previously synthesized and their physical properties reported (for references, see Table I).

Acknowledgment. We are grateful for the American Chemical Society Organic Divisional Fellowship to J.W.K. sponsored by the Rohm & Haas Co. We also express our appreciation to Philip L. Robinson for useful discussions and the Department of Energy (DE-AS05-80-ER10641), the National Research Council's Senior Postdoctoral Fellowship Program, and the Fulbright Research Scholar's Program (to S.A.E.) for support of this research.

Friedel-Crafts Acylation of Methyl Ester of Phenylacetic Acid: A Reinvestigation

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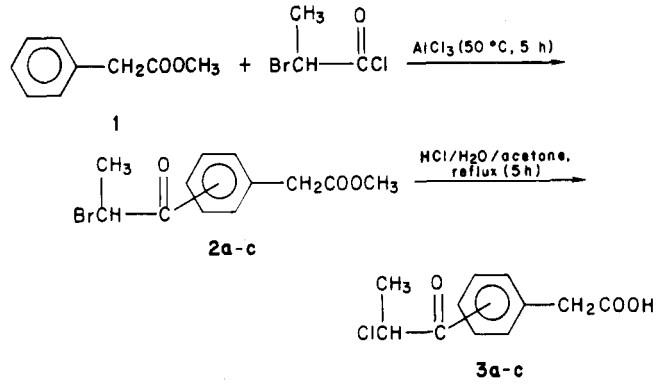
The Friedel–Crafts acylation of phenylacetic acid derivatives has been a conflicting matter, as far as positional selectivity is concerned.[1,2]

In 1966 Morgan[3] reported conclusive results on the Friedel–Crafts acylation of alkyl esters of phenylacetic acid with several acyl halides: a mixture of alkyl esters of acylphenylacetic acid (isomers ratio ortho/meta/para = (4–6)/(38–49)/(44–58)) was obtained, thus showing the lack of positional selectivity of the reaction.

Recently,[4,5] it has been reported that the methyl ester of phenylacetic acid is acylated with 2-bromopropionyl chloride, in the presence of aluminum chloride, to give the *p*-acyl isomer in 86% yield.

These results were of particular interest for two main reasons: (i) The unusual high para selectivity certainly should have had mechanistic involvements concerning the relationships among structure, reactivity, and selectivity in the Friedel–Crafts acylation. On the other hand the above result[4,5] was in agreement with the behavior of other electrophiles in aromatic electrophilic substitution of esters of phenylacetic acid. As a matter of fact, in the chloromethylation of ethyl ester of phenylacetic acid the para position is 10 times more reactive than the meta position[6] and in the not very selective nitration, the para position is 5 times more reactive than the meta position.[7] The $-CH_2COOR$ group appears to be, on the whole, activating[7] (the partial rate factors of both, meta and para position, are >1) though the reported substituent constants[8] σ_I = +0.19 and σ_R^+ = −0.08 are not fully consistent with the above conclusion.

Scheme I



(ii) The (α-bromopropionyl)arenes are important intermediates on the synthesis of α-arylpropionic acids,[9] which are well known as antiinflammatory drugs.[10]

Our interest in the synthesis of α-arylalkanoic acids from α-haloalkyl aryl ketones[9] and the unexpected and very promising result[4,5] prompted us to revisit the reaction between methyl ester of phenylacetic acid (1) and 2-bromopropionyl chloride in the presence of aluminum chloride in 1,1,2,2-tetrachloroethane. The reaction was carried out according to the given procedure: distillation of reaction crude gave an oil (bp 145–147 °C (0.2 mmHg)) in the described amount.

GC, ^1H NMR, and GC–MS analyses performed on the reaction crude as well as on the distilled fraction showed the presence of three isomeric acyl derivatives **2a–c** in the ratio 6:46:48, respectively (see Scheme I).

It is worth noting that the isomeric ratio does not change during the reaction course.

Moreover, when mixtures of **2a–c**, with diverse compositions, were treated under the reaction conditions described for the acylation of the methyl ester of phenylacetic acid (1), the starting products were recovered almost quantitatively and the isomeric ratio was found to be unchanged (see Experimental Section).

