reaction times. The acetate mixtures were then reduced to the alcohols with lithium aluminum hydride and the alcohols analyzed. Proton NMR spectroscopy was used to identify the acetolysis products.

Stability of Tosylates in Collidine. In a round-bottomed flask equipped with a reflux condenser, drying tube, and magnetic stirrer was placed a solution of the tosylate in collidine. The flask was immersed in a preheated oil bath at the prescribed temperature for 15–24 h, at which time either the reaction mixture was worked up or a 1-mL aliquot was removed for analysis and the remainder heated further at a higher temperature. The product isolations involved taking up the cooled mixture in ether, washing the ethereal solution with iced 10% sulfuric acid and water, and drying over magnesium sulfate. The products were analyzed by proton NMR spectroscopy.

Registry No. **1**, 5307-99-3; **2**, 13173-09-6; **3** (isomer 1), 75548-82-2; **3** (isomer 2), 75598-13-9; **4** (isomer 1), 75548-83-3; **4** (isomer 2), 75598-14-0; **5**, 32405-38-2; **6**, 53648-63-8; **7**, 53648-80-9; **8**, 75548-84-4; **9**, 53648-79-6; **10**, 75598-15-1; **11**, 75548-85-5; **12**, 75548-86-6; **13**, 75548-87-7; **14**, 75598-16-2; **15**, 6690-12-6; **16**, 41164-15-2; **17**, 40132-78-3; **18**, 10095-77-9; **19**, 40132-79-4; **20**, 17119-05-0; **21**, 32405-36-0; **22**, 75548-88-8; **23**, 75598-17-3; **24**, 40132-75-0; **25**, 41527-66-6; **26**, 41164-14-1; **27**, 75548-89-9; dichloroacetyl chloride, 79-36-7; cyclopentadiene, 542-92-7; trimethylsilyl cyanide, 7677-24-9; 1,3-cyclooctadiene, 1700-10-3.

Acylation of Monosubstituted Ferrocenes. Unusual Directive Effect of the Cyanomethyl Group

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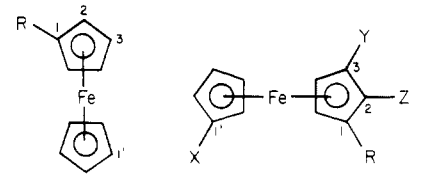
Ferrocenylacetonitrile (1) reacts with toluoyl chloride or acetic anhydride, under Friedel–Crafts conditions, to give largely heteroannular substitution (90% and 80%, respectively). By contrast, acylation reactions of methyl ferrocenylacetate (2) and methylferrocene (3) give mixtures of all three possible isomers with diminished regioselectivity and ca. 50% heteroannular substitution. ^{1}H and ^{13}C NMR data for ferrocene derivatives, which were used to characterize and/or quantitate the disubstituted ferrocenes in the isomeric mixtures, are reported.

Acyl ferrocenes, central intermediates for the preparation of ferrocene derivatives,[1,2] are generally available via the Friedel–Crafts ketone synthesis.[2] Acylation studies on substituted ferrocenes have defined some substituent directive effects.[2,3] Acyl, cyano, carbalkoxy, halo, and amido groups give almost exclusively heteroannular acylation, whereas alkyl and aryl groups give all possible isomers with a homoannular to heteroannular ratio around 1:1. Although the directive influence of simple alkyl groups on ferrocene acylation is known,[2,3] the influence of alkyl groups bearing polar residues has never been examined. This paper reports the unusually high regiochemical control of acylation caused by a cyanomethyl group.

Results and Discussion

Chemistry. In the course of synthetic work we found that acylation of ferrocenylacetonitrile (1) with *p*-toluoyl chloride and $AlCl_3$ affords an ca. 10:1 mixture of **6a** and **6b** (36–47% yield). Since this high regiocontrol of acylation by an alkyl group, giving almost exclusively heteroannular (i.e., 1,1′) product (**6a**), is unusual, we explored the toluoylation of methyl ferrocenylacetate (**2**) and methylferrocene (**3**). By contrast, **2** and **3** each gave a mixture of isomers corresponding to equal amounts of homoannular and heteroannular substitution.



1, R = CH_2CN
2, R = $CH_2CO_2CH_3$
3, R = CH_3
4, R = C_6H_5
5, R = $C(O)CH_3$
9, R = $C(O)C_6H_5$

6, R = CH_2CN
7, R = $CH_2CO_2CH_3$
8, R = CH_3
a, X = *p*-TolC(O), Y = Z = H
b, X = Z = H, Y = *p*-TolC(O)
c, X = Y = H, Z = *p*-TolC(O)

Our results for the toluoylation of **1–3** and acetylation of **3** are presented in Table I, along with selected reactions

(1) Rosenblum, M. "Chemistry of the Iron Group Metallocenes: Ferrocene, Ruthenocene, and Osmocene", Part 1; Interscience: New York, 1965; pp 146–148.
(2) (a) Reference 1, Chapter 4. (b) Rinehart, K. L., Jr. *Org. React.* **1969**, *19*, 1.
(3) (a) Peet, J. H.; Rockett, B. W. *Rev. Pure Appl. Chem.* **1972**, *22*, 145. (b) Slocum, D. W.; Ernst, C. R. *Organomet. Chem. Rev. A* **1970**, *6*, 337.

