Synthesis of Diacyl[3]ferrocenophanes.[1]
Heteroannular Directing Effects in Friedel–Crafts Acylations

JACK A. WINSTEAD,* RAYMOND R. McGUIRE, ROBERT E. COCHOY,
ALFRED D. BROWN, JR., AND GEORGE J. GAUTHIER

Directorate of Chemical Sciences, Frank J. Seiler Research Laboratory, United States Air Force Academy, Colorado 80840

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The Friedel–Crafts diacylation of [3]ferrocenophane (TMF) yielded four of the six theoretically possible heteroannular diacetyl isomers. The eclipsed isomers, 2,2' and 3,3', were not detected, but one homoannular isomer, 3,4-diacetyl TMF, was isolated. All possible acetyl–cinnamoyl TMF's were formed except the eclipsed ones, but only two of the dicinnamoyl isomers were produced in isolable quantities. Structure assignments of the acetyl–cinnamoyl and dicinnamoyl derivatives were based on the conversion to the diacetyl derivatives *via* a base-catalyzed reverse aldol type condensation (reverse Claisen–Schmidt). A significant directing effect of the acyl group of the monoacetyl derivative was noted. Using $AlCl_3$ as catalyst, the yield of the 2,3' isomer was six times that of the 2,4'. A 2,3'/2,4' isomer ratio of approximately 3 was obtained when BF_3 was used as the catalyst. A model based on BF_3 and $AlCl_3$ complexes with the carbonyl of the monoacyl derivative was used to explain the directing effects.

Recent investigations in our laboratories involving the synthesis of bridged ferrocenophanes required the synthesis, isolation, and purification of several of the isomeric heteroannular diacyl[3]ferrocenophanes. The diacylation of [3]ferrocenophane or 1,1'-trimethylene-ferrocene (1) (TMF) may lead to six isomers exclusive of optical isomers. Except for the work of Rinehart, *et al.,*[2] and Schlögl, *et al.,*[3] attempts to synthesize and identify pure isomers of diacetylated [3]ferrocenophane have not been reported. Rinehart, *et al.,*[2] identified a by-product from monoacetylation of 1 as 3,4'-diacetyl TMF (9) on the basis of the double ring closure of the dipropionic acid derived from 9 as well as the infrared and nmr spectra of 9.

Schlögl, *et al.,*[3] discussed the six isomeric compounds (4–9) which may in theory be obtained from the diacetylation of TMF (Figure 1). The acetyl chloride-aluminum chloride diacetylation of TMF and chromatography on alumina gave three fractions whose relative amounts, in order of elution, were 1:40:60. The general observation[2] that alkylferrocenes with α-acyl groups are eluted more quickly than β derivatives and the relative amounts of the fractions obtained led Schlögl to speculate that the smallest fraction might be a mixture of 5 and 6, the intermediate fraction a mixture of 4 and 7, and the largest fraction a mixture

of 8 and 9, though reliable structural assignments were not possible.

We have prepared, separated, and identified four of the six possible heteroannularly diacetylated [3]-ferrocenophanes and a number of cinnamoylated derivatives. Chemical interconversions and spectroscopic methods were used in determining the structural assignments. We have shown that Schlögl's tentative interpretation was in error. His smallest fraction was most probably 7, the intermediate fraction 5 and 6, and the largest fraction 9. If any 4 and 8 were present in Schlögl's mixture, they would probably be with 7 and 9, respectively. This elution sequence $(\alpha\alpha', \alpha\beta', \beta\beta')$ follows that previously suggested,[4] which can give mixtures such as 5 and 6 in the $\alpha\beta'$ fraction.

Results and Discussion

Acetylation of [3]Ferrocenophane (1).—The Friedel–Crafts acetylation of [3]ferrocenophane (1) with an excess of acetyl chloride-aluminum chloride yielded four of the six theoretically obtainable heteroannularly disubstituted products. A fifth isomer, the homoannularly disubstituted 3,4-diacetyl[3]ferrocenophane (10), was also obtained in small yield (see Table I).

The major product, 3,4'-diacetyl[3]ferrocenophane (9), has been described previously.[2] The remaining three isomeric products were identified as 2,3'-diacetyl-[3]ferrocenophane (5), 2,4'-diacetyl[3]ferrocenophane (6), and 2,5'-diacetyl[3]ferrocenophane (7) by nmr

(1) Ferrocenophane nomenclature conforms to that suggested by B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964, pp 8–23. For a review, see W. E. Watts, *Organometal. Chem. Rev.,* **2**, 231 (1967).

(2) K. Rinehart, D. Bublitz, and D. Gustafson, *J. Amer. Chem. Soc.,* **85**, 970 (1963).

(3) K. Schlögl, M. Peterlik, and H. Seiler, *Monatsh. Chem.,* **93**, 1309 (1962).

