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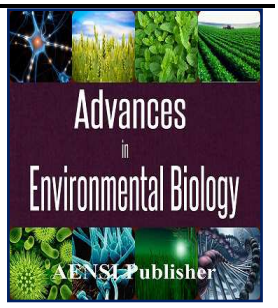

Synthesis of 2-Phenylethyl Esters By One-Pot The Yamaguchi Esterification

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ABSTRACT

A series of 2-phenylethyl esters were obtained rapidly and in high yields by a one-pot the Yamaguchi esterification reactions, and elucidated structurally by NMR, mass, and IR spectroscopies.

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INTRODUCTION

2-Phenylethanol and many of its derivatives have pleasant sweet-floral impressions. They are used in perfumery, cosmetics, and as flavors in food products. 2-Phenylethyl esters as 2-phenylethanol derivatives are also member of the aroma-active structural group aryl alkyl alcohol simple acid ester [1-3]. A number of 2-phenethyl esters are found as trace components in saw palmetto, guava fruit, guava peel, yellow passion fruit, mint, cheese, and peanut [4-5]. There are several methods by which 2-phenylethyl acetate has been prepared [6-9], and the synthesis of 2-phenylethyl octanoate has been also described [10]. Recently general procedure for synthesis of 2-phenethyl esters has been reported, by following the esterification and transesterification method of butter oil with methionol [1, 11]. The general enzymatic procedure was carried out for 24 h and gave 2-phenethyl esters (ie. 2-phenethyl butanoate, hexanoate, octanoate, decanoate, dodecanoate, octadecanoate, tetradecanoate, and hexadecanoate) in 50-88% yields. On the other hand, the general chemical synthesis involved reaction of 2-phenethyl alcohol with *N*,*N*'-dicyclohexylcarboidimide and *N*,*N*-dimethylamino-pyridine in dichloromethane for 24 h and gave the esters 47-66% yields.

A variety of esterification methods have been developed [12]. Yamaguchi esterification which is known as a rapid esterification method, has been used for instance in the synthesis of macrolactones, Lux-S aspartic acid inhibitor, thiol esters, (+)-cryptophycin 52, and (-)-borrelidin [13-18]. Accordingly, the objective of this research was to study one-pot Yamaguchi reaction of 2-phenyl-ethanol in order to develop better method for the synthesis of 2-phenylethyl esters.

Experimental:
Measurements:

NMR spectra were obtained in $CDCl_3$ on an Agilent Delta2 ECA spectrometer at 500 MHz. EI mass spectra analysis were carried out on an Agilent 6890 series plus Gas Chromatograph with Agilent 5973 N mass selective detector. Infrared spectra were recorded as thin film on a Shimadzu FTIR 8400S infrared spectrophotometer.

General Procedure for the Synthesis 2-phenylethyl esters:

A solution of the corresponding carboxylic acid (1.5 mmol), 2,4,6-trichlorobenzoyl chloride (1.5 mmol), and triethylamine (1.5 mmol) in anhydrous dichloromethane was stirred at room temperature for 1 h. *N*,*N*-Dimethylaminopyridine (1.5 mmol) and 2-phenylethanol (1.5 mmol) were added, and the solution was stirred further at room temperature and the progress of the reaction was monitored using TLC. Water was added and the product was extracted with dichloromethane. The organic extract was washed respectively with hydrogen