0022-3263/81/1946-0070$01.00/0

Table I. Isomer Distribution for Acylation Reactions

entry	compd	acylation product[a] 2	3	1′	reacn	% yield[b]	ref
1	1[c]	0	1	10.4[d]	e	36	this work
2	2[c]	1.5	1	2.5	e	76	this work
3	3[c]	1	2	2.6	e	63	this work
4	3	1	2.2	2.7	f	67	4a,b
5	4	1	1.3	4.1	f		4a,b
6	1[c]	0	1	4.8[g]	h	31	this work
7	3	1	1.4	2.2	h	73	4b,c
8	4	1.6	1	2.1	h		3a
9	5	1	0	60	i		5

[a] Relative amounts of once-acylated products. [b] Total yield of isomeric acylation products for 1–3. Method A results. [c] The composition of the product mixture was determined by ^{1}H NMR integration of the distinct resonances for the protons of the alkyl substituent (ref 4b, 6) and by GLC analysis. [d] Average of ^{1}H NMR value (9) and GLC value (11.7). [e] p-$CH_3C_6H_4C(O)Cl/AlCl_3$. [f] $C_6H_5C(O)Cl/AlCl_3$. [g] Average of ^{1}H NMR value (4.5) and GLC value (5.0). [h] $[CH_3C(O)]_2O/BF_3 \cdot Et_2O$. [i] $CH_3C(O)Cl/AlCl_3$.

from the literature for comparison.[4,5] The cyanomethyl group provides stronger regiocontrol for heteroannular substitution [ca. 90% for aroylation (entry 1) and ca. 80% for acetylation (entry 6)] than methyl [50% (entry 3) and 27% (entry 7)] and phenyl [64% (entry 5) and 45% (entry 8)] groups provide, but less control than an acetyl [98.5% for acetylation (entry 9)] group provides.

Compared to 3,[4b,e] nitrile 1 failed to undergo formylation under Vilsmeier conditions (no Lewis acid present), suggesting an intrinsic deactivation of the ferrocene nucleus in 1 to electrophilic attack. Toluoylation and acetylation reactions with 1 proceeded in lower yields than the same reactions with 3 (unreacted 1 was prevalent), again indicating deactivation by the cyanomethyl substituent. Complexation of the cyano moiety with the Lewis acid ($AlCl_3$ or BF_3) may play a role in the special regiochemistry observed, since the carbomethoxy group (in 2), a more weakly coordinating ligand, resulted in positional selectivity closer to that observed for hydrogen (of CH_3 in 3). The much higher yield in the toluoylation of 2 vs. 1 reinforces this view.

In reference to literature data for the corresponding benzene analogues of 1–3,[6] only Friedel–Crafts acetylation has been reported for all of the comparative substrates: toluene, phenylacetate, and phenylacetonitrile. The reaction of toluene with acetyl chloride (AcCl) and $AlCl_3$ gives a preponderance of para substitution ($o/m/p$ ratio = 1/1/98).[6a] Acetylation of methyl phenylacetate with AcCl and $AlCl_3$ was alleged to give largely para substitution,[6b] whereas acetylation of ethyl phenylacetate was claimed to give a substantial amount of meta substitution ($o/m/p$ = trace/60/40).[6c] Acetylation of phenylacetonitrile (AcCl and $AlCl_3$) affords equal amounts of meta and para substitution ($o/m/p$ = 0/50/50).[6d,7]

Isomer Characterization. The isomeric mixtures produced in our work were generally analyzed and characterized as mixtures since the isolation of individual isomers of this kind is difficult;[8] the isomer ratios are thus unperturbed by fractionation possible during isolation. TLC (silica gel) was unsuitable for analysis of isomeric mixtures, but GLC was effective (see Experimental Section). GLC/MS was used to confirm the isomeric relationship in two of the reactions (for toluoylation of 2 and 3). The individual isomers in each of the isomeric mixtures were characterized and assayed by ^{1}H NMR, which gave quantitative results consistent with the GLC data. Analysis using ^{13}C NMR reinforced the assignments, but quantitation with this method is not as reliable as quantitation with ^{1}H NMR.

Proton NMR. ^{1}H NMR chemical shift data are particularly valuable in assigning structures to or in identifying substituted ferrocenes.[2,3,4b,d,8] Both ring-proton chemical shifts[2,3,9] and substituent chemical shifts are reliable for the characterization of isomeric polysubstituted ferrocenes. The usefulness of substituent chemical shifts has been amply demonstrated for the methyl group of monosubstituted methylferrocenes.[4b,d,8] The characterization and quantitation of the individual isomers in the mixtures were unambiguously performed by using the distinct singlets for the CH_3, CH_2CN, and $CH_2CO_2CH_3$ substituents in 6–8. ^{1}H NMR data are presented in the experimental section.

Carbon-13 NMR. Because of the usefulness of the ^{13}C NMR data in pinpointing individual isomers in the isomeric mixtures and because of the paucity of ^{13}C NMR information on disubstituted ferrocenes in the literature, we present our ^{13}C NMR results in Table II with appropriate peak assignments. Assignments of certain peaks to various isomers were based on (1) data for model compounds 1, 2, 3, and 9, (2) literature data,[10] and (3) peak intensities. For each mixture, the unequal quantities of isomers, whose relative ratios had already been ascertained by ^{1}H NMR and GLC, facilitated the assignments. We did not make the assignments using a precise method such as specific ^{13}C enrichment or selective proton decoupling.