(4) M. Rosenblum and R. B. Woodward, *J. Amer. Chem. Soc.,* **80**, 5443 (1958).
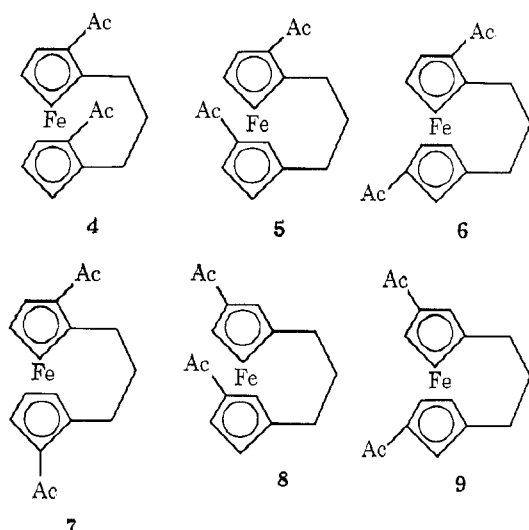
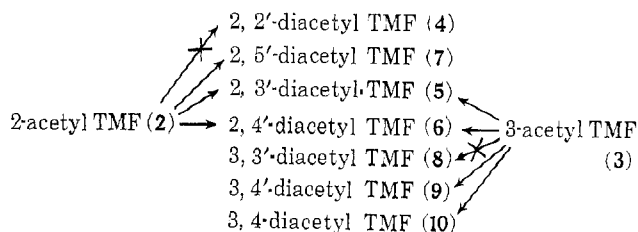Figure 1.—Heteroannularly diacetylated [3]ferrocenophanes.

Figure 2.—Acetylation products of 2-acetyl TMF and 3-acetyl TMF.

spectroscopy, by unambiguous synthesis from known starting materials, and by conversion of the 2,3'-diacetyl isomer 5 into a previously reported compound.[2] It should be noted that the two theoretical isomers not isolated from the reaction are the eclipsed products 2,2'-diacetyl[3]ferrocenophane (4) and 3,3'-diacetyl-[3]ferrocenophane (8).

Product Identification.—The acetylation of 2-acetyl-[3]ferrocenophane (2) and 3-acetyl[3]ferrocenophane (3) has provided evidence for the structures assigned to the unreported diacetyl isomers. Four heteroannularly diacetylated isomers are theoretically possible from the acetylation of each of these starting materials. Two of these four isomers are common to both reactions (see Figure 2). Again, the eclipsed isomers were not obtained.

The structures assigned to compounds 5 and 6 on the basis of their nmr spectra were supported by chemical evidence. Compound 5 was converted to 2,3'-[3]ferrocenophanyldipropionic acid (26), which was then cyclized and reduced to 2-[3][3]-1,3-ferrocenophanylpropionic acid (27). Attempts to cyclize and reduce 27 to the known [3][3][3]-1,2,3-ferrocenophane[2] were unsuccessful. Compound 27 was also synthesized by a known route[2] from 2-acetyl[3][3]-1,3-ferroceno-phane (28) and shown to be identical with the sample obtained from compound 5 (Figure 3).

The structural assignments for compounds 7 and 10 were made primarily on the basis of their very characteristic nmr spectra.[5] The 2,5'-diacetyl[3]ferrocenophane (7) shows a doublet of doublets at τ 6.11
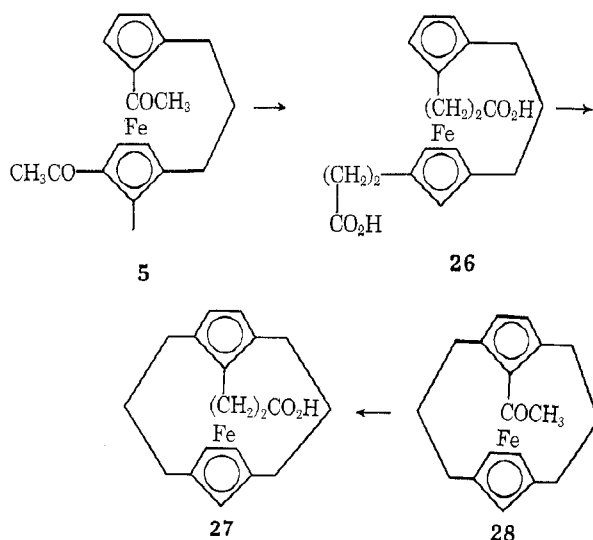
Figure 3.—Structure correlation of 2,3'-diacetyl[3]ferrocenophane (5).

for the 5 and 2' protons, a triplet at τ 5.70 for the 4 and 3' protons, and a doublet of doublets at τ 5.53 for the 3 and 4' protons. Compound 7 also shows two of the trimethylene bridge protons to be shifted downfield, indicating substitution α to the bridge.[5] The homoannularly disubstituted isomer, 3,4-diacetyl[3]-ferrocenophane (10), gives a singlet at τ 5.35 for the remaining protons on the substituted ring, *i.e.*, the 2 and 5 protons, and a multiplet centered at τ 5.88 for the protons of the unsubstituted ring. This multiplet is superimposable with the multiplet produced by [3]ferrocenophane (1) itself. Compound 10 shows no downfield bridge protons. A homoannular diacetyl-ferrocene has been reported[6,7] to be 1,2-diacetylfer-rocene, which is also $\alpha\alpha$-substituted with respect to the two acetyl groups.

The identification of mixed acetyl-cinnamoyl and dicinnamoyl isomers was made by converting them to the corresponding diacetyl compounds (see Experimental Section).

Mechanism of Acetylation.—The acetylation of 2-acetyl[3]ferrocenophane (2) and 3-acetyl[3]ferro-cenophane (3) leads to product isomer ratios which cannot be explained by steric or electronic effects.[8] For example, the acetylation of 2-acetyl[3]ferroceno-phane with acetyl chloride–aluminum chloride gives 6.0 times as much of the 2,3'-diacetyl[3]ferrocenophane (5), expected to be a minor product on steric grounds, as of the 2,4'-diacetyl[3]ferrocenophane (6). Similarly, the acetylation of 3-acetyl[3]ferrocenophane gives 2.5 times as much of the more hindered 5 as of the less hindered 6. (Overall yields of diacetylated products for these reactions are 90 and 91%, respectively.)