These results show unequivocally that the isomer distribution observed in the preparation of **2a–c** is determined by the kinetics of the reaction.

Hydrolysis, according to the procedure described by the authors,[5] of the isomer mixture gave the corresponding acids **3a–c** in unchanged ratio with respect to that of starting esters **2a–c**.

The GC–mass spectroscopy of **2a**, **2b**, and **2c** showed (see Experimental Section) the molecular ion M^+ *m/e* 284/286 as expected for isomeric methyl esters of (2-bromopropionyl)phenylacetic acid. Moreover, the fragmentation of **2b** and **2c** is identical whereas **2a** showed fragments *m/e* 174 and 146 related to typical cyclic structures of this ortho-substituted system.

Methyl esters **2b** and **2c** were separated as pure compounds, by preparative GC, respectively (see Experimental Section). The attribution of the para structure, by ^1H and ^{13}C NMR, to **2c** and **3c** (see Experimental Section) was straightforward on the basis of the analysis of the signal multiplicity of aromatic protons (AA′BB′ system) and on

(1) Papa, D.; Schwenk, E.; Klingshig, A. *J. Am. Chem. Soc.* **1946**, *68*, 2133.
(2) Bergmann, E. D.; Blum, J. *J. Org. Chem.* **1950**, *24*, 549.
(3) Morgan, E. D. *Tetrahedron* **1967**, *23*, 1735.
(4) Tjoeng, F. S.; Heavner, G. A. *Tetrahedron Lett.* **1982**, *23*, 4439.
(5) Tjoeng, F. S.; Heavner, G. A. *J. Org. Chem.* **1983**, *48*, 355.
(6) Nogarov, I. N.; Semenovskii, A. V. *Izv. Akad. Nauk SSSR* **1957**, 100.
(7) Knowles, J. R.; Norman, R. O. C. *J. Chem. Soc.* **1961**, 2938.
(8) Charton, M. In "Physical Organic Chemistry"; R. W. Toft, Ed.; Wiley–New York, **1981**; Vol. 13, pp 145, 211.
(9) Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem.* **1984**, *96*, 403; *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 413.
(10) Lednicer, D. and Metscher, L. A. "The Organic Chemistry of Drugs Synthesis"; Wiley: New York **1977**; Chapter 6. Shen, T. Y. *Angew. Chem.* **1972**, *84*, 512; *Angew Chem.; Int. Ed. Engl.* **1972**, 6, 460, Ferreira, S. H.; Vane, J. R. "Antiinflammatory Drugs"; Springer-Verlag: New York, **1979**; p 321; *Scrip.* **1980**, 497, 10.

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the basis of the equivalence of the unsubstituted aromatic carbons (only four signals for six carbons).

The meta structure was assigned to **2b** and **3b** on the basis of the analysis of the completely coupled ^{13}C NMR spectrum of compound **3b**;[11] accordingly the ortho structure was assigned to **2a**. From the above findings it comes out that the ratio among the isomers is ortho:meta:para (**2a**:**2b**:**2c**) = 6:46:48.

Similar results, as far as the isomer distribution is concerned, were obtained by carrying out the reaction between the methyl ester of phenylacetic acid **1** with other acyl halides such as acetyl chloride, propionyl chloride, and chloroacetyl chloride. Thus, the lack of positional selectivity in the acylation of phenylacetates, as anticipated by Morgan,[3] is confirmed also for the α-bromopropionyl chloride.

Our results indicate that the method is not suitable for large scale preparations of para-acylphenylacetates. It seems likely that in the previous work[4,5] the mixture of ortho, meta, and para isomers were not separated and were considered as a single isomer. It could appear surprising that a very selective aromatic electrophilic substitution, such as acylation, gives a lower positional selectivity even than the nitration, which is the less selective among the aromatic electrophilic substitutions. This discrepancy is only apparent because the interaction between the ester group and aluminum chloride changes the polar character of the substituent from a electron-donating to a electron-withdrawing group. In fact competitive experiments between benzene and the methyl ester of phenylacetic acid (see Experimental Section) showed the latter as deactivated. This substrate selectivity is reflected in the low positional selectivity of the para position.

