

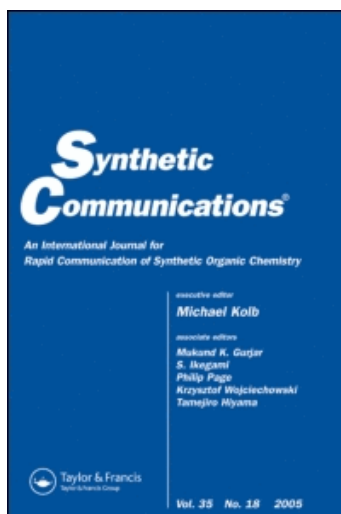
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RAPID AND REGIOSPECIFIC PHENYLTHIOLATION OF SOME ORGANIC ACIDS CATALYZED BY AlCl_3 IN THE PRESENCE OF EXCESS ANHYDROUS ZnCl_2

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Phenylthiolation of some carboxylic acids catalyzed by AlCl_3 in the presence of excess dehydrating agent (ZnCl_2) has been achieved. Moreover, regiospecificity was tested of some dioic acids and found to be specific at the aliphatic part of carboxylic functionality.

Keywords: Dioic acids; phenylthiolation; regiospecific esterification

INTRODUCTION

Today, thioesters are made to protect and activate COOH functionality in organic synthesis.^[1] Protection of thiol groups are most important in peptide^[2] and β -lactam synthesis^[3] for specific purposes. Thioester synthesis from organic acids and thiols catalyzed by mineral acids are of limited use because of the reversibility of C-S bond-breaking and bond-forming tendencies, the aptitude of the bridged S compounds, and above all the oxidation tendency of sulfur.^[4] Sometimes, reaction of acylhalides with thiols gave thioester^[5] in poor yields because of the C-S bond breaking. The yield and reaction conditions mostly depend on the solvent, the basic catalyst, and the acidity of the thiols.^[5] Sometimes, the reactions require very long refluxing time.

Now, various methods have been employed including palladium(0)-mediated alkylation,^[6] phase-transfer catalysis,^[7] bis(diphenylstannyl) telluride,^[8] tin sulfides with aryl halides,^[9] ligand transfer reaction,^[10] montmorillonite clay,^[11] and CsF-Celite ^[12] catalysis. Recently, Yin and Pidgeon^[13] reported a facile method for the preparation of unsymmetrical sulfides using very strong $n\text{-BuLi}$. In all cases, some restraints were there, either in the yield of the products or in the use of costly reagent and complicated procedures. In continuation of our interest in developing a new synthetic route for esterification^[14,15] in aromatic acids, we herein report the versatile use of a mixed AlCl_3 and ZnCl_2 catalyst for the synthesis of thioesters and some selective thioesters from some organic dioic acids (Fig. 1).

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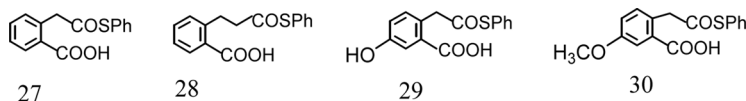


Figure 1. Specific thioesters.

RESULTS AND DISCUSSION



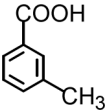
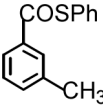
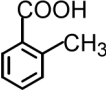
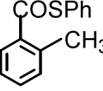
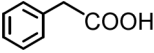
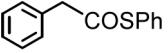




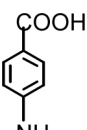
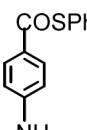
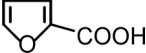
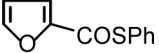
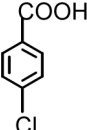
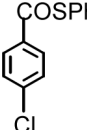
As a test case leading to phenylthiolation, benzoic acid was chosen as an initial starting material. It was dissolved into distilled EtOAc, and 5 mol% anhyd. AlCl_3 was added to it. One h later, an equivalent amount of distilled thiophenol with excess anhyd. ZnCl_2 was added and allowed to stir at room temperature for about 2 h with occasional thin-layer chromatography (TLC) monitoring. A tiny growing spot was observed above the starting acid. To complete the reaction, it was heated to reflux temperature over 3–4 h. Addition of 0.1 M cold HCl to the reaction mixture helped to break the salt formed during the reaction. Ether extraction and the usual workup procedure furnished the thioester **16** in 85% yield. In the same way, some other organic acids were reacted with PhSH and obtained in fair to good yield (see Table 1). To test the selectivity, four different dioic acids were reacted with equivalent amounts of PhSH. Dioic acid **12** gave the mono ester **27** with good yield at room temperature. Selectivity of the two $-\text{COOH}$ functionalities were verified by making phenylthiolate **19** from phenyl acetic acid **4**. Proton magnetic resonance (PMR) spectra of ester **19** completely matched with the monoester **27**, except one proton appeared at $\delta = 10.87$ for the other COOH in **27**. So, the monoester **27** contains the SPh group in the aliphatic part of the two choices. In infrared (IR) spectroscopy, compound **27** indicates two important peaks for $\text{C}=\text{O}$ and $\text{C}-\text{S}$ bonds at 1784 and 1283 cm^{-1} , respectively. Moreover, mass spectrum was taken of **27** to establish its structure. Three dioic acids (**13**, **14**, and **15**) under the same conditions gave three different monoesters (see Table 1) in excellent yields. AlCl_3 increased the electrophilicity of both carbon atoms in the COOH group equally, but this may be due to steric grounds. PhSH likes to attack at the aliphatic carboxylic carbon away from the phenyl ring. Whatever the mechanism, this is an expedient, regiospecific, inexpensive, and simple method for preparing thioesters, so it would be a valuable addition with the existing methodologies.