The results of experiments designed to investigate this phenomenon are shown in Table II and can be briefly summarized as follows. Aluminum chloride gives high yields of diacetylated products with the site of substitution being relatively specific; boron trifluoride gives lower yields and is less specific; and boron trifluoride etherate gives no diacetylated products. This,

(5) An in-depth discussion of the nmr spectra for all the isomers 1–9 and 24 has been presented at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, and is in press.

(6) P. Carty and M. F. A. Dove, *J. Organometal. Chem.*, **21**, 195 (1970).
(7) J. H. Richards and T. J. Curphey, *Chem. Ind. (London)*, 1456 (1956).
(8) H. L. Lentzner and W. E. Watts, *Chem. Commun.*, 906 (1970).

TABLE I
NMR Spectra[a]

No.	Compd[b]	Ring protons[c]	Bridge protons[c]	Acetyl group[c]	Cinnamoyl group[c,e]
1	TMF	6.02 (m, 8 H)	8.05 (s, 5 H)		
2	2-ATMF	5.41 (t, 1 H), 5.71 (d, 2 H), 5.7–5.85 (m, 1 H), 5.9–6.15 (m, 2 H), 6.27 (m, 1 H)	7.0–7.4 (m, 1 H)[d] 7.8–8.2 (m, 5 H)	7.66 (s, 3 H)	
3	3-ATMF	5.41 (b, 2 H), 5.72 (t, 2 H), 5.75–5.85 (m, 1 H), 6.12 (m, 2 H)	7.9–8.2 (m, 6 H)	7.65 (s, 3 H)	
4	2,2'-AATMF	Not detected			
5	2,3'-AATMF	5.3–5.6 (m, 4 H), 5.75 (m, 2 H)	7.0–7.4 (m, 1 H)[d] 7.96 (m, 5 H)	7.61 (s, 3 H) 7.73 (s, 3 H)	
6	2,4'-AATMF	5.2 (m, 2 H), 5.42 (t, 1 H), 5.5 (q, 1 H), 5.85 (t, 1 H), 6.03 (q, 1 H)	7.1–7.5 (m, 1 H)[d] 7.95 (m, 5 H)	7.66 (s, 3 H) 7.68 (s, 3 H)	
7	2,5'-AATMF	5.38 (q, 2 H), 5.56 (t, 2 H), 6.05 (q, 2 H)	7.0–7.5 (m, 2 H)[d] 7.8–8.1 (m, 4 H)	7.75 (s, 6 H)	
8	3,3'-AATMF	Not detected			
9	3,4'-AATMF	5.4 (t, 2 H), 5.48 (d, 4 H)	8.01 (s, 6 H)	7.66 (s, 6 H)	
10	3,4-AATMF	5.21 (s, 2 H), 5.80 (m, 4 H)	7.9–8.2 (m, 6 H)	7.53 (s, 6 H)	
11	2A-2'-CTMF	Not detected			
12	2A-3'-CTMF	5.25 (q, 1 H), 5.4–5.55 (m, 3 H), 5.67 (q, 1 H), 5.79 (t, 1 H)	6.9–7.3 (m, 1 H)[d] 7.8–8.1 (m, 5 H)	7.76 (s, 3 H)	2.39 (m, 7 H)
13	2A-4'-CTMF	5.04 (q, 1 H), 5.1–5.23 (m, 2 H), 5.46 (q, 1 H), 5.83 (t, 1 H), 5.92 (q, 1 H)	7.1–7.4 (m, 1 H)[d] 7.7–8.1 (m, 5 H)	7.64 (s, 3 H)	2.62 (m, 7 H)
14	2A-5'-CTMF	5.25 (q, 1 H), 5.35 (q, 1 H) 5.47 (m, 2 H), 5.95 (m, 2 H)	7.0–7.4 (m, 2 H)[d] 7.8–8.0 (m, 4 H)	7.72 (s, 3 H)	2.63 (m, 7 H)
15	3A-2'-CTMF	5.25–5.6 (m, 4 H), 5.65–5.8 (m, 2 H)	7.0–7.4 (m, 1 H)[d] 7.8–8.1 (m, 5 H)	7.65 (s, 3 H)	2.64 (m, 7 H)
16	3A-3'-CTMF	Not detected			
17	3A-4'-CTMF	5.2–5.45 (m, 4 H), 5.49 (d, 2 H)	7.99 (s, 6 H)	7.67 (s, 3 H)	2.55 (m, 7 H)
18	3A-5'-CTMF	5.1 (s, 2 H), 5.4 (m, 2 H), 5.77 (t, 1 H), 5.98 (q, 1 H)	7.0–7.4 (m, 1 H)[d] 7.8–8.1 (m, 5 H)	7.67 (s, 3 H)	2.58 (m, 7 H)
19	2-CTMF	5.28 (t, 1 H), 5.62 (d, 2 H), 5.65–5.75 (m, 1 H), 5.9–6.15 (m, 2 H), 6.22 (m, 1 H)	6.9–7.3 (m, 1 H)[d] 7.7–8.1 (m, 5 H)		2.58 (m, 7 H)
20	3-CTMF	5.22 (d, 2 H), 5.59 (t, 1 H), 5.71 (m, 2 H), 6.03 (m, 2 H)	7.8–8.2 (m, 6 H)		2.56 (m, 7 H)
21	2,2'-CCTMF	Not detected			
22	2,3'-CCTMF	5.17 (q, 1 H), 5.25–5.5 (m, 3 H), 5.67 (m, 2 H)	6.85–7.3 (m, 1 H)[d] 7.6–8.1 (m, 5 H)		2.58 (m, 7 H) 2.67 (m, 7 H)
23	2,5'-CCTMF	Not detected			
24	3,3'-CCTMF	Not detected			
25	3,4'-CCTMF	5.18 (t, 2 H), 5.25–5.45 (m, 4 H)	7.95 (s, 6 H)		2.57 (m, 14 H)
27		6.12 (m, 4 H), 6.59 (s, 1 H)	7.23–8.55 (m, 16 H)[f]		