Experimental Section

^1H and ^{13}C NMR spectra were taken at 200 MHz of solutions in deuteriochloroform unless otherwise noted and are referenced to internal Me_4Si.

GC analyses were performed on a Perkin-Elmer 8320 instrument using a glass column (3 mm, 2 m), 3% OV 225 on Gas chromatography Q (100–120); chromatographic conditions—programmed 2 min at 120 °C, then 10 °C/min to 240 °C, injector 250 °C, FID 280 °C; flow 66 mL/min, carrier He.

GC quantitative analyses were performed with 2-methoxynaphthalene as the internal standard on the reaction crude.

Preparative GC was performed by using a glass column (9 mm × 1 m) of 20% OV 17 on Chromosorb A (40–60 mesh) with a Carlo Erba 4200 instrument; chromatographic conditions—oven temperature 250 °C, HWD 320 °C, helium 1.4 kg/cm^2. Mass spectra were recorded on quadrupole mass system Hewlett-Packard 5992/B with 5993 data system operating at 70-eV ionization voltage.

Reaction between Methyl Phenylacetate and 2-Bromopropionyl Chloride in the Presence of Aluminum Chloride. 2-Bromopropionyl chloride (50 g, 0.29 mol) was added dropwise into a suspension of aluminum chloride (80 g, 0.6 mol) in 1,1,2,2-tetrachloroethane (200 mL). The mixture was heated to 50 °C for 20 min, and methyl phenylacetate (37 g, 0.26 mol) was added at a rate such that the temperature did not exceed 50 °C. The reaction mixture, which turned dark, was stirred for another 4 h at the same temperature and cautiously poured into a beaker with ice (500 g). The solution was acidified with concentrated HCl to pH 1–2 (pH paper) and transferred into a separatory funnel.

The aqueous phase was extracted with dichloromethane (2 × 200 mL), and the combined organic extracts were washed with 2% NaOH (3 × 100 mL) and water (2 × 100 mL). The organic phase was dried over sodium sulfate for 4 h and filtered. The solvent was removed by evaporation and the residue was distilled through a vigreux column (10 cm) under reduced pressure. A light yellowish oil (60g) (145–147 °C (0.2 mmHg)) was collected. GC analysis showed the presence of three compounds (**2a–c**) in area ratio **2a**:**2b**:**2c** = 6:46:48.

2a: MS, M^+ m/e 284/286 (bromine isotopes), m/e 253 (M − ·OCH_3), m/e 225 (M − ·$COOH_3$), m/e 204 (M − HBr), m/e 174 (M − ·Br − ·OCH_3), m/e 146 (m/e 174 − CO), m/e 118 (M − ·$CHBrCH_3$ − ·$COOCH_3$).

2b: MS, M^+ m/e 284/286 (bromine isotopes), m/e 253 (M − ·OCH_3), m/e 225 (M − ·$COOCH_3$), m/e 204 (M − HBr), m/e 177 (M − ·$CHBrCH_3$), m/e 149 (m/e 177 − CO), m/e 145 (m/e 177 − CH_3OH), m/e 118 (M − ·$CHBrCH_3$ − ·$COOCH_3$); ^1H NMR ($CDCl_3$) δ 1.86 (d, 3 H), 3.62 (s, 3 H), 3.62 (s, 2 H), 5.26 (q, 1 H), 7.30–7.80 (m, 4 H).

2c: MS, M^+ m/e 284/286 (bromine isotopes), m/e 253 (M − ·OCH_3), m/e 225 (M − ·$COOCH_3$), m/e 204 (M − HBr), m/e 177 (M − ·$CHBrCH_3$), m/e 149 (m/e 177 − CO), m/e 145 (m/e 177 − CH_3OH), m/e 118 (M − ·$CHBrCH_3$ − ·$COOCH_3$); ^1H NMR ($CDCl_3$) δ 1.86 (d, 3 H), 3.62 (s, 3 H), 3.60 (s, 2 H), 5.24 (q, 1 H), 7.38–8.00 (AA′BB′, 4 H).