EXPERIMENTAL

General Considerations

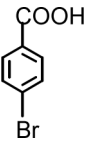
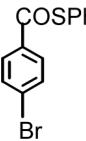
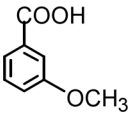

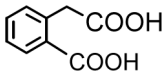
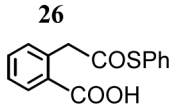
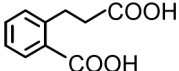
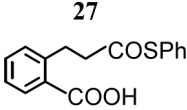
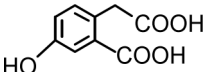
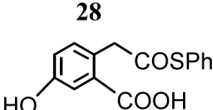
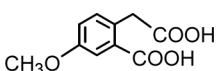
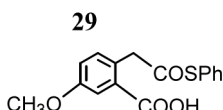

The melting points were determined on a capillary melting-point apparatus and are uncorrected. IR spectra were recorded using KBr pellets for solids and neat for liquids on Fourier Transform FT-IR-8400 Perkin-Elmer 883 grating spectrometer. ^1H NMR spectra was taken on an AC Bruker 400-MHz spectrometer in CDCl_3 , containing tetramethylsilane (TMS) as the internal standard. High solution mass spectra (HRMS) were recorded on an VG Micromass ZaB-2F. All J values are given in hertz, and chemical shifts are in δ units. EtOAc was simply distilled over CaCl_2 , and PhSH was collected by the fractionating distillation process. Reactions were

Table 1. Phenylthiolation for organic acids

Entry	Acids	Reaction time (h)	Product (esters)	Mp/bp (°C)	Yield (%)
1		4-5	 16	27	85
2		3-4	 17	52-53	90
3		4	 18	50-51	85
4		5	 19	28	90
5		4-5	 20	29	85
6		4-5	 21	32	85
7		5-6	 22	73-74	83
8		5-6	 23	47-48	85
9		3-4	 24	71-72	90

(Continued)

Table 1. Continued

Entry	Acids	Reaction time (h)	Product (esters)	Mp/bp (°C)	Yield (%)
10		3–4		69–70	90
11		5–6		64	85
12		3–4		165	84
13		3–4		128	82
14		5–6		168	85
15		4–5		172	80
					

Note. Mp/bp were compared with the literature values and the Aldrich chemical catalog.

monitored by TLC, and column chromatography was done on silica gel, 60–120 mesh (E. Merck).

General Method for the Preparation of Phenylthioesters

Anhydrous AlCl_3 (0.054 g, 0.41 mmol) was added to a stirred EtOAc (10 mL) solution of benzoic acid **1** (1 g, 8.2 mmol) at 0 °C. Two h later, 1 equivalent of thiophenol (0.91 mL, 8.2 mmol) and anhyd. ZnCl_2 (1 g, 8.1 mmol) were added to it. To monitor the progress of the reaction, TLC was checked in an *n*-hexane/EtOAc (5:1) solvent system, indicating a tiny spot above the starting materials. When the reaction was deemed to be completed after 4 h at reflux temperature, 0.1 M HCl (ice cold) was added to it. Subsequent ether (3 × 12 mL) extraction, washing with 5% NaHCO_3 (2 × 15 mL) followed by water (2 × 20 mL), drying over Na_2SO_4 , and

evaporating the bulk ether afforded a white product. Recrystallization from acetone furnished white crystals in excellent yield (1.49 g, 85%).

Selected Data

Compound 27. Mp 165 °C; IR (KBr): 1737, 1695, 1283 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 10.88 (s, 1H, COOH), 6.98–6.95 (m, 2H, Ar-H), 6.77–6.73 (m, 2H, Ar-H), 6.64–6.59 (m, 5H, Ar-H), 3.65 (s, 2H, CH₂). HRMS calcd. for C₁₅H₁₂O₃S, 272.1671; found, 272.1431.

Compound 28. Mp 128 °C; IR (KBr): 1740, 1693, 1287 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 10.85 (s, 1H, COOH), 7.01–6.99 (m, 2H, Ar-H), 6.95–6.92 (m, 2H, Ar-H), 6.66–6.62 (m, 5H, Ar-H), 3.45 (t, *J* = 6 Hz, 2H, CH₂), 2.52 (t, *J* = 6 Hz, 2H, CH₂). HRMS calcd. for C₁₆H₁₄O₃S, 286.3143; found, 286.3103.

Compound 29. Mp 168 °C; IR (KBr): 1735, 1698, 1286 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 10.91 (s, 1H, COOH), 7.43 (d, 1H, *J* = 2.4 Hz, Ar-H), 7.14 (d, 1H, *J* = 8 Hz, Ar-H), 6.98 (dd, 1H, *J* = 2, 8 Hz, Ar-H), 6.65–6.61 (m, 5H, Ar-H), 4.90 (s, 1H, Ar-OH), 3.40 (s, 2H, CH₂). HRMS calcd. for C₁₅H₁₂O₄S, 288.5237; found, 288.5215.

Compound 30. Mp 172 °C; IR (KBr): 1735, 1698, 1282 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 10.89 (s, 1H, COOH), 7.50 (d, 1H, *J* = 2.6 Hz, Ar-H), 7.34 (d, 1H, *J* = 8 Hz, Ar-H), 6.98 (dd, 1H, *J* = 2, 8 Hz, Ar-H), 6.77–6.67 (m, 5H, Ar-H), 3.74 (s, 2H, CH₂), 3.45 (s, 3H, CH₃). HRMS calcd. for C₁₆H₁₄O₄S, 302.2731; found, 302.2233.

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