Briefly, the carbon atoms useful for distinguishing isomers in the mixtures were C_1, C′ (carbons in the primed ring), C_α (substituent carbon adjacent to the ring), and

(4) (a) Rapič, V.; Schlögl, K.; Steinitz, B. *J. Organomet. Chem.* **1975**, *94*, 87. (b) Schlögl, K.; Falk, H.; Haller, G. *Monatsh. Chem.* **1967**, *98*, 82. (c) Benkeser, R. A.; Nagai, Y.; Hooz, J. *J. Am. Chem. Soc.* **1964**, *86*, 3742. (d) Moise, C.; Sautrey, D.; Tirouflet, J. *Bull. Soc. Chim. Fr.* **1971**, 4562. (e) Falk, H.; Haller, G.; Schlögl, K. *Monatsh. Chem.* **1967**, *98*, 592.

(5) Rosenblum, M.; Woodward, R. B. *J. Am. Chem. Soc.* **1958**, *80*, 5443.

(6) (a) Brown, H. C.; Marino, G.; Stock, L. M. *J. Am. Chem. Soc.* **1959**, *81*, 3310. (b) Bergmann, E. D.; Blum, J. *J. Org. Chem.* **1959**, *24*, 549. (c) Papa, D.; Schwenk, E.; Klingsberg, A. *J. Am. Chem. Soc.* **1946**, *68*, 2133. (d) Rorig, K. *Ibid.* **1953**, *75*, 5381.

(7) The inductive electronic withdrawing ($-I$) effect of the CH_2CN substituent is also evident in aromatic nitration. Phenylacetonitrile gives an $o/m/p$ ratio of ca. 15:15:70 [Baker, J. W.; Cooper, K. E.; Ingold, C. K. *J. Chem. Soc.* **1928**, 426] whereas toluene gives an $o/m/p$ ratio of ca. 60:5:35 [Kovacic, P.; Hiller, J. J., Jr. *J. Org. Chem.* **1965**, *30*, 1581]. The influence of the cyano group is seen at its ultimate extent in the nitration of $C_6H_5C(CN)_3$, wherein only meta substitution is obtained [Williams, J. K.; Martin, E. L.; Sheppard, W. A. *Ibid.* **1966**, *31*, 919].

(8) Benkeser, R. A.; Nagai, Y.; Hooz, J. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 482.

(9) Levenberg, M. I.; Richards, J. H. *J. Am. Chem. Soc.* **1964**, *86*, 2634.

(10) (a) Braun, S.; Abram, T. S.; Watts, W. E. *J. Organomet. Chem.* **1975**, *97*, 429. (b) Koridze, A. A.; Petrovskii, P. V.; Mokhov, A. I.; Lutsenko, A. I. *Ibid.* **1977**, *136*, 57. (c) Nesmeyanov, A. N.; Petrovskii, P. V.; Fedorov, L. A.; Robas, V. I.; Fedin, E. I. *Zh. Strukt. Khim.* **1973**, *14*, 49; *Chem. Abstr.* **1973**, *78*, 158509.

Table II. Carbon-13 NMR Data and Assignments

compd	C_1	C_2	C_5	C_3	C_4	$C_{1'}$	$C_{2',5'}$	$C_{3',4'}$	R
ferrocene	67.9	67.9		67.9		———	67.9	———	
3	83.7	69.0		66.9		———	68.4	———	14.7
2	80.4	68.8		67.8		———	68.7	———	35.3,[a] 51.8,[b] 171.5[c]
1	77.5	69.2		67.9		———	68.2	———	18.9,[d] 117.8[e]
9	78.2	71.5		72.5		———	70.2	———	199.0[f,g]
6a[h]	*i*	70.5[j]		70.0[j]		*i*	72.6	73.4	17.7,[d] 117.5[e]
6b	*i*	71.5[j,k]	71.9[j,k]	*i*	71.1[j,k]	———	71.4	———	18.9[d]
7a[l]	82.1[m]	70.9		70.1		*i*	72.2	73.1	34.2,[a,m] 51.8,[b] 171.1[c,m]
7b[l]	~84.6[n]	*i*	*i*	*i*	*i*	———	70.9	———	35.1,[a,n] 51.8,[b] 170.9[c,n]
7c[l]	~84.7[n]	*i*	*i*	*i*	*i*	———	70.9	———	34.6,[a,n] 51.8,[b] ~171.5[c,n]
8a[o]	85.5[m]	71.1		69.3		78.7	72.0	73.1	13.7[m]
8b[o]	88.8[p]	*i*	*i*	77.5	*i*	———	70.8	———	14.9[p]
8c[o]	88.3[q]	*i*	*i*	*i*	*i*	———	70.8	———	15.1[q]
6a (CD_2Cl_2)[r]	79.8	70.8[j]		70.4[j]		79.8	72.9	73.8	18.0,[d] 118.1[e]
7a (CD_2Cl_2)[s]	81.9[m]	70.6		69.7		78.7	71.7	72.8	33.7,[a,m] 170.7 or 171.4[c]
7b (CD_2Cl_2)[s]	84.0[n]	*i*	*i*	77.1[k]	*i*	———	70.6	———	34.2,[a,n] 170.7 or 171.4[c]
7c (CD_2Cl_2)[s]	84.1[n]	77.1[k]	*i*	*i*	*i*	———	70.6	———	34.7,[a,n] 170.7 or 171.4[c]