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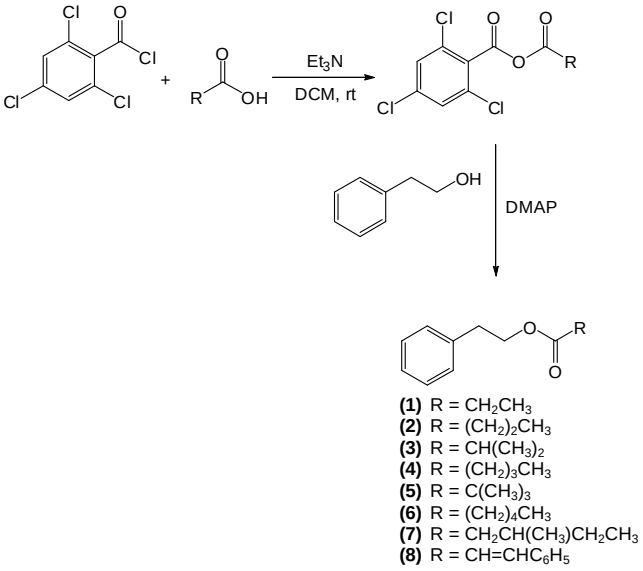
chloride solution (5%), sodium bicarbonate solution (10%), and water. It was dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to afford a phenylethyl ester as a light yellow oil.



Scheme 1: Synthesis of 2-Phehylethyl esters **(1-8)**

Characterization of the Synthesized Compounds:
2-Phenylethyl propanoate (1):

IR (ν cm^{-1}): 1738 (C=O), 1182 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (3H, t, J=7.6 Hz, CH_3), 2.33 (2H, q, J=7.6 Hz, CH_2), 2.96 (2H, t, J=7.1 Hz, CH_2Ar), 4.31 (2H, t, J=7.1 Hz, CH_2O), 7.23-7.34 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.23 (CH_3), 27.72 (CH_2), 35.28 (CH_2Ar), 64.91 (CH_2O), 126.65, 128.59, 129.03 (ArCH), 138.02 (ArC), 174.54 (C=O); mass spectrum (EI): *m/z* 178 (M, 2%), 149 (2), 121 (5), 105 (10), 104 (100), 91(15), 87(10), 77(5), 73 (2).

2-Phenylethyl butanoate (2):

IR (ν cm^{-1}): 1736 (C=O), 1179 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, t, J=7.4 Hz, (CH_3), 1.59-1.66 (2H, m, CH_2), 2.27 (2H, t, J=7.5, CH_2), 2,94 (2H, t, J=7.1 Hz, CH_2Ar), 4.29 (2H, t, J=7.1 Hz, CH_2O), 7.21–7.32 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.79 (CH_3), 18.56 and 36.36 (CH_2), 35.32 (CH_2Ar), 64.83 (CH_2O), 126.66, 128.61, 129.04, (ArCH), 138.04 (ArC), 173.77 (C=O); mass spectrum (EI): *m/z* 192 (M, 2%), 163 (2), 121 (2), 105 (20), 104 (100), 91(15), 71 (15), 43 (15).

2-Phenylethyl 2-methylpropanoate (3):

IR (ν cm^{-1}): 1736 (C=O), 1155 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (6H, d, J=7.0 Hz, CH_3), 2.52 (1H, sept, J=7.0 Hz, CH), 2.94 (2H, t, J=7.1 Hz, CH_2Ar), 4,29 (2H, t, J=7.1 Hz, CH_2O), 7.21-7.32 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.05 (CH_3), 34.11 (CH), 35.27 (CH_2Ar), 64.80 (CH_2O), 126.60, 128.54, 129.04 (ArCH), 138.05 (ArC), 177.15 (C=O); mass spectrum (EI): *m/z* 192 (M, 2%), 163 (2), 121 (2), 105 (15), 104 (100), 91(15), 71 (15), 43 (20).

2-Phenylethyl pentanoate (4):

IR (ν cm^{-1}): 1736 (C=O), 1173 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, J = 7.4 Hz, CH_3), 1.31-1.39 (2H, m, CH_2), 1.59-1.65 (2H, m, CH_2), 2.31 (2H, t, J=7.5 Hz, CH_2), 2,96 (2H, t, J=7.1 Hz, CH_2Ar), 4,32 (2H, t, J=7.1 Hz, CH_2O), 7.24-7.34 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.67 (CH_3), 22.19, 26.98, 33.96, (CH_2), 35.13 (CH_2Ar), 64.63 (CH_2O), 126.46, 128.44, 128,84 (ArCH), 137.85 (ArC), 173.61(C=O); mass spectrum (EI): *m/z* 206 (M, 2%), 176 (2), 164(2), 121(2), 105 (20), 104 (100), 85 (15), 57 (15), 41 (2).

