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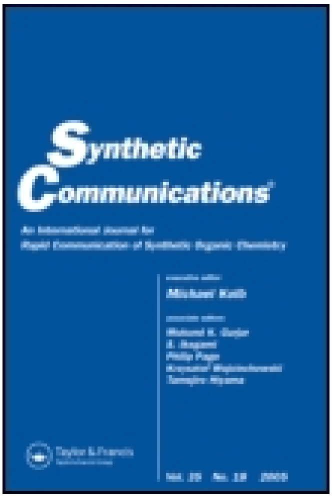

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One-Pot Preparation of 2,5-Dichloro-4′-phenyloxybenzophenone

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ONE-POT PREPARATION OF 2,5-DICHLORO-4′-PHENYLOXYBENZOPHENONE

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Friedel–Crafts-type acylation of phenyl ether with 2,5-dichlorobenzoic acid could be accomplished in a single step using trifluoroacetic anhydride and phosphoric acid. The method gave a greater yield (78%) than the conventional two-step process (71%) of acid chloride generation followed by aluminum trichloride–mediated acylation.

Keywords: Acylation; Friedel–Crafts; mixed anhydride; phosphoric acid; trifluoroacetic anhydride

To make products that can benefit from the excellent thermochemical and mechanical properties of poly(*p*-phenylene), the latter must be made with suitable substitution along the main chain to increase solubility and processability.[1–5] A recent commercial product that has achieved a solution to this problem is Parmax (poly(2,5-benzophenone), Fig. 1.[6,7] Polymers such as this are also interesting because of their low moisture absorption.[8–10] A new, one-pot method was used to synthesize the monomer **3**[11–13] for polymerization studies.

The typical synthesis of **3** is shown in Scheme 1. 2,5-Dichlorobenzoic acid (**1**) is first converted into its acid chloride **2**[14] with thionyl chloride. In the second step, aluminum trichloride–catalyzed Friedel–Crafts acylation of an equimolar quantity of phenyl ether with **2** furnished **3** in 71% overall yield. Although there are two potential sites for acylation of phenyl ether, no diacylated by-product was observed.

Mixed anhydrides of trifluoromethanesulfonate[15] or trifluoroacetate[16–26] have been shown to react in a Friedel–Crafts manner with activated aromatic substrates. In the new method, **1** is converted into its mixed anhydride of trifluoroacetic acid (TFA) in an endothermic reaction with excess trifluoroacetic anhydride (TFAA), Scheme 1. The reaction of **1** with TFAA is fast, yielding upon dissolution the corresponding mixed anhydride **4** in TFAA/TFA. The ^{1}H, ^{19}F, and ^{13}C nuclear magnetic resonance (NMR) spectra for **4** were collected (Table 1). It was postulated that some of the anhydride of **1** might be generated under these conditions.[27] However, no unidentified peaks were found in the NMR analyses. Addition of

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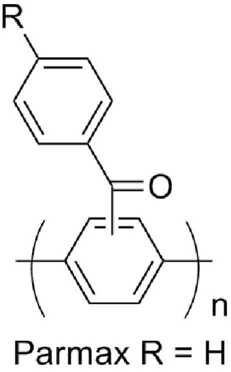
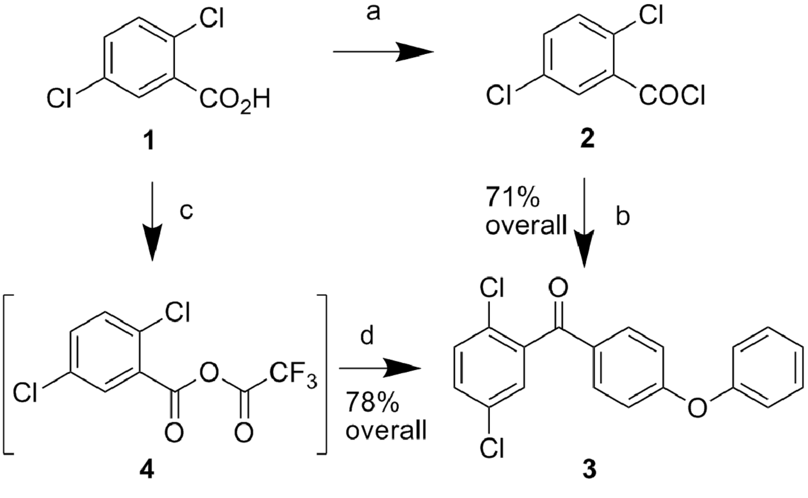