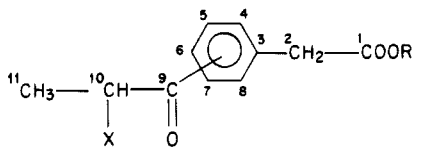
The ^{13}C NMR data for esters **2a–c** are reported below (see Table I); the chemical shift assignments obtained from ^{13}C coupled and undecoupled spectra are in nice agreement with the literature values.[11a–c]

Stability of the Mixture of 2a–c under Friedel–Crafts Reaction Conditions. A mixture of **2a**, **2b**, and **2c** (**2a**:**2b**:**2c** = 13.5:50.5:32.5; fraction collected in the distillation of a mixture of **2a–c** in a ratio of 6:46:48 through a vigreux column (30 cm) at 0.2 mmHg) (0.9 g, 3,2 mmol), **1** (0.1 g, 0.7 mmol), aluminum chloride (0.97 g, 7.3 mmol), and 1,1,2,2-tetrachloroethane (2.5 mL) was heated, under stirring, to 50 °C. The reaction mixture was saturated with hydrogen chloride and kept under these conditions for 7 h. The reaction mixture was cooled to room temperature, poured into water/ice and extracted with 1,1,2,2-tetrachloroethane (2 × 5 mL). GC analysis showed the presence of **1** (0.095 g) and of **2a–c** (0.88 g) in unchanged ratio.

Similar results were obtained starting from a mixture of **2b** and **2c** in a ratio of 32:68.

Preparation of [(2-Chloropropionyl)phenyl]acetic Acids 3b and 3c: General Procedure. The ester **2b** or **2c** (0.10 g) was refluxed in a mixture of acetone (1 mL), concentrated HCl (0.3 mL), and H_2O (0.7 mL) for 5 h. The progress of the reaction was monitored by thin-layer chromatography (silica gel Merek 60 F_{254}; $CHCl_3$/HOAc, 97.5:2.5) and judged complete by the disappearance of the ester (R_f 0.53). The mixture was filtered, and the acetone was removed with a rotary evaporator. The remaining aqueous phase was extracted with chloroform (3 × 50 mL). The acid was

Table I. ^{13}C NMR Chemical Shift Values for Compounds 2a–c and 3a–c[a]



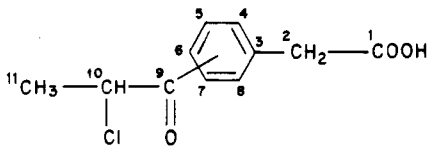
2a–c, R = CH_3; X = Br
3b–c, R = H; X = Cl

ppm	2a	2b	2c	3b	3c
R	51.9	52.2	52.24		
C_1	*b*	171.3	171.0	173.7	173.4
C_2	43.7	40.8	41.1	41.8	42.2
C_3	133.1	134.3	132.9	135.5	133.9
C_4	132.5	134.6	129.7	136.45	131.5
C_5	132.9	128.95	129.0	130.3	130.4
C_6	127.4	127.7	139.9	131.25	142.9
C_7	128.9	134.7	129.0	137.5	130.4
C_8	135.6	129.8	129.7	128.8	131.5
C_9	*a*	193.0	192.8	195.3	195.0
C_{10}	40.0	41.4	41.4	55.0	55.0
C_{11}	20.3	20.1	20.1	21.4	21.4

[a] Solvent: Me_2SO-d_6. [b] Undetected.

(11) (a) Levy, G. C.; Licher, R. L.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance" 2nd ed.; Wiley: New York, 1980. (b) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972. (c) Wehrli, F. W.; Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Meyden and Son Ltd: London, 1978.