[a] Chemical shifts (τ) measured in $CDCl_3$ solution. [b] TMF = 1,1'-trimethyleneferrocene, A = acetyl, AA = diacetyl, C = cinnamoyl, CC = dicinnamoyl. [c] In order: chemical shift, multiplicity, number of protons. [d] These resonances indicate ring acylation α to the trimethylene bridge: G. J. Gauthier, J. A. Winstead, and A. D. Brown, Jr., *Tetrahedron Lett.*, 1593 (1970). [e] Includes phenyl group resonances. [f] Includes aliphatic protons of propionic acid side chain.

TABLE II
Subsequent Acylation of Acyl[3]ferrocenophane

Substrate	Catalyst	Moles of catalyst/ moles of substrate	Yield (overall) of acetylated product, %	Isomer distribution
2-acetyl TMF	AlCl₃	1	0	
	AlCl₃	2	90	**5:6:7** = 9.8:1.6:1.0
	BF₃	2	69	**5:6:7** = 6.7:2.4:1.0
	BF₃:O(C₂H₅)₂	2	0	
3-acetyl TMF	AlCl₃	1	0	
	AlCl₃	2	91	**9:5:6:10** = 39.0:11.4:- 4.5:1.0
2-cinnamoyl TMF	AlCl₃	2	60	**15:18:14** = 3.2:1.2:1.0
3-cinnamoyl TMF	AlCl₃	2	65	**17:12:13** = 8.6:2.0:1.0

along with the isomer distributions obtained from the acetylation of various acetyl and cinnamoyl [3]ferrocenophanes, indicates that the first acyl substituent directs the attacking group to a position on the second, unsubstituted ring as indicated in Figure 4 by arrows. A transition state such as that shown in Figure 4 would account for all of the above observations. Such a complex[9] would be of approximately the right length to reach the positions on the unsubstituted ring, which are indicated by arrows and would be too short to reach

(9) Figure 4 is meant only to be indicative and no significance should be placed on coordinations shown for aluminum species.
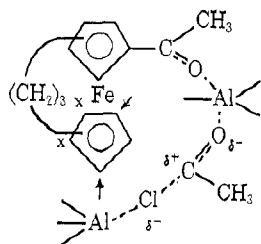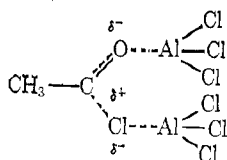
Figure 4.—Complex intermediate.

Figure 5.—Acetyl chloride–aluminum chloride 1:2 complex.

the positions indicated by x's. (It should be noted that the configurations of the rings are frozen with respect to each other by the presence of the trimethylene bridge.)

If the complex pictured in Figure 4 is plausible, the acetyl[3]ferrocenophane must be capable of complexing with aluminum chloride at the carbonyl oxygen and the acetyl chloride must be capable of complexing with two aluminum chloride molecules. That this is true can be seen by examining the infrared spectra summarized in Table III. The complexation of the carbonyl

TABLE III

CARBONYL STRETCHING FREQUENCIES OF AlCl₃ COMPLEXES

Compd	Molar ratio of AlCl₃	C=O, cm⁻¹
3-Acetyl TMF	0	1660[a]
3-Acetyl TMF	1	1510[a]
3-Acetyl TMF	2	1510[a]
Acetyl chloride	0	1805[b]
Acetyl chloride	1	1630,[b] 2200, 2300
Acetyl chloride	2	∼1780[a]

[a] Measured in methylene chloride solution. [b] Data from D. Cassimatis, J. P. Bonnin, and T. Theophanides, *Can. J. Chem.*, **48**, 3860 (1970), and references cited therein.

oxygen of 3-acetyl[3]ferrocenophane with aluminum chloride is shown by the strong bathochromic shift (150 cm⁻¹) of the carbonyl stretching band on addition of an equivalent amount of aluminum chloride. (The addition of a second equivalent of aluminum chloride does not affect this absorption.)

Cassimatis, *et al.*,[10] have shown that acetyl chloride forms a 1:1 complex with aluminum chloride that shows a strong hypsochromic shift corresponding to complexation by aluminum at the chlorine of acetyl chloride and a bathochromic shift (175 cm⁻¹) corresponding to complexation at the carbonyl oxygen. The infrared spectrum of an acetyl chloride–aluminum chloride 1:2 mixture shows only a broad absorption at ∼1780 cm⁻¹ for the carbonyl which would be indicative of a structure such as that shown in Figure 5, that is, a complexation by aluminum at both the chlorine and the carbonyl oxygen of acetyl chloride, giving a car-

(10) D. Cassimatis, J. P. Bonnin, and T. Theophanides, *Can. J. Chem.*, **48**, 3860 (1970).

bonyl stretching absorption between the two extremes previously cited.[10]

It can be seen from Table II that Lewis acids which are poorer complexing agents than aluminum chloride, *e.g.*, boron trifluoride[11] and boron trifluoride etherate, give poorer overall yields and less specificity than aluminum chloride. An investigation of this phenomenon has been undertaken by this laboratory. Results will be published in the near future.