Figure 1. Polymer structure.

phenyl ether created a biphasic mixture, and no reaction would take place at reflux temperature without the addition of 85% phosphoric acid. The 0.18 equivalents of phosphoric acid that were added slowing formed a semisolid precipitate of unknown identity, presumed to be pyrophosphate.[23,28,29] Refluxing the reaction mixture for a few hours brought the acylation to completion, conveniently determined by periodic ^{1}H NMR analysis. The TFA/TFAA solvent mixture was collected by distillation, and **3** was isolated by a typical workup procedure. The recrystallized yield for this one-pot method was 78%, slightly better than the acid chloride method.

For safety concerns, many iterations of the TFA mixed anhydride acylation reaction were run, culminating in 3.2 mol of **1**. In all cases, an uncontrolled or spontaneous exotherm never appeared. This is in keeping with a report from Smyth and Corby[22] that only 20% of the total heat of reaction in a similar system was attributed to the actual acylation step.



Scheme 1. Alternate routes to monomer 3. *Reagents & conditions*: a) $SOCl_2$; b) PhOPh, $AlCl_3$, heat; c) TFAA; d) 85% H_3PO_4, PhOPh, TFA, TFAA, 45 °C.

Table 1. Key nuclear magnetic resonance chemical shifts (ppm) in the synthesis of intermediate **4**[a]

Compound	δ_H	δ_C	δ_F
1	8.01 (dd, $J = 2.1$ and 0.7 Hz, 1H), 7.49–7.41 (m, 2H)	169.97, 133.84, 133.46, 133.05, 132.93, 132.54, 129.75	
CF_3CO_2H		162.59 (q, $J_{CF} = 44$ Hz), 114.55 (q, $J_{CF} = 283.8$ Hz)	−76.35
$(CF_3CO)_2O$		150.05 (q, $J_{CF} = 48.2$ Hz), 113.54 (q, $J_{CF} = 285.6$ Hz)	−75.69
4	7.93 (d, $J = 2.5$ Hz, 1H), 7.58 (dd, $J = 8.7$ and 2.5 Hz, 1H), 7.52 (d, $J = 8.7$ Hz, 1H)	156.63, 152.49 (q, $J_{CF} = 46.4$ Hz), 135.78, 134.83, 133.93, 133.60, 132.88, 127.26, 114.18 (q, $J_{CF} = 286.1$ Hz)	−75.90

[a] Solvent $CDCl_3$, room temperature, carboxylic acid proton resonances not shown.

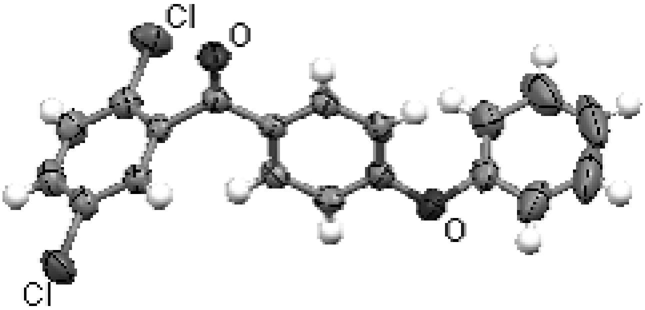


Figure 2. Crystal structure of **3**.

A crystal structure for **3** was obtained by room-temperature x-ray diffraction (Fig. 2). Even with two crystals run, there appears to be a small amount of disorder of the distal phenyloxy ring.