Table II. Significative Values of Long-Range Coupling Constants $^{2,3}J$(C-H) (Hz) of Aromatic Carbons for Isomers 3b-c[a]



	3b	3c
C_3	$J_{C_3-H_5}$ 7.3	$J_{C_3-H_{5,7}}$ 7.8
C_4	*b*	$J_{C_4-H_2}$ 6.3; $J_{C_4-H_8}$ 6.9
C_5		$J_{C_5-H_7}$ 6.5
C_6	*b*	$J_{C_6-H_{5,7}}$ 6.7; $J_{C_6-H_{4,8}}$ 7.8; $J_{C_6-H_{10}}$ 1.5
C_7	$J_{C_7-H_8}$ 6(6.5)[c]; $J_{C_7-H_6}$ 6.5(6)[c]; $J_{C_7-H_5}$ 7.8; $J_{C_7-H_{10}}$ 1.4	$J_{C_7-H_5}$ 6.5
C_8	*b*	$J_{C_8-H_2}$ 6.3; $J_{C_8-H_4}$ 6.9

[a] An iterative computer analysis with LAOCOON 3 Program confirmed these coupling constant values. [b] Broad signal. [c] The values can be exchanged.

then extracted from chloroform with saturated sodium bicarbonate solution (3 × 50 mL). The pH of the sodium bicarbonate solution was brought to 1.5–2.0 with 6 N HCl under ice-bath cooling, and the product was back-extracted with chloroform (4 × 50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum to give **3b** or **3c**.

3b: ^{1}H NMR (Me_2SO-d_6) δ 1.68 (d, 3 H), 3.76 (s, 2 H), 5.79 (q, 1 H), 7.45–8.00 (m, 4 H).

3c: ^{1}H NMR (Me_2SO-d_6) δ 1.68 (d, 3 H), 3.76 (s, 2 H), 5.79 (q, 1 H), 7.55–8.20 (AA'BB', 4 H).

The ^{13}C NMR chemical shifts and the long-range ^nJ(C–H) values[12,13] available from ^{13}C coupled spectra for acids (**3b,c**) are reported in Tables I and II, respectively.

Preparation of 2-Bromopropiophenone. 2-Bromopropionyl chloride (19.9 g, 0.116 mol) was added dropwise into a suspension of aluminum chloride (16 g, 0.12 mol) in 1,1,2,2-tetrachloroethane. The mixture was heated to 50 °C for 20 min and benzene (7.8 g, 0.1 mol) was added at a rate such that the temperature did not exceed 50 °C. The reaction mixture was kept at the same temperature for 4 h, then worked up as described above for the preparation of compounds **2a–c**. Distillation of the reaction crude gives the 2-bromopropiophenone (identified by comparison with an authentic sample purchased from Aldrich) as an oil, bp 109–111 °C (5 mmHg) (19 g; 0.89 mol) 89% yield.

Competitive Reaction between the Methyl Ester of Phenylacetic Acid and Benzene with 2-Bromopropionyl Chloride in the Presence of Aluminum Chloride. (a) 2-Bromopropionyl chloride (3.85 g, 0.023 mol) was added dropwise into a suspension of aluminum chloride (6.65 g 0.05 mol) in 1,1,2,2-tetrachloroethane (20 mL). The mixture was heated to 50 °C for 20 min, and a mixture of methyl ester of phenylacetic acid (3.75 g, 0.025 mol) and benzene (1.95 g, 0.025 mol) was added at a rate such that the temperature did not exceed 50 °C. The reaction mixture was kept at the same temperature for 4 h and worked up as described above for the preparation of compounds **2a–c**.

Quantitative GC analysis of the reaction crude showed a mixture of the methyl ester of phenylacetic acid (2.55 g, 0.017 mol), (2-bromopropiophenone (3.29 g, 0.015 mol), and a mixture of ortho, meta, and para methyl esters of [(2-bromopropionyl)-phenyl]acetic acid (2.08 g, 0.007 mol) in the ratio **2a:2b:2c** = 6:46:48.

