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Syntheses of Liquid Crystal Intermediates: 4-Alkylbenzoyl Chlorides

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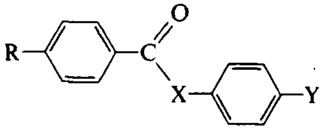
Acylation of seven alkyl- and four halobenzenes with oxalyl chloride-aluminum chloride, to give 4-substituted benzoyl chlorides in one step and free of positional isomers, was studied for variations in reactant ratios, temperatures and times. The addition of one equivalent of arene over sixty minutes to a 2 : 1 ratio of oxalyl chloride to aluminum chloride at 5° gave best results. Evidence was obtained for phosgene as the active reagent. The product acid chlorides are directly useful for and can be converted to a variety of other intermediates for syntheses of liquid crystalline materials.

INTRODUCTION

The greater chemical stabilities of 4,4′-disubstituted esters, **1a**, and thioesters, **1b**, than structural analogs with other central groups such as anils, azoxybenzenes, stilbenes, etc., makes them attractive for investigating new



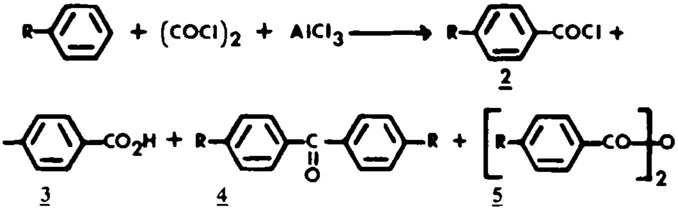
1a: X = O

1b: X = S

mesomorphic materials and for study of structural effects on mesogenic behaviour. Such studies have been discussed by us and others elsewhere.[1-6]

To facilitate preparation of esters we have developed a high-yield, high-purity general synthesis of 4-substituted benzoyl chlorides in one step from the corresponding arenes. The specific application to syntheses of 4-alkylbenzoyl chlorides is reported here.

This method resulted from a study of the procedure first reported by Fahim[7] for acylation of alkylbenzenes with oxalyl chloride (Scheme 1, R = alkyl) and isolation of alkylbenzoic acids, **3**. We have developed a procedure which avoids hydrolysis of the intermediate acid chlorides, **2**, which can be isolated directly in yields of ca. 80% and in only one step. This procedure also is a significant improvement over the alternate synthesis via oxidation of 4-alkylacetophenones, an overall three step process.[8] It also avoids the problem of separation of isomeric mixtures obtained from other reported procedures.[2,9–11]



SCHEME 1

EXPERIMENTAL

Materials and procedures

All reagents were obtained commercially and were certified 99.5% pure or better; oxalyl chloride (Eastman or Terrochem) was redistilled if not colorless; methylene chloride was dried over Linde 4A molecular sieves for > 12 hr. Reagent grade anhydrous aluminium chloride (J. T. Baker Chemical Co.) was used. Adsorption chromatography was done on 60/200 mesh grade 950 silica gel (Grace-Davison Chemical Co.). Preparatory tlc was performed with 2000 μ silica gel GF on 20 × 20 cm glass plates (Anal-Tech).

Analytical tlc was done with 250 μ silica gel GF or GHLF on 2.5 × 10 cm Uniplates® (Anal-Tech) by development with $CHCl_3$ and UV detection. GLC analyses were performed on a Varian-Aerograph Hy-FI model 600-B (25 ml/min N_2 carrier; 5% SE-30 on 60/80 mesh Chromasorb-AW, 6′ × $\frac{1}{8}$″ stainless steel column; 200° isothermal; flame ionization detector). Melting points corrected) were determined with a Thomas-Hoover® apparatus (Arthur H. Thomas Co.).