[a] $CH_2C(O)$. [b] OCH_3. [c] $CH_2C(O)$. [d] CH_2CN. [e] CH_2CN. [f] ArC(O). [g] Aromatic carbons: 128.1 (C_4), 128.2 (C_3, C_5), 131.4 (C_2, C_6), 139.8 (C_1). [h] X: 21.6 (CH_3), 128.3, 129.0, 136.5 (C_1), 142.5 (C_4), 197.9 (C=O). [i] Not discernible or indeterminate. [j] These resonance assignments for the same compound may be interchanged. [k] Peaks are tentative. [l] X, Y, Z: 21.6 (CH_3), 128.2 (1.4 C), 128.4 (0.6 C), 128.7 (0.6 C), 128.8 (1.4 C), 136.9 (C_1), 142.1 (C_4), ~199.5 (C=O, 7a and 7b), ~201 (C=O, 7c). Unassigned minor peaks: 71.1, 72.7, 74.1 (all doublets). [m] Intensity corresponds to 0.5 carbons. [n] Resonance assignments for the same group in the isomeric compounds may be interchanged. [o] X, Y, Z: 128.1 (0.6 C), 128.2 (1.0 C), 128.4 (0.4 C), 128.8 (2.0 C), 137.2 (C_1), 141.7 (C_4). 198.3 and 198.9 (C=O, 8a/8b), ~201 (C=O, 8c). Unassigned minor peaks: 71.1, 72.3, 73.6, 74.3 (doublets). [p] Intensity corresponds to 0.3 carbons. [q] Intensity corresponds to 0.2 carbons. [r] X: 21.7 (CH_3), 128.6, 129.3, 137.2 (C_1), 142.9 (C_4), 197.9 (C=O). [s] 197.5 (C=O, 7a and 7b), ~199 (C=O, 7c).

C=O. The data in Table II for C_1, C′, and C_α allow a clear distinction to be made between heteroannular products (**6a, 7a, 8a**) and homoannular products (**6b, 6c; 7b, 7c; 8b, 8c**). However, the distinction between the homoannular isomers is only evidenced clearly by data for ArC=O, which show a deshielding of 1.5 to 3 ppm for the 1,2-isomer vs. the 1,3-isomer.

Experimental Section

General. Proton NMR spectra were determined on a Perkin-Elmer EM-360 (60 MHz) or R32 (90 MHz) spectrometer, using $CDCl_3$ as solvent and tetramethylsilane as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened). Mass spectra (electron impact) were obtained on a Hitachi Perkin-Elmer RMU-6E instrument at an ionizing voltage of 70 eV. Carbon-13 NMR spectra were recorded on a JEOL FX60Q spectrometer (15.00 MHz) in $CDCl_3$, unless otherwise noted, with Me_4Si as an internal reference. Both proton noise-decoupled and off-resonance decoupled ^{13}C spectra were determined; only noise-decoupled data are presented. GLC analyses were performed on a Perkin-Elmer 3920B instrument with a flame-ionization detector, equipped with Hewlett-Packard Model 3352B data system and 18652 A/D converter. The following 6 ft × $^1/_8$ in. glass columns were used: (1) 1.35% OV-17 on Chromsorb W AW/DMS (100/120 mesh); (2) 3% SE-30 on Chromosorb Q (100/120 mesh); (3) 3% OV-225 on Chromosorb W HP (100/120 mesh). TLC analyses were performed on Whatman MK1F silica gel (80 Å) plates (1 × 3 in.). Melting points are corrected; melting ranges may be preceded by softening ranges, in parentheses.

Materials. Ferrocenylacetonitrile was synthesized according to a known procedure[11] or purchased from Research Organic/Inorganic Chemical Corp. (ROIC). Methylferrocene and ferrocenylacetic acid were purchased from Parish Chemical Company and ROIC, respectively. *p*-Toluoyl chloride was distilled and protected from moisture.

Reaction of 1 with *p*-Toluoyl Chloride. Method A.[4b] Ferrocenylacetonitrile (13.56 g, 60 mmol) was dissolved in 50 mL of dry CH_2Cl_2 and treated slowly, under nitrogen, with a mixture of *p*-toluoyl chloride (9.72 g, 63 mmol) and anhydrous $AlCl_3$ (8.16 g, 61 mmol) in 85 mL of dry CH_2Cl_2. After standing at 25 °C for 48 h, the reaction mixture was poured onto crushed ice and extracted with CH_2Cl_2. The CH_2Cl_2 extract was rinsed with 10% Na_2CO_3, dried ($MgSO_4$), and evaporated to a dark resin. TLC (ethyl acetate/hexane, 1:1) showed one major mobile spot and origin material. The sample was chromatographed on a dry column of silica gel (550 g; petroleum ether/ethyl acetate, 2:1, then 1:1) and the major, red band was excised. The impregnated silica gel was thoroughly extracted with CH_2Cl_2 and the extract was evaporated to a photosensitive, deep red oil (7.5 g, 36%), clean by TLC, which crystallized to a soft, deep red solid, mp (54–56 °C) 56–66 °C. GLC analysis (SE-30 column) showed only one peak, and GLC analysis (OV-17 column) showed two peaks (ΔR_f = 0.4 min) in a ratio of ca. 9:1 (order of increasing retention).