Experimental Section

Methylene chloride (Baker Analyzed) was dried immediately prior to use in the acylation reactions by passing it through a column of activity I alumina. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian A-60 nmr spectrometer using tetramethylsilane as an internal standard and deuteriochloroform as a solvent. The nmr data is presented in Table I. Infrared spectra were obtained in methylene chloride solution in 1.0 mm solution cells with sodium chloride windows. Spectra were obtained on a Beckman IR-20 in double beam mode with solvent in the reference beam. All melting points were determined using a Reichert Austria melting point apparatus and are uncorrected. Analyses were performed at Galbraith Laboratories, Inc., Knoxville, Tenn., and at Huffman Laboratories, Inc., Wheatridge, Colo.

Acylation of [3]Ferrocenophane (1).—Monoacyl[3]ferrocenophanes were prepared by reacting equimolar amounts of acid chloride, aluminum chloride, and [3]ferrocenophane. Diacyl[3]ferrocenophanes required a 2:1 or greater molar ratio of the acid chloride and the aluminum chloride to [3]ferrocenophane. As a typical experiment, diacetyl[3]ferrocenophanes were prepared by adding a solution of 5.7 g (73 mmol) of acetyl chloride and 12.6 g (95 mmol) of AlCl₃ in 150 ml of methylene chloride to a solution of 6.0 g (26 mmol) of [3]ferrocenophane in 150 ml of methylene chloride. The reaction was allowed to proceed with stirring in a nitrogen atmosphere for 5 hr at 25° and then was quenched by pouring into 200 ml of ice water. The organic layer was separated and the aqueous solution was extracted with methylene chloride. The combined organic solutions were dried (MgSO₄) and concentrated *in vacuo* to an oily residue. The separation of isomers is described below.

Acylation of Acyl[3]ferrocenophane.—Acylation of an acyl[3]ferrocenophane required 1 mol of acid chloride and 2 mol of AlCl₃ to 1 mol of the acyl[3]ferrocenophane. The synthesis of the acetyl derivatives of 3-cinnamoyl[3]ferrocenophane illustrates a typical reaction. To a solution of 1.6 g (4.5 mmol) of 3-cinnamoyl[3]ferrocenophane (20) and 0.74 g (5.6 mmol) of AlCl₃ in 60 ml of dry methylene chloride was added dropwise, under nitrogen, a solution of 0.44 g (5.6 mmol) of acetyl chloride and 0.74 g (5.6 mmol) of AlCl₃ in 60 ml of methylene chloride. The reaction was allowed to proceed for 5 hr at 25° and was quenched by pouring into 100 ml of ice water. Acetylations of 2- and 3-acetyl[3]ferrocenophanes were run for 16 hr. The organic layer was combined with the methylene chloride extractions of the aqueous layer, dried (MgSO₄), and concentrated *in vacuo*.

Acetylation of 2-Acetyl[3]ferrocenophane with Acetic Anhydride and BF₃.—2-Acetyl[3]ferrocenophane (2) was acetylated using the acetic anhydride/BF₃ procedure of Carty and Dove[6] to determine the 2,3':2,4' isomer ratio. A stirred solution of 0.89 g (3.3 mmol) of 2 and 0.51 g (5 mmol) of acetic anhydride in 50 ml of dry, oxygen-free methylene chloride was saturated with purified BF₃ at 0°. The BF₃ was purified by bubbling through concentrated sulfuric acid saturated with boric oxide and then through a Dry Ice–acetone trap. The reaction mixture was stirred for 4 hr at 0° and then the excess boron trifluoride was expelled with nitrogen. Saturated sodium acetate was added and the methylene chloride layer was separated, washed with water, dried (MgSO₄), and evaporated to yield an oily residue.

The isomers were separated as described below to yield a trace of starting material, 0.07 g of the 2,5'-diacetyl isomer 7, 0.48 g

(11) BF₃ has been shown to cause a bathochromic shift of carbonyl stretching frequencies on the order of 75 cm⁻¹: M. Rabinovitz and A. Grinvold, *Tetrahedron Lett.*, 641 (1971).

of the 2,3' isomer 5, and 0.17 g of the 2,4'-diacetyl[3]ferroceno-phane (6) for a 70% overall yield.

Separation of Isomers. Diacetyl Isomers of [3]Ferroceno-phane.—The oily residue from the diacylation of 6.0 g (26.5 mmol) of 1 was chromatographed on deactivated neutral alumina. Six bands developed. The first band, eluted with petroleum ether (bp 20–40°)–diethyl ether (3:2), gave 1.6 g of starting material. The second band, also eluted with petroleum ether-diethyl ether, yielded 0.06 g (0.8%) of yellow-orange needles of 3-acetyl[3]ferrocenophane (3). The third band yielded 0.12 g (1.5%) of the 2,5'-diacetyl isomer 7, which was recrystallized from hexane as red-orange plates, mp 144–146°. The fourth band contained a mixture of the 2,3' and 2,4' isomers (5 and 6, respectively). The 2,3'-diacetyl[3]ferrocenophane (5) crystal-lized from a hexane solution of the mixture to yield 1.16 g of orange plates, mp 113–114°. The fifth band was eluted with methylene chloride and yielded 0.024 g of 3,4-diacetyl[3]fer-rocenophane (10), which crystallized from hexane as orange plates, mp 109–111°. The sixth band, also eluted with meth-ylene chloride, yielded 1.6 g (19%) of 3,4'-diacetyl[3]ferro-cenophane (9) as orange plates, mp 132–134°.

