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TETRAHEDRON

Ring Opening of Cyclic Anhydrides: Synthesis of Achiral Half-Esters Using Lewis Acids

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Abstract: A rapid and high yield preparation of half-esters from cyclic anhydrides using alcohols and Lewis acids is described.

Keywords *: Anhydrides,Esterification, Regioselection.*

INTRODUCTION

Half-esters are versatile synthons for the synthesis of various natural products. A general method for the preparation of half-esters or acid-esters involves the esterification or transesterification with alcohols[1] and the hydrolysis of diesters with $Ba(OH)_2$[2] or with pig liver esterase.[3] Ring opening of cyclic anhydrides with alkoxides[4] is also a popular method for the synthesis of half-esters. So far, practical non-enzymatic protocols for asymmetric versions of these reactions are rare.[5-7]

Very recently, great attention has been focused on Lewis Acid (LA) catalyzed reactions[8,9] and their mechanistic details. Extending our recent studies[10] on the protection of aldehydes as diacetates and their deprotection using Lewis acids, we now report an efficient, simple, high yielding and general synthesis of hemiesters starting from cyclic anhydrides using readily accessible Lewis acids.

RESULTS AND DISCUSSIONS

The BF_3-Et_2O mediated ring opening of cyclic anhydrides with alcohols like methanol and ethanol proceeded spontaneously to afford the corresponding pure hemiesters in excellent yields (**Scheme-1**). The scope of the reaction can be evaluated by the regioselective ring opening of homophthalic anhydride (entry 2), tetralic anhydride (entry 3) and phenylitaconic anhydride (entry 4) with exclusive monoesterification of the aliphatic carboxylic acid function, the aromatic acid remaining unaffected. This outcome was determined by the identification of half-esters through spectral analysis and also by comparing with the known half-ester of homophthalic anhydride,

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2-methoxycarbonylmethylbenzoic acid,[11] as a standard. Cyclic *meso*-anhydrides (entries 5 and 6) also gave monoesters exclusively.

Scheme 1

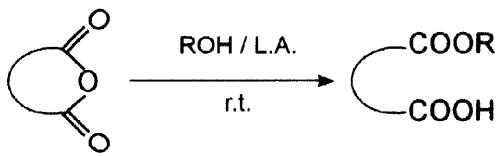
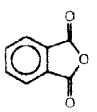
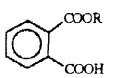
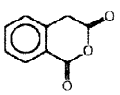
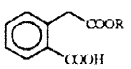
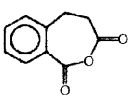
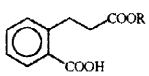
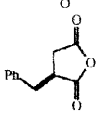
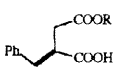
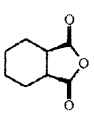
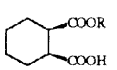
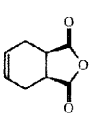
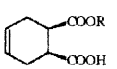
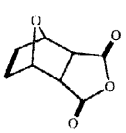
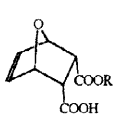
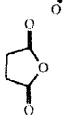
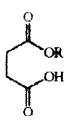
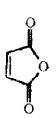
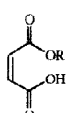


Table 1 Preparation of half esters from cyclic anhydrides

Entry	Anhydride	Half-Ester	ROH	BF_3-Et_2O Molar ratio	BF_3-Et_2O Time (min)	BF_3-Et_2O Yield %	$AlCl_3$ Molar ratio	$AlCl_3$ Time (min)	$AlCl_3$ Yield %	$FeCl_3$ Molar ratio	$FeCl_3$ Time (min)	$FeCl_3$ Yield %
1			MeOH	0.5	0.5	95	0.5	1	78	1.0	10	68
			EtOH	0.5	0.75	93	0.5	3	73	1.0	15	60
2			MeOH	0.5	0.5	96	0.5	2	76	1.0	12	66
			EtOH	0.5	0.75	95	0.5	3	70	1.2	15	62
3			MeOH	0.5	0.5	98	0.5	2	75	1.0	12	65
			EtOH	0.5	0.5	90	0.5	3	71	1.0	15	58
4			MeOH	0.5	0.5	97	0.5	1	85	1.0	10	66
			EtOH	0.5	0.5	90	0.5	2	82	1.0	15	60
5			MeOH	0.75	0.5	96	0.5	1	90	1.0	10	66
			EtOH	0.75	0.5	89	0.5	2	86	1.0	15	57
6			MeOH	0.75	0.5	98	0.5	1	92	1.0	12	68
			EtOH	0.75	0.5	90	0.5	2	83	1.0	15	59
7			MeOH	0.75	0.5	93	0.5	3	63	1.0	10	58
			EtOH	0.75	0.5	87	0.5	4	58	1.0	15	53
8			MeOH	0.5	0.5	88	0.5	1	68[a]	1.0	10	53[a]
			EtOH	0.5	0.5	80	0.5	1	66[a]	1.0	15	48[a]
9			MeOH	0.5	0.5	89	0.5	1	70[a]	1.0	10	56[a]
			EtOH	0.5	0.5	86	0.5	2	63[a]	1.0	15	49[a]