Spectral analyses were obtained using the following instruments: Perkin-Elmer Model 700 (IR); Varian FT-80 (C^{13} or H^1 nmr, in $CDCl_3$ with TMS

TABLE I

4-Substituted benzoyl chlorides from substituted benzenes

Substituent	Yield %	b.p. °C (torr)
n-C_4H_9	66.5	113 (1.7)
i-C_4H_9	77.5	115 (1.6)
n-C_5H_{11}	75.3	136 (3.2)
n-C_6H_{13}	80.3	143 (1.3)
n-C_7H_{15}	79.3	160 (5)
n-C_9H_{19}	71.8	182 (2.6)
n-$C_{10}H_{21}$	68.0	169 (0.6)
n-$C_{12}H_{25}$[a]	28.8	208 (3.2)
F	84.4	50 (1.1)
Cl	77.7	86 (2.1)
Br	75.9	103 (2.5)
I	74.1	100 (0.7)

[a] Worked up directly; basic extraction and solvent exchange eliminated.

internal standard) and AEI Model MS-12 (mass spectra, 70 eV, 100 μA, RP ≃ 1500).

Acyl chlorides reported in Table I were prepared by procedures analogous to that for:

4-n-Pentylbenzoyl Chloride, 2 ($X = n$-C_5H_{11}) (highest-yield procedure). Oxalyl chloride (17.1 g, 0.134 m) was added over 5 min to a stirred suspension of anhydrous aluminium chloride (10 g, 67.4 mmoles) in 27 ml dry methylene chloride. *n*-Pentylbenzene (10.0 g, 67.4 mmoles) in 40 ml dry methylene chloride was added dropwise (constant addition funnel, Ref. 12) to the stirred acylation mixture over a one-hour period. Unused oxalyl chloride (phosgene) was stripped to one-half the volume and fresh methylene chloride (40 ml) was added. The mixture was cooled to 0° (ice-salt bath) and then poured into an efficiently stirred mixture of calcium chloride (9.5 g) and crushed ice (170 g) at a rate to maintain the temperature below 5°. The organic layer was separated (immediately!), dried by filtering through anhydrous sodium sulfate and stripped of solvent *in vacuo*. The residual liquid was dissolved in ether (50 ml), cooled to 0° and extracted sequentially with cold 5% aq. KOH (50 ml, 0°) and water (50 ml, 0°); the combined basic aqueous extract was set aside (see later analysis) and the organic solution was dried (Na_2SO_4, then #4A molecular sieves) and stripped of solvent *in vacuo*. The crude liquid was distilled at reduced pressure and gave pure 4-*n*-pentylbenzoyl chloride, 2 (10.7 g, 80.4%); bp 136°/3.2 torr; IR (neat, film) 1735, 1770 (—COCl) and 1600 cm^{-1} (Ar, C$=$C); ^{1}H nmr, δ8.03, 7.93 (d, 2, ArH *o*- to C=O, J 8.4), 7.32, 7.22 (d, 2, ArH *o*- to alkyl, J 8.2), 2.75, 2.67, 2.57 (t, 2, $ArCH_2$, J 6.8, 7.8), 1.71–0.80 (m, 9, aliph H); ^{13}C nmr, δ167.5 (C=O), 151.7 (ArC_4), 131.6 (ArC_2,C_6) 131.0 (ArC_1), 129, 1 (ArC_3, C_5), 36.1 (aliph C_α), 31.6 (aliph C_β), 30.6 (aliph C_γ), 22.6 (aliph C_α) and 13.0 (CH_3); and MS, m/z 210 (M^+, 1.9), 175 ($ArC{\equiv}O^+$, 100).

No spectroscopic evidence for positional isomers other than the 4-substitutedbenzoyl chloride was obtained for any of the compounds in Table I.

The methyl ester prepared directly from acid chloride with methanol/triethylamine, gave a single peak well separated from solvent and amylbenzene on GLC analysis. An independent GLC-MS analysis† under conditions known to separate ring-positional isomers showed *only* methyl 4-*n*-pentylbenzoate and small amounts (~4%) of 4-substituted branched-alkyl esters.

The aqueous base extract was acidified (HCl), extracted with ether, washed with water, dried (Na_2SO_4) and stripped of solvent *in vacuo* to give crude 4-*n*-pentylbenzoic acid (150 mg, 1.2%); IR, 3400-2400 (broad, —OH), and 1690 cm^{-1} (C=O).

