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Regiospecific Phenyl Esterification to Some Organic Acids Catalyzed by Combined Lewis Acids

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Abstract: A new and efficient method for the preparation of various phenyl esters has been achieved by a simple reaction of an acid with phenol in the presence of anhyd. $ZnCl_2$ and a catalytic amount of $AlCl_3$. This combined Lewis acid also catalyzes the selective phenyl esterification to different dioic acids and is very simple and high yielding.

Keywords: Dicarboxylic acid, esterification, mixed Lewis acid catalysts, regiospecific

INTRODUCTION

Phenolic esters of organic acids, especially those of cresols and phenols, are good flavor compounds because they possess a combination of sweet, floral, and fruity odors, which are very desired in food chemistry.[1] Substituted phenyl esters have wide application in the manufacture of fine chemicals such as insecticides, antioxidant, and photosensitizers.[2] Moreover, selective esterification is required in the synthesis of natural products that contain two or more carboxylic groups.[3,4] Fischer esterification, a strong protic acid in an alcohol solvent, has been used for more than a century to convert carboxylic acids into their corresponding carboxylate esters, but strong acid-catalyzed esterification to carboxylic acid, containing double bonds or other reactive functionalities, often leads to polymeric products in addition to ester. Thus, isolation of esters becomes tedious.[5] Phenyl ester formation by acylation[6] is a well-known procedure, although some

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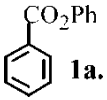
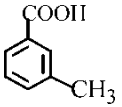
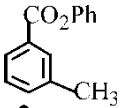
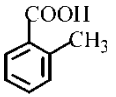
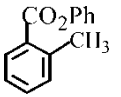
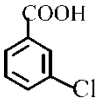
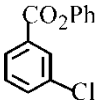
acylchlorides revert to their mother acid. Many catalytic processes[7] are available for the alkyl esterification, but phenyl esterification by catalytic processes is still unusual. The lesser nucleophilicity of the phenol generally makes the strong acid-catalyzed reaction difficult. Recently, enzymatic phenyl esterification[8] have received success, but they are still few in numbers and in most cases are reversible and slow. So far, mixed Lewis–acid catalyzed esterifications are still unavailable for phenyl esterification. Therefore, we used Lewis acid mixtures for phenyl esterification. Our aim in using Lewis acid ($AlCl_3$) as a catalyst is to enhance the electrophilicity of carbon in the carboxylic group instead of protic acids, and subsequent addition of anhyd. $ZnCl_2$ is intended to dehydrate the reaction mixture.

RESULTS AND DISCUSSION

Catalytic esterification, especially tin(II) chloride,[7c] of some organic acids with alcohols has allowed us to develop a new method in phenyl esterification using $AlCl_3$ and $ZnCl_2$ mixed catalyst. Previously, it was done by the addition of strong protic acid or tosic acid to a alcohol–acid mixture. However, we avoided mineral acids for esterification. In the present work, an aliquot of $AlCl_3$ was initially added to organic acids to increase the electrophilicity of COOH group. A few minutes later, dry phenol (1 equiv.) was added in addition to an equivalent amount of anhyd. $ZnCl_2$. In a few cases, the reaction mixture was heated at reflux temperature in EtOAc solvent. Progress and completion of the reaction was monitored by thin-layer chromatography (TLC) in an *n*-hexane/ethylacetate solvent system (5:1). The top spot in TLC showed the formation of esters. Quenching of the reaction was done with dilute hydrochloric acid (1 M) at 0°C. Quick silica-gel filtration furnished the required phenyl esters in good to excellent yields (see Table 1). All the data are in good agreement with the literature values. Phenol with organic acids in the presence of $AlCl_3$ did not bring about any phenyl esters; instead, a Friedel–Crafts product was isolated. In the same way, as a test case, $ZnCl_2$ alone did not give any phenyl esters.