a) Yields of diesterified products

With these results in hand, we investigated the effect of other Lewis acids, $AlCl_3$ and $FeCl_3$ (Table 1) on monocyclic (entries 4, 8, 9), bicyclic (entries 1, 2, 3, 5, 6) and tricyclic (entry 7) anhydrides. Comparision of the results show that in all the cases, the reactions promoted by BF_3-Et_2O were spontaneous giving cleaner products with a simpler work-up procedure. However, the

reactions with $AlCl_3$ gave the products with comparatively lower yields and longer reaction times. Even though the ring opening reactions were successful with $FeCl_3$, we could not achieve good yields and the reactions also took 10-15 minutes for completion.

It is important to note that the ring opening reactions of succinic (entry 8) and maleic (entry 9) anhydrides with alcohols using BF_3-Et_2O resulted in monoesterified products whereas with $AlCl_3$ and $FeCl_3$ diesterified products were observed even under controlled reaction conditions.

In conclusion, the above results prove that BF_3-Et_2O acts as a very efficient Lewis acid catalyst under mild conditions. Also, the ease of the work-up procedure, the selectivity and the higher yields offer many advantages over existing procedures.

EXPERIMENTAL

Products were characterised by comparision of spectral data and physical properties with those of authentic samples.[11-16] Progress of the reactions were followed by TLC using silical gel coated glass plates-MERCK. ^1H NMR and ^{13}C NMR spectra were run on a Varian Gemini spectrometer apparatus at 200 MHz with TMS as an internal reference. Melting points were determined on a Fischer-Johns apparatus and are uncorrected. Mass spectra were recorded on 7070H or Finningan Mat 1020B mass spectrometer. CHN analyses were performed on ELEMENTOR, Germany, CHN Analyser.

General procedure for the synthesis of half-esters using BF_3-Et_2O

To a well stirred solution of the anhydride (0.01 mol) in alcohol (0.15 mol), BF_3-Et_2O (0.005-0.0075 mol) was added dropwise. The reaction, on completion (t.l.c monitored), was added to a saturated solution of sodium bicarbonate (20 mL) and extracted with ether (3x20 mL) to remove the traces of any unreacted anhydride. The aqueous layer was neutralised with conc. HCl at 0 °C and extracted with ether (3x20 mL). The organic phase was washed with brine (3x20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a pure half-ester in 80-98% yield.

2-Ethoxycarbonylmethylbenzoic acid (hemiester from 2) Pale white solid, **M.P.** : 63 °C; [Found: C, 63.34; H, 5.71. $C_{11}H_{12}O_4$ requires C, 63.46; H, 5.81%]; **IR** (KBr) : 3121, 1728, 1679 cm^{-1}; **^1H NMR** (200 MHz, $CDCl_3$) : δ 1.25 (t, *J* 14.8 Hz, 3H, $-CH_3$), 3.98-4.18 (m, 4H, $2xCH_2$), 7.18-7.50 (m, 3H, ArH), 8.0 (d, *J* 7.4 Hz, 1H, ArH), 8.78 (br s, 1H, COOH); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 14.3, 41.0, 60.6, 124.4, 128.2, 131.9, 132.4, 136.0, 137.0, 167.2, 173.4; m/z : 190 (M^+-18).