Preparative scale tlc analysis of the pot residue from reduced pressure distillation of the acid chloride gave 4-*n*-pentylbenzoic acid (infrared indentification), the corresponding anhydride; IR (film), 1780 and 1720 cm^{-1} (C=O), and a ketone fraction: IR (film), 1650 cm^{-1} (C=O). Identification of the anhydride was based on the 60 cm^{-1} separation for the doublet. Benzoyl chlorides also exhibit a carbonyl doublet generally ascribed to Fermi resonance[13,14] but with only a separation of ~30 cm^{-1}.

Reaction variables; *acylations* Experiments for study of variations in temperatures, times and reactant ratios were run by a procedure analogous to that given for preparation of 4-*n*-pentylbenzoyl chloride excepting necessary changes to study the variables. The arene used was *n*-butylbenzene; workup included recovery of 4-*n*-butylbenzoic acid from aqueous extracts and separation analyses of distillation pot residues by tlc with $CHCl_3$ development on silica gel followed by extraction, then infrared and mass spectrometric analyses. Three regions were examined; the origin contained unidentifiable polar substances, $R_f \simeq 0.11$ was 4-*n*-butylbenzoic acid and $R_f \simeq 0.71$ was a mixture of ketones. The ketones were separable by benzene development on silica gel and gave 4,4′-bis-*n*-butylbenzophenone, $R_f = 0.47$, ir, 1650 cm^{-1} (C=O), molecular ion, m/z = 294 and 4,4′-bis-*n*-butylbenzil, $R_f = 0.55$, ir, 1670 cm^{-1} (C=O) and m/z 161 ($ArC{\equiv}O^+$) but no molecular ion peak.

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† We are indebted to Mr. Leo Carlino of Hewlett-Packard Laboratories, Santa Clara, California for the analysis on an HP-5980A GC-MS instrument equipped with a 6″ × ¼″ glass column with 3% SP2250 on 100/120 mesh Supelcoport and 40 ml/min He carrier gas flow rate.

TABLE II

Effect of reaction temperature

Reaction temperature	Conversion to ArCOCl %	Ketone %
|−40 to −50°|	77	7[a]
|−20° to −30°|	61[b]	7[a]
25°	81	2
~37°[c]	5	72[d]

Reaction time ~2 hrs; solvent: CH_2Cl_2; one equivalent $AlCl_3$; analyses by adsorption chromatography.

[a] "Total" ketone (benzophenone plus benzil).

[b] Reaction time = 1 hr.

[c] Temperature of refluxing mixture.

[d] Primarily benzophenone.

TABLE III

Yield Variation with Change in Reagent Ratios

Reactant ratio[a]	Conversion to ArCOCl %	Ketone[b] %
1 : 2 : 1	78	3
1 : 3 : 2	81	2
2 : 1 : 2	3	86

[a] Ratios are for arene : oxalyl chloride : aluminum chloride.

[b] Ketone was principally 4,4′-disubstituted benzophenone. Reaction temperature ~25°, yields were estimated from adsorption chromatography; polymer was not measured.

Data from these studies are summarized in Tables II, III, and IV; additional details are footnoted there.

RESULTS AND DISCUSSIONS

Although Staudinger suggested many years ago that phosgene is the acylating agent in mixtures of oxalyl chloride with aluminium chloride,[15] no convincing evidence for this has been published. Time resolved infrared spectra

TABLE IV

Variation in Work-Up Procedures

Variation	ArCOCl %	Acid %	Ketone %	Total
A	64	5[1]	24	93
B	27	31	17	75
Std.	74	7	2	83
C[2]	58	16	19	93

Reaction temperature = 25°; ratio: 1 : 3 : 1 of arene : oxalyl chloride : $AlCl_3$; solvent = CH_2Cl_2

Work-up variations:

A No basic extraction or solvent exchange; temperature not controlled.

B Fahim's procedure (Ref. 7).