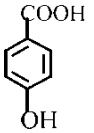
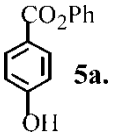
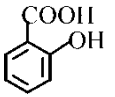
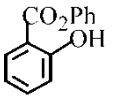
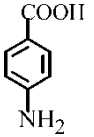
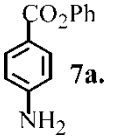
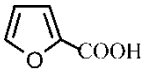
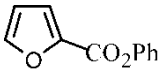
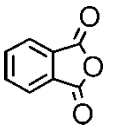
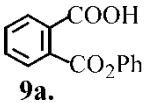
After achievement of some phenyl esters, regiospecific phenyl esterification was carried out using a few dioic acids (entries **13**, **14**, and **15**) by the same method. At an ice-cold temperature, a 1:1 molar mixture of dioic acids with phenol directs the phenyl group to the aliphatic part of the COOH functionality. This is confirmed by the proton magnetic resonance (PMR) spectra of phenyl phenyl acetate **12a**. Selectivity was good and phenyl group was directed to the aliphatic part of the COOH functionality regiospecifically. The same reaction was continued to aliphatic alcohol with the dioic acids, but in this case regiospecificity has drastically changed and the alkyl group was found to attach at the aromatic ring-connected COOH group. Whatever may be the mechanism, the net outcome of this work is to generate different phenyl esters with excellent yields. From the yield and

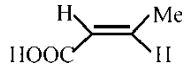
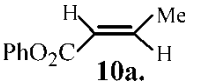
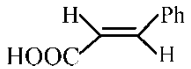
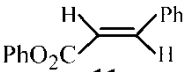
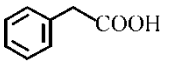
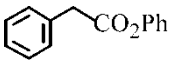
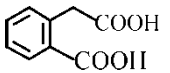
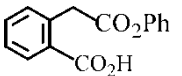
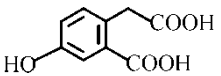
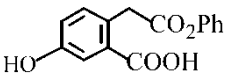
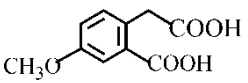
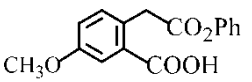
Table 1.

Entry	Acids	Reaction time (h)	Product (esters)	IR and ^{1}H NMR	Yield (%)
1		7	 **1a.**	IR (KBr): 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59–7.51$ (m, 5H, Ar-H), 7.39–7.32 (m, 5H, Ar-H).	90
2		9	 **2a.**	IR (KBr): 1738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.49$ (d, 1H, $J = 9$ Hz, Ar-H), 7.44 (d, 1H, $J = 10$ Hz, Ar-H), 7.32–7.22 (m, 5H, Ar-H), 6.95 (s, 1H, Ar-H). 6.84 (m, 1H, Ar-H), 2.32 (s, 3H, CH_3)	83
3		10	 **3a.**	IR (KBr): 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58–7.53$ (m, 2H, Ar-H), 7.51 (d, 1H, $J = 8$ Hz, Ar-H), 7.45–7.41 (m, 5H, Ar-H), 7.25 (d, 1H, $J = 8$ Hz, Ar-H), 2.28 (s, 3H, CH_3)	85
4		9	 **4a.**	IR (KBr): 1742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.16$ (d, 1H, $J = 8$ Hz, Ar-H), 7.50–7.44 (m, 2H, Ar-H), 7.33–7.21 (m, 5H, Ar-H), 6.94 (d, 1H, $J = 8$ Hz, Ar-H).	87

(*continued*)

Table 1. Continued

Entry	Acids	Reaction time (h)	Product (esters)	IR and ^{1}H NMR	Yield (%)
5		8	 **5a.**	IR (KBr): 3410, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.16$ (d, 2H, $J = 8$ Hz, Ar-H), 6.98 (d, 2H, $J = 8$ Hz, Ar-H), 6.87–6.77 (m, 5H, Ar-H), 4.05 (s, 1H, OH).	83
6		10	 **6a.**	IR (KBr): 2865, 1746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$–7.55 (m, 2H, Ar-H), 7.52 (d, 1H, $J = 8$ Hz, Ar-H), 7.38–7.32 (m, 5H, Ar-H), 7.19 (d, 1H, $J = 8$ Hz, Ar-H), 4.25 (s, 1H, OH).	85
7		11	 **7a.**	IR (KBr): 1743, 3151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$-7.42 (m, 5H, Ar-H), 7.39 (d, 2H, $J = 9$ Hz, Ar-H), 7.19 (d, 2H, $J = 9$ Hz, Ar-H), 3.88 (br s, 2H, NH_2)	80
8		12	 **8a.**	IR (KBr): 1731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (dd, 1H, $J = 7$, 2 Hz), 7.55 (dd, 1H, $J = 7.2$ Hz), 7.42 (dd, 1H, J = 7, 2 Hz). 7.28-7.20 (m, 5H, Ar-H).	75
9		11	 **9a.**	IR (KBr): 1744, 1693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 11.08$ (s, 1H, COOH), 7.48–7.45 (m, 5H, Ar-H), 7.43–7.41 (m, 2H, Ar-H), 7.38–7.35 (m, 2H, Ar-H).	88