(b) 2-Bromopropionyl chloride (0.9 g, 0.0058 mol) was added dropwise into a suspension of aluminum chloride (4.78 g, 0.036 mol) in 1,1,2,2-tetrachloroethane (20 mL). The mixture was heated to 50 °C for 20 min, and a mixture of methyl phenylacetate (3.75 g, 0.025 mol) and benzene (1.95 g, 0.025 mol) was added at a rate such that the temperature did not exceed 50 °C. The reaction mixture was kept at the same temperature and worked up as described above for the preparation of compounds **2a–c**.

Quantitative GC analysis of the reaction crude showed a mixture of methyl phenylacetate (3.75 g, 0.025 mol) and 2-bromopropiophenone (1.23 g, 0.0058 mol).

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(12) (a) Mooney, E. F. "Annual Report on NMR Spectroscopy" Academic Press: New York, 1975; 6A. (b) Marshall, J. L. "Carbon–Carbon and Carbon–Proton NMR Coupling"; Verlag Chemie International: Deerfield Beach, Florida, 1983.

(13) Castellano, S.; Bothner-By, A. A. *J. Chem. Phys.* **1964**, *41*, 3863.

N-(Trimethylsilyl)methylphenylsulfoximine: A Convenient Intermediate for the Preparation of Functionalized Sulfoximines

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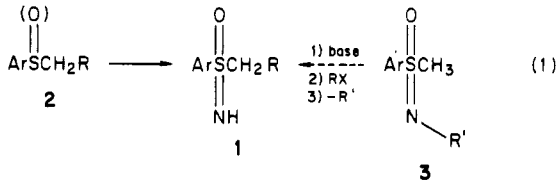
Because of their interesting chemical properties and biological activities,[1] heterocyclic sulfoximines[2] have recently attracted considerable attention. During a study aimed at the synthesis of such compounds, we required several functionalized free sulfoximines as intermediates. Although several methods are available for the preparation of free sulfoximines from di- and trivalent sulfur compounds (**2** → **1**, eq 1),[3] they are often of limited applica-



(1)

bility when the desired sulfoximines contain labile functional groups. An alternative approach of alkylating the readily generated anion derived from N-substituted methylsulfoximines (**3** → **1**, eq 1) has been studied in some cases,[4] but preparation of the desired *free* sulfoximines is again difficult and limited. Furthermore, alkylation chemistry of N-protected sulfoximines has not been studied in a systematic way.

We now report that carbon–carbon bond formation between *N*-(trimethylsilyl)(lithiomethyl)phenylsulfoximine and various electrophiles, followed by ready desilylation, provides simple access to a variety of free sulfoximines that

(1) For some leading references, see the recent reviews: P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, **9**, 477 (1980); C. R. Johnson in "Comprehensive Organic Chemistry", Vol. 3, D. N. Jones, Ed., Pergamon Press, Oxford, 1979, p 223 and references cited therein.

(2) (a) C. H. Levenson and R. B. Meyer, Jr., *J. med. Chem.* **27**, 228 (1984); (b) R. D. Dillard, T. T. Yen, P. Stark, and D. E. Davey, *J. Med. Chem.*, **23**, 717 (1980); (c) K. Schaffner-Sabba, H. Tomaselli, B. Henrici, and H. B. Renfroe, *J. Org. Chem.*, **42** (6), 952 (1977); (d) P. Stoss and G. Satinger, *Chem. Ber.*, **109**, (1976); *ibid.*, **108**, 3855 (1975); (e) T. R. Williams and D. J. Cram, *J. Org. Chem.*, **38**, 20 (1973).

(3) (a) From sulfoxides and NaN_3/H_2SO_4: J. K. Whitehead and H. R. Pentley, *J. Chem. Soc.*, 1572 (1952); (b) From sulfoxides and mesitylenesulfonylhydroxylamine; Y. Tamura, K. Sumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 4137 (1972); C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, *J. Org. Chem.*, **39**, 2458 (1974); (c) From sulfide and via indirect routes; references cited in review articles.

(4) C. R. Johnson and C. J. Stark, Jr., *J. Org. Chem.*, **47**, 1193 (1981) and references cited therein.

0022-3263/86/1951-0099$01.50/0