C Excess reagent and solvent removed at <20°.

Notes: 1 "Acid" isolated as anhydride.

2 2.9% alkylbenzene recovered.

of evolved gases from a reaction (~25°) of oxalyl chloride and aluminum chloride are given in Figure 1 for the carbonyl region with a spectrum for oxalyl chloride. Carbon monoxide was detected at once by its doublet at 2200 cm^{-1}.[16] The 1800 cm^{-1}, 1900 cm^{-1} doublet of oxalyl chloride [17] soon (~15 min) appeared to coalesce into the strong peak at 1820 cm^{-1} identified for phosgene.[16] A second phosgene peak at 1700 cm^{-1} also appeared. After fifty minutes only the peaks for carbon monoxide and phosgene were present.

Isolation of gaseous phosgene without the necessity of heating is evidence for an equilibrium between free phosgene and aluminum chloride-complexed phosgene, and supports the need for excess oxalyl chloride when reactions are done in relatively open equipment.

Both chlorinated solvents and carbon disulfide were used as reaction media; the most useful was methylene chloride both because it effectively solvates the reagents and because it can be easily removed. Emulsions that occurred during work-up of medium chain length alkylbenzoyl chlorides were avoided by replacing methylene chloride with ether before extraction.

Three side-reactions may occur during the overall preparation to lower the yield of the acyl chloride (see Scheme 1). The most important is the competing acylation of unreacted alkylbenzene by the product acid chloride to give ketone, **4**. Hydrolysis of the acyl chloride to carboxylic acid, **3**, may occur during work-up and following which, the acid may react with still more of the acid chloride to give anhydride, **5**.

The extent of ketone formation is affected by the temperature, the ratio: $AlCl_3$/alkylbenzene and the concentration of alkylbenzene. A significant amount of 4,4′-dialkylbenzophenone was formed if the reaction mixture was refluxed during the addition of alkylbenzene. In contrast, if very low

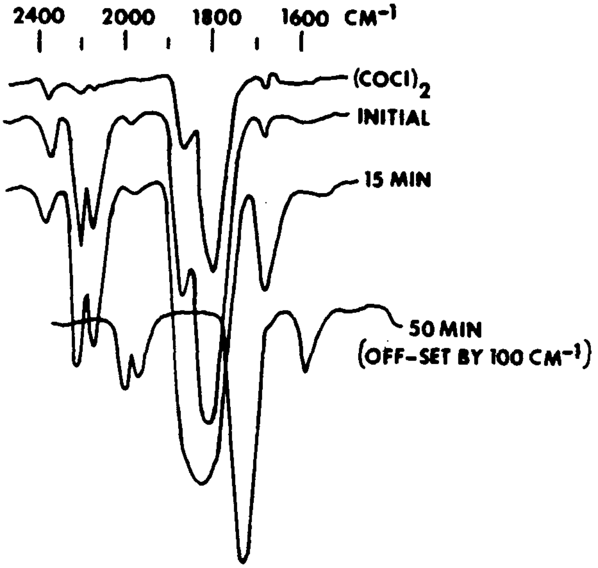

FIGURE 1 Infrared Absorption Curves

reaction temperatures are maintained, diketones (4,4′-dialkylbenzils) are formed, presumably via arylglyoxalyl chloride from acylation with oxalyl chloride. Temperature effects are summarized in Table II. Excepting reactions run at very low temperatures (> −20°), similar yields were obtained from reactions which were immediately worked-up after the addition of alkylbenzene *vs* those stirred for an hour at room temperature after addition was complete.

Good conversions to acid chloride with minimum ketone formation was achieved when excess oxalyl chloride was used with equimolar aluminum chloride/alkylbenzene. Excess aluminum chloride or "old," partially hydrolyzed aluminum chloride gave more ketone. Maintenance of a low concentration of alkylbenzene throughout the reaction by slow addition of a relatively dilute solution, predictably, minimizes ketone formation. Experiments on variation in reagent ratios are summarized in Table III; the optimum ratio was determined to be 1:2:1 for arene:oxalyl chloride:aluminum chloride.