10		9	 **10a.**	IR (KBr): 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41–7.37$ (m, 2H, Ar-H), 7.23 (d, 1H, $J = 15$ Hz, CH), 7.18–7.15 (m, 3H, Ar-H). 6.07 (d, 1H, $J = 15$ Hz, CH), 1.93 (s, 3H, CH_3).	87
11		9	 **11a.**	IR (KBr): 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (d, 1H, $J = 16$ Hz, CH), 7.60–7.59 (m, 2H, Ar-H), 7.45–7.42 (m, 5H, Ar-H). 7.29–7.22 (m, 3H, Ar-H), 6.67 (d, 1H, $J = 16$ Hz, CH).	80
12		8	 **12a.**	IR (KBr): 1749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.52–7.39$ (m, 5H, Ar-H), 7.19 (d, 2H, $J = 8$ Hz, Ar-H), 7.04–7.00 (m, 1H, Ar-H), 6.92 (d, 2H, $J = 8$ Hz, Ar-H), 3.96 (s, 2H, CH_2).	85
13		8	 **13a.**	IR (KBr): 1743, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.12$ (s, 1H, COOH), 7.52–7.42 (m, 5H, Ar-H), 7.19 (d, 1H, $J = 8$ Hz, Ar-H), 7.02 (m, 2H, Ar-H), 6.92 (d, 1H, $J = 8$ Hz, Ar-H), 3.96 (s, 2H, CH_2).	80
14		8	 **14a.**	IR (KBr): 3400, 1751, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.08$ (s, 1H, COOH), 7.48–7.42 (m, 5H, Ar-H), 7.39 (d, 1H, $J = 8$ Hz, Ar-H), 7.35 (s, 1H, Ar-H), 7.28 (d, 1H, $J = 9$ Hz, Ar-H), 4.65 (s, 1H, OH). 4.01 (s, 2H, CH_2).	75
15		9	 **15a.**	IR (KBr): 1747, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 11.13$ (s, 1H, COOH). 7.54–7.42 (m, 5H, Ar-H), 7.19 (d, 1H, $J = 8$ Hz, Ar-H), 7.02 (s, 1H, Ar-H), 6.92 (d, 1H, $J = 8$ Hz, Ar-H), 4.26 (s, 2H, CH_2), 3.77 (s, 3H, CH_3).	77

Note: Melting/boiling points were checked from the literature data.[9–11]

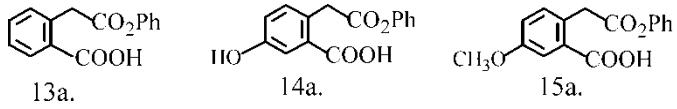


Figure 1.

considering the reaction simplicity, we can adopt the present method as a procedure for phenyl esterification over other existing methodologies (Figure 1).

EXPERIMENTAL

General

The melting points were determined on a capillary melting-point apparatus and are uncorrected. Infrared spectra were recorded using KBr pellets for solids and neat for liquids on a FTIR-8400 and a Perkin-Elmer 883 grating spectrometer. ^{1}H NMR and ^{13}C NMR spectra were taken on an AC Bruker 200-MHz spectrometer in $CDCl_3$, containing TMS as the internal standard. Mass spectra were taken on Kratos MS 80 system. All J values are given in Hertz and chemical shifts in δ units. EtOAc was simply distilled over $CaCl_2$. Reactions were monitored by TLC, and column chromatography was done on 60–120 mesh E. Merck silica gel.

General Method for the Preparation of Phenyl Esters

To a stirred solution of acid **13** (1 g, 5.5 mmol), anhyd. $AlCl_3$ (0.01 g, 0.20 mmol) was added at ice-cold temperature. Five min later, phenol (0.522 g, 5.5 mmol) and anhyd. $ZnCl_2$ (0.755 g, 5.5 mmol) were added to the reaction mixture, and stirring was continued at 0°C for 2 h. The reaction mixture was additionally stirred at room temperature for about 6 h. Completion of the reaction was monitored by TLC in *n*-hexane/EtOAc (5:1) solvent systems. Reaction mixture was quenched by 1M HCl solution at ice-cold temperature, and it was extracted by ether (3 × 25 mL), washed with water (3 × 25 mL), and dried over Na_2SO_4. Evaporation of the ether extract gave crude ester, which upon silica-gel filtration to the same solvent system, gave compound **13a** in 80% yield (1.24 g).

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