Although TFAA and TFA are expensive reagents, the ability to recover and dehydrate the spent TFAA/TFA may make this process cost-effective over the long term. This alternate acylation process is environmentally benign by eliminating hydrogen chloride and sulfur dioxide by-products.

EXPERIMENTAL

The melting points were collected on a Mel-Temp II apparatus from Laboratory Devices (Holliston, MA) and are not corrected. All NMR data were collected on a Bruker Avance II 300 MHz spectrometer (^1H at 300 MHz, ^{13}C at 75 MHz, ^{19}F at 282 MHz). Nuclear magnetic resonance data (free-induction decays) were processed using NUTS software from Acorn NMR (Livermore, CA). All spectra are referenced to solvent, tetramethylsilane or fluorotrichloromethane. Phenyl ether (99%) was purchased from Sigma-Aldrich (Milwaukee). Trifluoroacetic anhydride (TFAA, 99%) was purchased from Alfa Aesar (Ward Hill, MA). Phosphoric acid

(85%) was purchased from J. T. Baker Chemical Co. (Phillipsburg, NJ). All other reagents were obtained commercially and used as received. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

The 2,5-dichlorobenzoic acid (**1**, 97%), a product of Polarchem, was purchased through Amico Scientific Corporation (Garden Grove, CA). However, the product contained ~15% of an insoluble substance. The material was purified by dissolving in hot toluene and filtering through diatomaceous earth. The product precipitated as colorless needles from the cooled filtrate. Elemental analysis calculated for $C_7H_4Cl_2O_2$ (C, 44.02; H, 2.11) as received indicated C, 42.51; H, 1.91, and after purification showed C, 44.30; H, 2.09.

2,5-Dichlorobenzoyl Chloride (2)

A 1-L round-bottomed flask equipped with magnetic stirbar was charged with 100 g **1** (0.526 mol) and 150 mL $SOCl_2$. The mixture was then stirred. An N_2 bubbler was set up, and the effluent gas was piped through two consecutive aqueous NaOH scrubbing flasks. A heating mantle was equipped, and the mixture was gently refluxed for 3 h. During this time, copious gas (HCl/SO_2) was generated and the solids completely dissolved. The excess $SOCl_2$ was distilled under vacuum (20 torr) at 55 °C. Further distillation (0.1 torr) gave the title compound as a colorless liquid that crystallized in the receiver to a low-melting white solid (102.4 g, 93%). δ_H ($CDCl_3$): 8.04 (d, $J = 2.5$ Hz, 1H), 7.50 (doublet of doublets, $J = 8.7$ and 2.4 Hz, 1H), 7.44 (d, $J = 8.6$ Hz, 1H); δ_C ($CDCl_3$): 164.3, 134.5, 134.4, 133.3, 132.9, 132.8, 132.1. Elemental analysis calculated for $C_7H_3Cl_3O$: C, 40.14; H, 1.44. Found: C, 40.19; H, 1.35.

2,5-Dichloro-4′-phenyloxybenzophenone (3)

From 2. A 100-mL round-bottomed flask equipped with magnetic stirbar was charged with 102.4 g **2** (580 mmol) and 100 g phenyl ether (590 mmol, 1.01 equiv). The mixture was allowed to stir briefly until all the solids dissolved. Portionwise, 76.4 g $AlCl_3$ (580 mmol, 1 equiv) was added over 25 min. The color of the reaction became blood red and copious HCl evolved as the reaction progressed. The mixture reached 63 °C. After the addition, the mixture was heated to 100 °C for 2 h to complete the reaction. The mixture was allowed to cool to ~60 °C, a reflux condenser was equipped, and 500 mL $CHCl_3$ were slowly added to dissolve the thick mixture. Then 500 mL H_2O were added slowly by addition funnel to quench the reaction. After stirring 1 h to allow all the solids to dissolve, the organic phase was separated. It was washed with 500 mL H_2O, followed by 250 mL 1 M NaOH and then 500 mL brine. The mixture was dried over anhydrous $MgSO_4$, followed by treatment with 3 g Darco G-60. The solvent was then stripped at the rotovap, leaving an off-white solid (194.5 g, theory 198.6 g). The crude product was recrystallized from 1 L 50% MeOH/EtOH to give 153 g of the title compound as colorless needles (77%). Mp 94–96 °C (lit.[12] 97 °C). δ_H ($CDCl_3$): 7.79 (d, $J = 8.9$ Hz, 2H), 7.47–7.30 (m, 5H), 7.23 (triplet of multiplets, $J = 7.4$ Hz, 1H), 7.10 (doublet of multiplets, $J = 7.6$ Hz, 2H), 7.01 (d, $J = 9.0$ Hz, 2H); δ_H (DMSO): 7.76 (d, $J = 9.1$ Hz, 2H), 7.63 (s, 3H), 7.47