2-Phenylethyl 2,2-dimethylpropanoate (5):

IR (ν cm^{-1}): 1728 (C=O), 1150 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.16 (9H, s, CH_3), 2.94 (2H, t, J=7.0 Hz, CH_2Ar), 4.28 (2H, t, J=7.1 Hz, CH_2O), 7.22-7.34 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.30

(CH_3), 35.29 (CH_2Ar), 38.85 ($\underline{C}(CH_3)_3$), 64.97 (CH_2O), 126.60, 128.54, 129.10, (Ar$\underline{C}$H), 138.14 (Ar$\underline{C}$), 178.64 (C=O); mass spectrum (EI): *m/z* 206 (M, 2 %), 121 (2), 105 (20), 104 (100), 91 (10), 77(5), 57 (25).

2-Phenylethyl 3-methylpentanoate (6):

IR (v cm^{-1}): 1736 (C=O), 1179 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (3H, t, J=7.7 Hz, CH_3), 0.91 (3H, d, J=6.8 Hz, CH_3), 1.17-1.25 and 1.30-1.39 (2H, m, CH_2), 1.83-1.90 (1H, m, CH), 2.11 (1H, dd, J=14.7 Hz, J=8.1 Hz, CH), 2.30 (1H, dd, J=14.7 Hz, J=6.2 Hz, CH), 2.95 (2H, t, J=7.1 Hz, CH_2Ar), 4.32 (2H, t, J=7.1 Hz, CH_2O), 7.23-7.34 (5H, m, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.36 (CH_3), 19.34 (CH_3), 29.39 (CH_2), 31.99 (CH), 35.27 (CH_2Ar), 41.59 (CH_2), 64.72 (CH_2O), 126.60, 128.55, 128.98, (Ar$\underline{C}$H), 137.99 (Ar$\underline{C}$), 173.37 (C=O); mass spectrum (EI): *m/z* 220 (M, 2%), 145 (2), 131(2), 121 (2), 105 (25), 104 (100), 91 (10), 71(10), 57 (2), 43 (5).

2-Phenylethyl hexanoate (7):

IR (v cm^{-1}): 1734 (C=O), 1169 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.0 Hz, CH_3), 1.26-1.38 (4H, m, $(CH_2)_2$, 1.60-1.66 (2H, m, CH_2), 2.30 (2H, t, J = 7.6 Hz, CH_2), 2.96 (2H, t, J = 7.1 Hz, CH_2Ar), 4.32 (2H, t, J = 7.1 Hz, CH_2O), 7.24-7.34 (5H, m, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.92 (CH_3), 22.35, 24.65, 31.30, 34.29, 39.29 (CH_2), 35.18 (CH_2Ar), 64.70 (CH_2O), 126.39, 128.47, 128.90 (ArCH), 137.91 (ArC), 173.75 (C=O); mass spectrum (EI): *m/z* 220 (M, 2%), 205 (2), 191(2), 177 (2), 149 (2), 145 (2), 143 (2), 129 (2), 121(10), 115 (10),105 (25), 104 (100), 99(2), 91 (5), 77 (8), 71 (15), 57 (30), 56 (5), 43 (10), 42 (5), 29(5).