Method B.[4a] The reaction was also conducted with 40 mmol of ferrocenylacetonitrile, 42 mmol of *p*-toluoyl chloride, and 41 mmol of $AlCl_3$ in 200 mL of CH_2Cl_2, under nitrogen in the dark (Al foil). All materials except the $AlCl_3$ were combined and the $AlCl_3$ was added last in small portions at 0 °C. After 2 h at 25 °C, the reaction mixture was poured onto cracked ice (the product was protected from light during the workup). The CH_2Cl_2 solution was separated, rinsed with water, 5% aqueous ethanolamine, and water, dried ($MgSO_4$), and evaporated to dryness. A red oil (10.5 g), which was comprised (^1H NMR) of 70 mol % adduct (9:1 isomer ratio) and 30 mol % starting nitrile (corrected yield of product is 8.2 g, 60%), was obtained. Dry-column chromatography was performed on 400 g of silica gel (ethyl acetate/hexane, 1:2) in dim light. The major red band was extracted to afford 6.5 g (47%) of deep red oil that crystallized to a red solid.

Analysis. The final products from methods A and B were identical. TLC (ethyl acetate/hexane, 1:1) showed a large red spot at R_f 0.61 and a very small vermillion spot at R_f 0.65: ^1H NMR δ 2.42 (s, 3), 3.33 and 3.49 (pair of s, 2, 9:1 ratio, respectively, CH_2 in **6a–6b**), 4.1–4.4 (m, 4, **Cp**CH_2CN and Cp), 4.64 (t, 2, J = 2 Hz, β-CpCO), 4.97 (t, 2, J = 2 Hz, α-CpCO), 7.2–7.9 [m (AB q), 4]; mass spectrum, m/e (relative abundance) 344 (15, M + 1), 343 (61, molecular ion), 119 (85), 106 (26), 105 (38), 97 (31), 91 (81), 85 (35), 84 (31), 71 (46), 70 (31), 69 (38), 57 (77), 55 (58), 43 (100), 41 (54); IR (5% solution in $CDCl_3$) ν_{max} (relative intensity[12]) 3010 (m), 2254 (w), 1729 (s), 1636 (m-s), 1448 (m-s), 1313 (m), 1295/1285 (s), 1171 (w-m), 1048 (w-m), 1029 (w-m), 857 (m) cm^{-1}.

(11) Lednicer, D.; Hauser, C. R. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, pp 434, 578. ^1H NMR for 1 ($CDCl_3$) δ 3.46 (s, 2), 4.2–4.6 (m, 9; s for Cp at δ 4.30).

(12) s = strong, m = medium, w = weak.

A sample of the nitrile was hydrolyzed to the corresponding primary amide with KOH (85% assay) in refluxing *tert*-butanol. A pure sample of red, oily amide (1.3 g from 5.5 g of nitrile), isolated by dry-column chromatography (silica gel, ethyl acetate eluant), was converted to an amorphous red solid under high vacuum: IR (KBr) ν_{max} (relative intensity[12]) 3417 (s), 1671 (s), 1630 (s), 1605 (s), 1446 (m), 1286 (m), 756 (m) cm^{-1}; ^1H NMR δ 2.42 (s, 3), 3.15 (br s, 2, CH_2CO), 4.17 (br s, 2, α-CpCO), 5.93 (br s, 2, NH_2), 7.1–7.9 (m, 4); UV (CH_3OH) λ_{max} (ϵ) 472 (600), 355 (1700), 280 (11 290, shl), 257 (14,820) nm. Anal. Calcd for $C_{20}H_{19}FeNO_2 \cdot 0.4H_2O$: C, 65.20; H, 5.42; H_2O, 1.96. Found: C, 65.20; H, 5.48; H_2O, 2.28.

Reaction of 2 with *p*-Toluoyl Chloride. Methyl ferrocenylacetate was prepared from the acetic acid. Ferrocenylacetic acid (68.3 g, 0.28 mol) was added to a slurry of anhydrous K_2CO_3 (77.3 g, 0.56 mol) in 260 mL of dry dimethylformamide (DMF). After the solution was stirred for 1.0 h, dimethyl sulfate (37.8 g, 0.30 mol) was slowly added over 30 min. The reaction was stirred for 4 h and let stand overnight. Water (600 mL) was added and the mixture was extracted with ether (2 × 400 mL). The combined ethereal extract was rinsed with water, dried ($MgSO_4$), and evaporated. Residual DMF was removed under high vacuum. The crude oil (52.7 g) was distilled by kugelrohr (150–160 °C pot temperature, 0.5 torr) to afford 48.0 g of red liquid (66%), which was homogeneous by TLC (hexane/ethyl acetate, 3:1); ^1H NMR δ 3.32 (s, 2), 3.68 (s, 3), 4.0–4.3 (m, 9, s for Cp at δ 4.11).