(t, $J = 7.8$ Hz, 2H), 7.26 (t, $J = 7.4$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 2H), 7.07 (d, $J = 8.2$ Hz, 2H); δ_C ($CDCl_3$): 192.3, 163.2, 155.3, 140.4, 133.1, 132.7, 131.4, 131.2, 130.5, 130.3, 129.9, 128.9, 125.16, 120.6, 117.5. Elemental analysis calculated for $C_{19}H_{12}Cl_2O_2$: C, 66.49; H, 3.52. Found: C, 66.42; H, 3.48.

From 1. A 3-L, three-necked, round-bottomed flask equipped with magnetic stirbar, thermometer, reflux condenser, and addition funnel was charged with 609.5 g **1** (3.2 mol), followed by 1820 mL TFAA (2695 g, 12.83 mol, 4 equiv). The mixture was stirred, and after 20 min all the solids had dissolved in an endotherm reaction, dropping to 13 °C, to give a solution of **4**. After it was stirred 20 min further, 598.4 g phenyl ether (3.52 mol, 1.1 equiv) were added in one portion. The addition funnel was charged with 68 g 85% H_3PO_4 (0.59 mol, 0.18 equiv), which was added dropwise over 20 min. The internal temperature reached 26 °C. The mixture was then heated to reflux (44 °C) for 3 h. After this time, the reaction was complete by ^1H NMR. A distillation head was equipped, and 2120 g of a colorless mixture of TFA/TFAA were distilled at atmospheric pressure. The remaining orange liquid was partitioned between 3 L $CHCl_3$ and 2 L H_2O. The organic layer was separated and washed with 1 L NaOH and then 1 L brine. The mixture was dried over anhydrous $MgSO_4$ followed by treatment with 10 g Darco G-60, and then the solvent was rotary evaporated, leaving the crude product. Recrystallization from 4 L 50% MeOH/EtOH gave 850 g of the title compound as colorless needles (78%). Spectroscopic and analytical data were identical with those of the previous preparation.

Table 2. Crystal structure data and refinement details for compound **3**

Parameter	Value
Empirical formula	$C_{19}H_{12}Cl_2O_2$
Formula weight	343.19
Temperature (K)	296 (2)
Crystallization solvent	toluene
Crystal system	Monoclinic
Space group	P12(1)/c1
Unit cell dimensions (Å, °)	
a	15.4487(11)
b	19.0861(13)
c	5.5265(4)
α	90
β	93.8380(10)
γ	90
Volume ($Å^3$)	1625.9(2)
Z	4
Density (Mg/cm^3)	1.402
Crystal size (mm)	$0.35 \times 0.54 \times 0.55\,mm^3$
Reflections collected	15031
Independent reflections	2871
Completeness (%)	100
Data/restraints/parameters	15031/0/245
Goodness-of-fit on F^2	1.084
Final R [I > 2sigma(I)]	$R_1 = 0.0362$, $wR_2 = 0.0872$

X-Ray Structure Determination of 3

Some selected data and refinement details are collected in Table 2. CCDC 744718 (**3**) contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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