The supernatant from fraction four, after the fractional crystallization of 5, was chromatographed on silica columns using methylene chloride–chloroform (1:1) and loading each column with a very small amount of the mixture. Combination of the first fraction from six 3 × 50 cm silica columns gave, after crystallization from petroleum ether (bp 60–110°), 0.29 g (3.5%) of the 2,4'-diacetyl[3]ferrocenophane (6) as red-orange blocks, mp 94–96°. The second fractions yielded an additional 0.14 g of 5 for a total yield of 1.3 g (16%) of 2,3'-diacetyl[3]ferroceno-phane.

Anal. Calcd for $C_{17}H_{18}O_2Fe$: C, 65.85; H, 5.85; Fe, 18.01. Found—2,5' isomer (7): C, 65.97; H, 5.93; Fe,17.85. 2,4' isomer (6): C, 65.74; H, 5.86; Fe, 17.83. 2,3' isomer (5): C, 65.69; H, 5.94; Fe, 18.05. 3,4 isomer (10): C, 65.96; H, 5.95; Fe, 17.52. 3,4' isomer (9): C, 65.95; H, 5.94; Fe, 17.83.

Diacetyl Isomers from Acetylation of 3-Acetyl[3]ferroceno-phane.—The product mixture from the acetylation of 3.89 g (14.5 mmol) of 3 was first chromatographed on deactivated neutral alumina. Four bands developed. The first band, eluted with petroleum ether (bp 20–40°)–diethyl ether (3:2), gave a trace of starting material. The second band, eluted with the same solvent, was a mixture of 5 and 6. The third band yielded 0.074 g of 10. The fourth band, eluted with chloroform, yielded 2.87 g (64%) of 9. After fractional crystallization of 0.68 g of 5 from fraction 2, the remaining mixture was rechromat-ographed on silica columns. The first band, eluted with meth-ylene chloride–chloroform (1:1), yielded 0.33 g (7%) of 6. The second band, eluted with chloroform, gave 0.16 g of 5 for a total yield of 0.84 g (19%) of 5. Overall yield for the diacetyl isomers was 91%.

Diacetyl Isomers from Acetylation of 2-Acetyl[3]ferroceno-phane.—The oily residue obtained from the acetylation of 1.68 g (6.3 mmol) of 2, after work-up, was chromatographed on de-activated neutral alumina. The first band, eluted with pe-troleum ether–diethyl ether (2:1), yielded 0.14 g of 7. The second band, eluted with methylene chloride, was a mixture of 5 and 6. After fractional crystallization of 1.06 g of 5 from fraction 2, the remaining mixture was chromatographed on silica, as described above, to yield 0.23 g of 6 and an additional 0.32 g of 5. Total yield of the diacetyl isomers was 90%.

Dicinnamoyl Isomers of [3]Ferrocenophane.—The mixture of isomers from the dicinnamoylation of 2.6 g (11.5 mmol) of 1 was chromatographed on neutral alumina employing mixtures of petroleum ether (bp 20–40°), methylene chloride, and chloro-form as eluents. Two bands developed. The first band gave, after recrystallization from hexane, 0.8 g (14%) of 2,3'-di-cinnamoyl[3]ferrocenophane (22) as red-orange needles, mp 138–140°. The second band yielded, after recrystallization from petroleum ether (bp 30–60°), 2.6 g (47%) of 3,4'-dicin-namoyl[3]ferrocenophane (25) as red blocks, mp 205–207°.

Anal. Calcd for $C_{31}H_{26}O_2Fe$: C, 76.55; H, 5.39; Fe, 11.48. Found—3,4' isomer (25): C, 76.59; H, 5.49; Fe, 11.39. 2,3' isomer (22): C, 76.57; H, 5.61; Fe, 11.51.

Cinnamoyl Isomers of [3]Ferrocenophane.—The oily residue from the monocinnamoylation of 4.0 g (17.6 mmol) of 1 was chromatographed on neutral alumina. Three bands developed. The first was eluted with petroleum ether (bp 20–40°)–ether (3:2) yielding 0.2 g of starting material. The second band,

eluted with ether, gave, after recrystallization from petroleum ether, 1.15 g (18%) of 2-cinnamoyl[3]ferrocenophane (19) as reddish-orange needles, mp 131–133°. The third band was eluted with a mixture of methylene chloride and chloroform. After recrystallization from low-boiling petroleum ether, the third band yielded 3.45 g (55%) of 3-cinnamoyl[3]ferrocenophane (20) as red plates, mp 145–146°.

Anal. Calcd for $C_{22}H_{20}OFe$: C, 74.17; H, 5.66; Fe, 15.68. Found—2 isomer (19): C, 73.95; H, 5.72; Fe, 15.70. 3 isomer (20): C, 74.12; H, 5.74; Fe, 15.43.

Acetyl Isomers of 3-Cinnamoyl[3]ferrocenophane.—The mix-ture of isomers from the acetylation of 1.6 g (4.5 mmol) of 20 was chromatographed on neutral alumina. Three bands de-veloped. The first band was eluted with hexane–benzene (1:1) and yielded 0.10 g (5.5%) of 2-acetyl-4'-cinnamoyl[3]ferroceno-phane (13) (or 3-cinnamoyl-5'-acetyl[3]ferrocenophane) which crystallized from petroleum ether (bp 30–60°) as orange plates, mp 58–60°. The second band, eluted with benzene, gave 0.20 g (11%) of 2-acetyl-3'-cinnamoyl[3]ferrocenophane (12). This isomer crystallized from cyclohexane as orange plates, mp 131–133°. Petroleum ether (bp 20–40°)–diethyl ether (3:2) eluted the first two bands in reverse order (i.e., compound 12 before 13). In both cases the separation was difficult. Methylene chloride eluted a third band which yielded 0.86 g (48%) of 3-acetyl-4'-cinnamoyl[3]ferrocenophane (17) (3-cinnamoyl-4'-acetyl[3]-ferrocenophane) as orange plates, mp 163–165°.