The ester (19.4 g, 75 mmol) in 40 mL of dry CH_2Cl_2 was treated with a solution of 10.2 g of $AlCl_3$ and 12.2 g of *p*-toluoyl chloride in 110 mL of CH_2Cl_2. The reaction was stirred at room temperature for 18 h and worked up as before (method A) to furnish 27.4 g of crude red oil, which was chromatographed on a dry column of silica gel (750 g) using hexane/ethyl acetate (2:1). The major red band was extracted to give 21.4 g of photosensitive deep red oil (76%). GLC analysis (SE-30 column) showed three peaks, one completely resolved and two combined (ΔR_f 1.5 min) in a ratio of 1:2.5 (order of increasing retention); the two unresolved peaks had an approximate ratio of 2.5:1. TLC (ethyl acetate/hexane, 1:2) showed a small vermillion spot at R_f 0.47 and a large red spot at R_f 0.39: ^1H NMR δ 2.43 (s, 3), 3.24 (s, 0.5, CH_2 in **7a**), 3.42 (s, 0.2, CH_2 in **7b**), 3.67 and 3.73 (m, 3.3; br s for 3 H at δ 3.67 for OCH_3; s for 0.3 H at δ 3.73 for CH_2 in **7c**), 4.1–4.3 (m, 5, Cp and $\mathbf{Cp}CH_2$), 4.5–4.7 (m, 2, β-CpCO), 4.8–5.0 (m, 1.4, α-CpCO), 7.1–8.0 (m, 4); isomer ratio **7a/7b/7c** = 2.5:1:1.5.

A sample of the ester mixture (11.3 g, 30 mmol) was saponified with NaOH (15 mL, 2 N, 30 mmol) in 15 mL of ethanol at reflux. The progress of the reaction was followed by TLC (ethyl acetate). After 6 h, the hydrolyzed mixture was concentrated, diluted with 15 mL of water, and washed with ether. The aqueous layer (pH 8–9) was treated with a solution of $CaCl_2$ (1.5 g, 13.5 mmol) in 10 mL of water. A dark red resin separated, which slowly solidified. The mixture was cooled to 0 °C and the solid was collected by filtration and dried (6.0 g). TLC showed some brown origin material. Since the solid would not recrystallize, it was converted to the free acid with excess 1 N HCl and extracted into CH_2Cl_2. Dry-column chromatography on 300 g of silica gel (ethyl acetate/hexane, 2:1) furnished TLC-homogeneous acid as a photosensitive red syrup (2.1 g). This purified acid (5.5 mmol) in 10 mL of methanol was neutralized with 5.2 mL of 1.0 N NaOH, and the solution of the sodium salt was treated with a solution of $CaCl_2$ (0.30 g, 5.4 mmol) in 2 mL of water to afford a brick red solid on cooling to 0 °C, which was dried under high vacuum at 25 °C (1.3 g), mp (145–165 °C) 185–200 °C dec. TLC (ethyl acetate) was clean, showing only two spots at R_f 0.54 (red) and 0.61 (vermillion). Anal. Calcd for $C_{20}H_{17}FeO_3 \cdot 0.5\ Ca \cdot 0.7\ H_2O$: C, 61.00; H, 4.71; H_2O, 3.20. Found: C, 61.18; H, 4.76; H_2O, 3.30. Reaction of the free acid from this calcium salt with diazomethane gave a mixture of methyl esters (**7a–c**) virtually identical with the one before saponification (GLC analysis on the OV-225 column; ^1H NMR).

Reaction of 3 with *p*-Toluoyl Chloride. A solution of methylferrocene (1.00 g, 5 mmol) in 2 mL of dry CH_2Cl_2 was treated with a mixture of *p*-toluoyl chloride (810 mg, 5.2 mmol) and anhydrous $AlCl_3$ (680 mg, 5.1 mmol) in 7 mL of CH_2Cl_2. The reaction was stirred for 18 h under nitrogen and then poured over cracked ice. The CH_2Cl_2 solution was separated, rinsed with 10% aqueous Na_2CO_3, dried ($MgSO_4$), and concentrated to furnish 1.25 g of red syrup. This material was chromatographed on a dry column of silica gel (100 g), using hexane/ethyl acetate (6:1). The major red band was extracted to give 1.00 g of red syrup (63%). TLC (hexane/ethyl acetate, 2:1) revealed two spots at R_f 0.58 (major, red) and 0.66 (minor, orange): ^1H NMR δ 1.83 (s, 1.3, $CpCH_3$ in **8a**), 2.04 (s, 1.1, $CpCH_3$ in **8b**), 2.35 (s, 0.5, $CpCH_3$ in **8c**), 2.42 (s, 3, $ArCH_3$), 4.0–4.2 (m, 4.4; s at δ 4.05 for $\mathbf{Cp}CH_3$ and at δ 4.11 for Cp, $Cp/\mathbf{Cp}CH_3$ = ca. 1), 4.48 (m, 2, β-CpCO), 4.81 (m, 2, α-CpCO), 7.1–7.9 (m, 4); isomer ratio **8a/8b/8c** = 2.6:2.2:1. A 200-mg sample was recrystallized from chloroform/hexane (1:10) to give a vermillion powder (80 mg), mp 80–85 °C. ^1H NMR indicated mainly a mixture of **8a** and **8b** in a 1.4:1 ratio, respectively. Anal. Calcd for $C_{19}H_{18}FeO$: C, 71.71; H, 5.70. Found: C, 71.48; H, 5.78. The mother liquor returned 120 mg of red oil, enriched in the minor isomer **8c** (**8a:8b:8c** = 1.6:1.3:1). ^1H NMR of the residue showed enhancement of the singlet at δ 2.35, a triplet (J = 3 Hz) at δ 4.33, and the Cp singlet at δ 4.13, and depletion of the singlet at δ 4.07 and the multiplet at δ 4.83 ($Cp/\mathbf{Cp}CH_3$ = 3.3). A minor, trailing red band was also extracted to give 0.10 g (5%) of deep red resin, mass spectral analysis of which indicated bistoluoylated product [m/e 436 (molecular ion), 318, 317 (M – COAr), 136, 119 (ArCO), 91 (Ar), 65]; ^1H NMR supported this assignment; TLC (hexane/ethyl acetate, 2:1) R_f 0.42 (minor spot), 0.33 (major spot).