Hydrolysis during work-up was not extensive; no more than five percent of the corresponding benzoic acid was isolated when work-up involved contact with aqueous solutions for 30–40 minutes. We suspect that formation of carboxylic acid is predominantly by way of the ionic form of the aluminum chloride complex which may be formulated as an oxocarbenium ion salt with tetrachloroaluminate counter-ion. Evidence for this structure of the

Friedel-Crafts complex in equilibrium with a molecular donor-acceptor complex has been extensively reviewed by Chevrier and Weiss.[18] In non-polar solvents such as methylene chloride, the position of the equilibrium lies far toward the molecular complex so long as steric factors do not intervene. This may be presumed to be the "condition" of the reaction mixture prior to work-up. The molecular complex decomposes (on addition to ice-water) into "free" acyl chloride and aluminum chloride.

Although rates for hydrolysis of aroyl chlorides in highly aqueous media are high,[19] solubilities in water are quite low. This important limitation (toward hydrolysis) may be enhanced by use of a significant amount of solvent which is immiscible with water to extract the acyl chloride during the decomposition of the complex. Steric factors are significant in shifting the equilibrium for the complex toward the ionic structure which would decompose in water directly to the carboxylic acid. This is the result for acylation of mesitylene with oxalyl chloride which gives only mesitoic acid, as previously reported[20] and confirmed by our own work.

The presence of $\sim 4\%$ of branched-chain methyl 4-pentylbenzoates in the ester derivative indicates either that side chain isomerization of the *n*-alkylbenzenes may occur prior to their acylation or that small amounts of branched-chain isomers are already present. Assuming the former, the oxalyl chloride-alumunum chloride ratio should be high enough, not only to provide a high concentration of chloroformylation reagent relative to product acid chloride (and to make up for "lost" phosgene) but also to ensure that "free" aluminum chloride is minimized to reduce side-chain isomerization.

Substrates which were successfully used to test the generality of this method for direct chloroformylation included several C_4-branched as well as straight chain alkylbenzenes through dodecylbenzene, the halobenzenes and *para*-terphenyl which was diacylated then converted directly to the diethyl ester by work-up with ethanol.[21] Oh has also recently reported the successful conversion of 4-alkylbiphenyls to the corresponding 4-alkylbiphenyl-4′-carboxyl chloride with our procedure.[22] Long chain (C_{10}- and C_{12}-) 4-alkylbenzoyl chlorides presented difficulty during isolation owing to emulsion formation; 4-decylbenzoyl chloride was isolated in good yield, however, by changing solvent to ether for extraction prior to distillation.

Neither alkoxybenzenes nor acetanilide could be converted to the acid chloride by any variation of the present procedure. Thus, butoxybenzene gave ketone 4 (R=BuO) as the principal product; infrared analyses suggest that lactonic materials were also formed. Although acetanilide has been successfully acylated by us with alkanoyl chlorides, it fails to undergo significant reaction by the present method. The isolation of carboxylic acid rather than acid chloride using mesitylene has already been noted. A similar result was obtained from anthracene, presumably for the analogous reason that the ionic complex with chloroaluminate ion is the stable intermediate; considerable insoluble product was also obtained but this was not further investigated.

Scale-up of this procedure to runs of one mole were accomplished with only small diminution in yield which may be ascribed to the somewhat greater times involved during work-up. Long contact with moisture, even that associated with drying agents, should be avoided to minimize hydrolysis.

The 4-alkylbenzoyl chlorides are useful synthetic intermediates beyond their use in preparation of esters and thioesters. They may be reduced to aldehydes, for example, with any one of a number of mild and selective reagents developed in the past twenty years.[23–29] Another interconversion of interest to investigators of mesomorphic materials is the route to nitrile via the amide which has been improved recently by Graham.[30] We obtained an overall yield of 80% for the conversion of 4-*n*-pentylbenzoyl chloride to 4-*n*-pentylbenzonitrile[31] by this method which obviates the separate preparation of the amide.

Acknowledgments

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