Anal. Calcd for $C_{24}H_{22}O_2Fe$: C, 72.38; H, 5.57; Fe, 14.02. Found—2-Acetyl-3'-cinnamoyl isomer (12): C, 72.45; H, 5.60; Fe, 13.75. 2-Acetyl-4'-cinnamoyl isomer (13): C, 72.44; H, 5.60; Fe, 13.75. 3-Acetyl-4'-cinnamoyl isomer (17): C, 72.47; H, 5.62; Fe, 14.30.

Acetyl Isomers of 2-Cinnamoyl[3]ferrocenophane.—The mix-ture of isomers from the acetylation of 0.8 g (2.2 mmol) of 19 was chromatographed on neutral alumina employing mixtures of petroleum ether (bp 20–40°), diethyl ether, and methylene chloride as eluents. Four bands developed. The first band yielded 0.05 g of starting material. The second band gave, after recrystallization from hexane, 0.10 g (11%) of 2-acetyl-5'-cinnamoyl[3]ferrocenophane (14) as red plates, mp 155–157°. The third band yielded 0.12 g (13%) of 3-acetyl-5'-cinnamoyl-[3]ferrocenophane (18) which crystallized from hexane as rods, mp 180–181°. The fourth band gave 0.32 g (37%) of 3-acetyl-2'-cinnamoyl[3]ferrocenophane (15), mp 212–213.5°.

Anal. Calcd for $C_{24}H_{22}O_2Fe$: C, 72.38; H, 5.57; Fe, 14.02. Found—2-Acetyl-5'-cinnamoyl isomer (14): C, 72.49; H, 5.68; Fe, 13.90. 3-Acetyl-2'-cinnamoyl isomer (15): C, 72.44; H, 5.45; Fe, 14.30. 3-Acetyl-5'-cinnamoyl isomer (18): C, 72.49; H, 5.33; Fe, 14.19.

Interconversion of Acetyl and Cinnamoyl Derivatives of [3]Ferrocenophane.—The cinnamoyl derivatives of trimethylene-ferrocene were converted to acetyl derivatives by heating them to 68° in aqueous ethanol under nitrogen in the presence of NaOH for 24 hr. As a typical experiment, 0.7 g (1.75 mmol) of 3-acetyl-4'-cinnamoyl[3]ferrocenophane (17) was dissolved in 100 ml of 95% ethanol, and 20 ml of aqueous 15% NaOH was added. The solution was then heated under nitrogen for 24 hr at 68°, diluted with two volumes of water, extracted with methylene chloride, and dried (MgSO₄). After concentrating, the residue from the work-up of the reaction mixture was chro-matographed on neutral alumina employing petroleum ether (bp 20–40°)–diethyl ether (3:2). The major band yielded 0.36 g (66%) of 3,4'-diacetyl[3]ferrocenophane (9), mp 131–134°.

Acetyl derivatives were converted to cinnamoyl derivatives by addition of benzaldehyde to a solution of the acetyl derivative and NaOH in aqueous ethanol. For example, 0.24 g (2.4 mmol) of benzaldehyde was added to a solution of 0.5 g (1.6 mmol) of 3,4'-diacetyl[3]ferrocenophane (9) in 50 ml of 95% ethanol and 5 ml of aqueous 15% NaOH. The reaction mixture was stirred under nitrogen at 25° for 24 hr. The solution was diluted with 50 ml of water, extracted with methylene chloride, dried (Mg-SO₄), concentrated, and chromatographed on neutral alumina. The first band, eluted with petroleum ether–diethyl ether (3:2), gave 0.19 g (30%) of 3-acetyl-4'-cinnamoyl[3]ferrocenophane (17), mp 162–164°. The second band, eluted with diethyl ether, yielded 0.09 g of starting material. The third band, eluted with methylene chloride, yielded 0.2 g (25%) of 3,4'-dicinnamoyl[3]ferrocenophane (25), mp 203–207°. This re-action in the presence of excess benzaldehyde (10:1) yielded only the dicinnamoyl derivative 25.

The results of a number of interconversions are summarized in Table IV. The melting points of the products are given and

TABLE IV
RESULTS OF INTERCONVERSION OF ISOMERS OF
[3]FERROCENOPHANE

Starting isomer	Product	Yield, %	Mp, °C
9 (9:PhCHO; 1:1.5)	17	30	162–164
	9	18	132–134
	25	25	203–207
9 (9:PhCHO; 1:10)	25	61	205–207
12	5	64	113–114
13	6	64	93–96
14	7	53	145–146
15	5	51	110–113
17	9	66	131–134
18	6	64	94–96
22	5	78	112–114
25	17	57	163–165
	9	Trace	

in all cases the nmr spectra of the products were identical with those of the isomer assigned.