Acetylation of 1. Nitrile **1** (1.07 g, 5 mmol) and acetic anhydride (0.81 g, 8 mmol) in 20 mL of dry CH_2Cl_2 at 0 °C was treated with distilled BF_3–etherate (1.7 g, 12 mmol). The reaction was held at 0 °C for 30 min and then let stand at ambient temperature for 1.5 h. Crushed ice was added and the CH_2Cl_2 solution was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 solutions were washed with aqueous Na_2CO_3, dried ($MgSO_4$), and evaporated to an orange-brown oil. ^1H NMR indicated 60% starting material and mainly heteroannular substitution product in the crude sample. Dry-column chromatography (50 g of silica gel; ethyl acetate/petroleum ether, 1:2) afforded 0.40 g (31%) of orange oil, which eventually crystallized, mp (64–67 °C) 67–77 °C: ^1H NMR δ 2.47 (s with shoulder on upfield side, 3), 3.52 and 3.66 (pair of s, 2; CH_2CN for 1,1′-isomer at δ 3.52; CH_2CN for 1,3-isomer at δ 3.66; 4.5:1, respectively), 4.3–4.5 (m, 4, $\mathbf{Cp}CH_2CN$ and Cp), 4.73 (t, 2, J = 2 Hz, β-CpCO), 4.99 (t, 2, J = 2 Hz, α-CpCO); IR (KBr) ν_{max} 2251 (CN), 1659 (CO) cm^{-1}; mass spectrum, m/e (relative abundance) 268 (22, M + 1), 267 (100, molecular ion), 252 (<10, M – CH_3), 225 (31), 224 (82, M – $COCH_3$), 134 (22), 121 (22), 43 (24, $COCH_3$). GLC analysis (OV-17 column) partially resolved two peaks (ΔR_f 0.6 min) in a ratio of ca. 5:1 (order of increasing retention).

GLC and GLC/MS Analyses. Isomeric mixtures from *p*-toluoylation of **1–3** were cleanly separated on a 6 ft × $^1/_8$ in. glass column packed with 3% OV-225 on Chromosorb W HP (100/120 mesh). The product mixture from **1** (method A) was analyzed at a column temperature of 258 °C. The two isomers [R_f(major) 13.2 min, R_f(minor) 15.0 min] comprised 99% of the volatile material detected. An average of three runs with baseline separation gave an isomer ratio (**6a:6b**) of 11.7:1. The product mixture from **2** was analyzed at 250 °C and the three isomers (R_f 9.3, 12.5, 13.5 min) comprised 97% of the volatile material. An average of two runs gave an isomer ratio (**7c:7a:7b**) of 1.3:2.3:1 (order of increasing retention). GLC/MS analysis of the mixture from **2** gave related mass spectra for each peak, supporting their isomeric relationship and their identity [no molecular ion; m/e 317 (M – $COOCH_3$), 184, 119, 91, 65]. The product mixture from **3** was analyzed at 225 °C (R_f 6.7, 8.6, 9.3 min) and 215 °C (R_f 9.1, 11.8, 12.9 min) and the three isomers comprised 99% of the volatile material. An average of these two runs, with well-separated peaks, gave an isomer ratio (**8c:8a:8b**) of 1:2.6:2.0 (order of increasing retention). GLC/MS analysis of the mixture from **3** identified the three substances as isomers of **8** (intense molecular ion at m/e 318; m/e 224, 202, 199, 121, 119, 91, 56).

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Registry No. **1**, 1316-91-2; **2**, 33503-17-2; **3**, 1271-44-9; **6a**, 75458-51-4; **6b**, 75458-52-5; **7a**, 75458-53-6; **7b**, 75458-54-7; **7c**,

75458-54-7; **8a**, 75458-55-8; **8b**, 75458-56-9; **8c**, 75458-56-9; **9**, 1272-44-2; 2-(1′-*p*-toluoyl-1-ferrocenyl)acetamide, 75458-57-0; 2-(3-*p*-toluoyl-1-ferrocenyl)acetamide, 75458-58-1; ferrocenylacetic acid, 1287-16-7; calcium (1′-*p*-toluoyl-1-ferrocenyl)acetate, 75458-59-2; calcium (3-*p*-toluoyl-1-ferrocenyl)acetate, 75458-60-5; calcium (2-*p*-toluoyl-1-ferrocenyl)acetate, 75458-61-6; 1′-acetyl-1-ferrocenylacetonitrile, 75458-62-7; 3-acetyl-1-ferrocenylacetonitrile, 75458-63-8; ferrocene, 102-54-5.