2-Phenylethyl (E)-3-phenyl-2-propeonate (8):

IR (v cm^{-1}): 1710 (C=O), 1171 (C-O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.05 (2H, t, J = 7.1 Hz, CH_2Ar), 4.46 (2H, t, J = 7.1 Hz, CH_2O), 6.46 (1H, d, J=16.1 Hz, CH=), 7.27-7.54 (10H, m, ArH), 7.71 (1H, d, J=16.1 Hz, CH=); ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.30 ($\underline{C}H_2Ar$), 65.11 (CH_2O), 118.14 and 144.95 (CH=), 126.66, 128.17, 128.61, 128.96, 129.02, 130.37, (ArCH), 134.48 and 137.97 (ArC), 166.97 (C=O); mass spectrum (EI): *m/z* 252 (M, 2%), 147 (10), 131 (45), 105 (10), 104 (100), 91 (10), 77 (25), 65 (5).

RESULT AND DISCUSSION

Synthesis of 2-phenylethyl esters (1-8) were carried out by one-pot Yamaguchi esterification in two steps, as can bee seen in Scheme 1. The first step involved reaction of carboxylic acid with triethylamine at room temperature to form carboxylate ion which on reaction with 2,4,6-trichlorobenzoyl chloride furnished aliphatic-aromatic anhydrides. Nucleophilic acyl substitution of the aliphatic-aromatic anhydrides with 2-phenylethanol and *N*,*N*-dimethylaminopyridine in the second step furnished the esters (1-8) [13]. The ^{1}H NMR spectra of the esters exhibited three signals for the phenylethyl groups of the esters (1-8). The two triplets about δ 2.95 and 4.30 ppm due to the signals of the two methylene groups protons, and a multiplet signal about δ 7.21-7.34 ppm for the five aromatic protons. The presence of the olefin group in (*E*)-2-Phenylethyl 3-phenyl-2-propeonate (8) strucure shifted the chemical shift of the phenylethyl group more downfield at δ 3.05 and 4.46 ppm for the two methylene groups protons and at δ 7.27-7.54 ppm for the five aromatic protons due to anisotropy effect. The ^{13}C NMR spectra clearly showed the carbonyl signals of the esters (1-7) at about δ 175 ppm, and lowered by conjugation to 169.97 ppm for (*E*)-2-phenylethyl 3-phenyl-2-propeonate (8). The IR spectra of the esters (1-7) exhibited strong stretching absorption at about 1735 cm^{-1} proved the existence of carbonyl the groups, whilst the conjugation of the carbonyl group with α,β-unsaturated double bond and phenyl group of (*E*)-2-phenylethyl 3-phenyl-2-propeonate (8) resulted in a shift to a frequency 1710 cm^{-1}.

Synthesis of 2-phenylethyl esters by one-pot Yamaguchi esterification as can be seen in Table 1 were conducted in shorter time (2-3.5 h) compare with previous method (ie. 24 h) [1]. Synthesis involved (*E*)-3-phenylprop-2-enoic acid by one-pot Yamaguchi esterification needed longer time (3.5 h) compare with aliphatic acid, which may caused by the steric effect of the conjugated aromatic acid. In addition, the Yamaguchi esterification of aliphatic acids in general gave higher yields (79-86% yields) compare with previous method which gave 50-88% yields for the enzymatic synthesis and 47-66% yields for the chemical synthesis [1]. One-pot Yamaguchi esterification of 2-phenylethanol afforded 2-phenyl-ethyl (*E*)-3-phenyl-2-propeonate (8) in 67% yield.

Table 1: Synthesis Data of 2-Phenylethyl esters (1-8)

2-Phenylethyl Esters	Time (h)	Yield (%)*
(1)	2	79
(2)	2	87
(3)	2	91
(4)	3	89
(5)	3	84
(6)	3	80
(7)	3	86
(8)	3.5	67

*Isolated yield

Conclusion:

One-pot Yamaguchi esterification has shown as more convenient procedure for synthesis of 2-phenylethyl esters, in comparison with the lipase-catalysed synthesis or chemical synthesis with *N*,*N*'-dicyclohexyl-carboidimide and *N*,*N*-dimethylaminopyridine [1].

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