Conversion of 2,3'-Diacetyl[3]ferrocenophane (5) to 2-[3][3]-1,3-ferrocenophanylpropionic Acid.—A mixture of 2.38 g (7.6 mmol) of 5 was converted to 1.56 g (55%) of 2,3'-[3]ferrocenophanyldipropionic acid (26), mp 158–162°, according to the procedure of Rinehart, *et al.*[2]

The diacid 26 (1.56 g, 4.2 mmol) was dissolved in 100 ml of dry methylene chloride and added slowly to a solution of 5 g (26 mmol) of trifluoroacetic anhydride in 50 ml of cold methylene chloride. The solution was maintained at 0° in a nitrogen atmosphere for 22 hr, then quenched by the addition of 100 ml of 5% sodium bicarbonate. The pH of the solution was adjusted to 6 so that the acid would remain in the organic layer. After separation of the organic layer and the extraction of the aqueous layer, the combined organic fractions were dried (MgSO₄) and concentrated. The material was chromatographed on a silica gel column packed in chloroform. Four bands developed. The first band, eluted with chloroform, and the second band,

eluted with chloroform–ethyl acetate (3:1), were unidentified. The third band, also eluted with the chloroform–ethyl acetate mixture, yielded 0.63 g (43%) of the crude yellow oily dibridged keto acid. The fourth band, eluted with methanol, was probably a mixture of decomposition products. The keto acid was dissolved in 50 ml of acetic acid and hydrogenated over 0.5 g of platinum oxide at 52 psi for 65 hr. After work-up, a yield of 0.57 g of oil was obtained. Repeated recrystallization from petroleum ether gave 0.28 g (46%) of 2-[3][3]-1,3-ferrocenophanylpropionic acid (27), mp 146–148°.

Anal. Calcd for C₁₉H₂₂O₂Fe: C, 67.47; H, 6.56; Fe, 16.51. Found: C, 67.63; H, 6.60; Fe, 16.41.

Preparation of 27 from 2-Acetyl[3][3]-1,3-ferrocenophane.—A solution of 3.0 g (11 mmol) of [3][3]-1,3-ferrocenophane (28, synthesized according to Rinehart, *et al.*[2]) and 2.75 ml of acetic anhydride in 50 ml of dry methylene chloride was cooled to 0° under nitrogen. BF₃ etherate (4 ml) was added and the solution was stirred at 0° for 30 min and then at 25° for 16 hr. The reaction was quenched by pouring into 50 ml of ice water. After work-up, the crude product was transferred to an alumina column and eluted with petroleum ether (bp 20–40°) to remove a trace of starting material and then 0.60 g (17%) of 2-acetyl[3][3]-1,3-ferrocenophane (28). Recrystallization of 28 from hexane yielded orange rods, mp 101–102° (lit.[2] mp 101–102.5°). A third band, eluted with petroleum ether–ether (4:1), yielded 1.9 g (55%) of 4-acetyl[3][3]-1,3-ferrocenophane, mp 148–149° (lit.[2] mp 148.5–149.5°).

A mixture of 0.5 g (1.6 mmol) of 28, 32 mmol of sodium hydride, and 0.6 g (4.8 mmol) of diethyl carbonate in 30 ml of dry benzene was heated at reflux for 48 hr in a nitrogen atmosphere. After the usual work-up, the crude keto acid was dissolved in 50 ml of acetic acid and hydrogenated over 0.3 g of platinum oxide at 52 psi for 48 hr. The reduced ester was isolated and saponified in refluxing ethanolic 2 N sodium hydroxide (1:1 ethanol–water). The crude acid obtained after work-up was purified on a silica gel column packed in chloroform. The first fraction, eluted with chloroform, was a mixture of nonacidic compounds. The acid was eluted with chloroform–ethyl acetate (3:1). Recrystallization from hexane yielded 0.25 g (46%) of yellow needles, mp 146.5–148°, whose nmr and infrared spectra were identical with those of 27 obtained from 5 described above.

Anal. Calcd for C₁₉H₂₂O₂Fe: C, 67.47; H, 6.56; Fe, 16.51. Found: C, 67.64; H, 6.59; Fe, 16.53.

The Base-Induced Rearrangement of Epoxides. IV. Reaction of Cyclohexene Oxide with Various Lithium Alkylamides[1]

CHARLES L. KISSEL AND BRUCE RICKBORN*

Department of Chemistry, University of California, Santa Barbara, California 93106

The effect of variation of base structure in the reaction with cyclohexene oxide has been explored. The yields of the products 2-cyclohexenol, cyclohexanone, and amino alcohol (nucleophilic substitution) were determined for an extensive series of lithium alkylamides. The yield of 2-cyclohexenol is maximized with lithium di(primary alkyl)amide, being effectively quantitative with lithium di-n-propylamide and di-n-butylamide. Lithium monoalkylamides in general give low to moderate yields of the allylic alcohol, very little ketone, and extensive amino alcohol adduct formation. Bulky bases favor the formation of ketone at the expense of allylic alcohol. Certain bases cause the rearrangement of 2-cyclohexenol to 3-cyclohexenol, and the mechanism of this transformation has been briefly explored.

The reaction of epoxides with strong bases can occur by at least three major pathways, *viz.*, rearrangement to allylic alcohol, to ketone, or by direct nucleophilic substitution. Our earlier studies have been directed to the first process.[1b] The regiospecificity and stereospecificity exhibited in the reaction of a number of epoxides with lithium diethylamide to give allylic alcohol suggest the considerable synthetic potential

of this procedure. This paper describes the results of treating a single model system, cyclohexene oxide, with a wide range of lithium alkylamides, to test the effect of structural variation of the base on the yields of the various possible products.

Results and Discussion

The lithium alkylamide reagents were prepared by treating the appropriate amine in ether with n-butyllithium in hexane; 2.5 mol of base were used for each mole of epoxide. The excess of base was used because