Reactions of 2-Functionalized 4*H*-Thiopyran-4-ones with Nucleophiles. 2.[1] Reactions with Primary Amines

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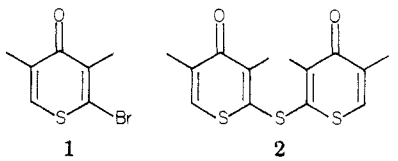
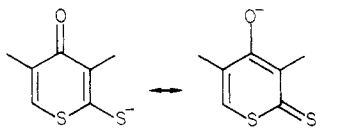
Two thiopyrones (**1**, **2**) substituted with a leaving group at position 2 were reacted with methylamine and benzylamine. The products ranged, according to the amine and reaction conditions, from a 2-(methylamino)-thiopyrone (**4**) to a pyridonyl thiopyronyl sulfide (**10**) and included 2-thiol-4(1*H*)-pyridone derivatives (**5a,b**) and 2-amino-4(1*H*)-pyridone derivatives (**8a,b**). A major product from the cleavage of **2** with the amines is the tautomeric thiopyranthiodione derivative **9** which is also formed from **2** and sodium hydrogen sulfide. The formation of the aminopyridones **8** through open-chain intermediates is discussed.

The introduction of additional functional groups into the thiopyrone and related thiochromone molecules is of interest for various potential applications.[4,5] We have found that a convenient approach to such functionalization could be the substitution of leaving groups at the 2-position of 2-bromo-3,5-dimethyl-4*H*-thiopyran-4-one (**1**) and of



1 **2**

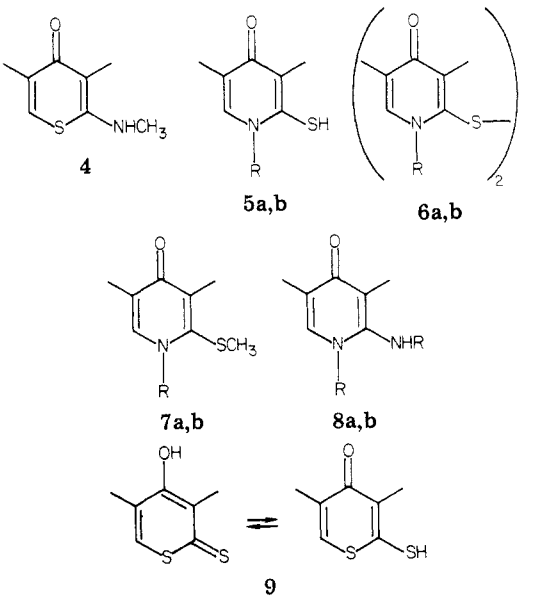


3

bis(3,5-dimethyl-4-oxo-4*H*-thiopyran-2-yl) sulfide (**2**), two substances which had been concomitantly obtained from readily available starting materials.[6] Sulfide **2** may, indeed, be looked upon as a thiopyrone substituted at position 2 by the leaving group **3**. It may, therefore, be expected to undergo substitution reactions of the ring heteroatom or of the 2-group, analogous to those observed with bromide **1**.[1]

The present work is concerned mainly with the reactions of **1** and **2** with methyl- and benzylamine. By analogy to the reactions with the hydroxide ion,[1] reactions with the amines were carried out in the absence or in the presence of water to try to attain selectivity in the formation of either pyridone derivatives or 2-aminothiopyrone derivatives. Such a selectivity has, however, not been realized in the present case.

Chart I[a]



4 **5a,b** **6a,b**

7a,b **8a,b**

9

[a] a, R = CH_3; b, R = $CH_2C_6H_5$.

Treatment of **1** with excess aqueous methylamine/ethanol at room temperature yielded a mixture of the aminothiopyrone **4** and the mercaptopyridone **5a** (with the disulfide **6a** derived from **5a**; see Chart I) in up to 25% and 55% yields, respectively. These were separated by column chromatography and characterized through their analytical and spectral properties. The distinction between **4** and **5a** was made through the ready oxidation of the latter with iodine to **6a** and through its methylation with diazomethane to **7a**. The 2-thiol structure was assigned to **5a** on the basis of the UV spectrum: **5a** has the longest wavelength maximum at 308 nm (320 nm for **7a**) while the tautomeric 2-thione-4-ol structure would be expected to show a maximum at around 350 nm.[7] A similar observation is also made for **4**, which, like its benzo analogues,[5] does not seem to tautomerize to the imino form.

(1) Part I: Greenberg, F. H.; Gaoni, Y. *J. Org. Chem.* **1978**, *43*, 4966-8.
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(3) To whom correspondence should be addressed.
(4) Chen, C. H.; Reynolds, G. A. *J. Org. Chem.* **1979**, *44*, 3144-7.
(5) Zmurenko, L. A.; Glozman, O. M.; Zagorevskii, V. A. *Chem. Heterocycl. Compd.* **1978**, 182-5; *Chem. Heterocycl. Compd. (Engl. Transl.)* **1978**, 141-4.
(6) Gaoni, Y. *Tetrahedron Lett.* **1976**, 2167-70.
(7) Krowicki, K. *Pol. J. Chem.* **1979**, *53*, 701-7.

0022-3263/81/1946-0074$01.00/0