α-Methylester of 2-carboxybenzenepropionic acid (hemister from 3) White solid, **M.P.** : 66 °C; [Found : C, 63.2; H, 5.69. $C_{11}H_{12}O_4$ requires C, 63.46; H, 5.81%]; **IR** (KBr) 2925, 1695, 1665 cm^{-1}; **^1H NMR** (200 MHz, $CDCl_3$) : δ 2.7 (t, *J* 15.7 Hz, 2H, CH_2), 3.35 (t, *J* 15.7 Hz, 2H, CH_2), 3.68 (s, 3H, -COOMe), 7.25-7.4 (m, 2H, ArH), 7.48 (m, 1H, ArH), 8.1 (d, *J* 7.8 Hz, 1H, ArH), 10.6 (br s, 1H, COOH); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 30.0, 35.5, 51.3, 126.5, 128.3, 131.3, 132.0, 133.0, 143.6, 172.6, 173.0; m/z :190 (M^+-18).

α-Ethylester of 2-carboxybenzenepropionic acid (hemister from 3) White solid, **M.P.** : 64 °C; [Found : C, 64.7; H, 6.0. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%]; **IR** (KBr) 2935, 1705, 1676 cm^{-1}; **^1H NMR** (200 MHz, $CDCl_3$) : δ 1.28 (t, *J* 12.5 Hz, 3H, CH_3), 2.65 (t, *J* 12.5 Hz, 2H, CH_2),

3.28 (t, *J* 12.5 Hz, 2H, -CH_2), 4.06-4.19 (m, 2H, CH_2), 7.22-7.49 (m, 3H, ArH), 7.93 (d, *J* 5 Hz, 1H, ArH); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 15.1, 28.1, 37.2, 59.2, 127.3, 130.4, 131.3, 133.4, 134.7, 139.7, 170.6, 174.2; m/z : 204 (M^+-18).

α-Methylester of phenylitaconic acid (hemister from 4) Colourless oil, [Found : C, 65.3; H, 5.3. $C_{12}H_{11}O_4$ requires C, 65.45; H, 5.49%]; **IR** (Liquid film) 3125, 1695, 1665 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 3.55 (s, 2H, CH_2), 3.75 (s, 3H, CH_3), 7.28 (s, 2H, ArH), 7.38 (br s, 2H, ArH), 8.01 (s, 1H, =CH); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 43.2, 51.4, 123.4, 126.3, 127.3, 128.2, 130.6, 131.8, 135.5, 143.7, 167.6, 172.3; m/z : 202 (M^+-18).

α-Ethylester of phenylitaconic acid (hemister from 4) Brown oil, [Found : C, 66.5; H, 5.9. $C_{12}H_{14}O_4$ requires C, 66.6; H, 6.02%]; **IR** (Liquid film) 3110, 1690, 1660 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 1.3 (t, *J* 14.2 Hz, 3H, CH_3), 3.52 (s, 2H, CH_2), 4.18-4.29 (q, *J* 21.7 Hz, 2H, -CH_2), 7.4 (s, 5H, ArH), 8.02 (s, 1H, =CH), 9.89 (br s, 1H, COOH); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 14.9, 42.3, 62.1, 124.4, 129.1, 129.9, 130.0, 130.3, 133.1, 135.5, 143.6, 166.1, 171.9; m/z : 216 (M^+-18).

α-Ethylester of *cis*-3,4-cyclohexenedicarboxylic acid (hemister from 6) White solid, **M.P.** : 72 °C ; [Found : C, 60.5; H, 7.0. $C_{10}H_{14}O_4$ requires C, 60.61; H, 7.12%]; **IR** (KBr) 3120, 1690, 1655 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 1.23 (t, *J* 15.1 Hz, 3H, CH_3), 2.12-2.45 (m, 2H, -CH_2), 2.47-2.62 (m, 2H, CH_2), 2.95-3.08 (m, 2H, CH_2), 4.05-4.18 (q, *J* 21 Hz, 2H, CH_2), 5.65 (s, 2H, CH=CH), 8.5 (br s, 1H, COOH); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 13.9, 23.2, 24.0, 43.6, 45.5, 58.9, 123.8, 125.6, 172.8, 173.1; m/z : 180 (M^+-18).

3,6-Epoxy-2-(2-ethoxycarbonyl)hex-4-ene-1-carboxylic acid (hemister from 7) Brown oil, [Found : C, 56.5; H, 5.5. $C_{10}H_{12}O_5$ requires C, 56.60; H, 5.70%]; **IR** (Liquid film) 3118, 1702, 1670 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$) : δ 1.24 (t, *J* 14.8 Hz, 3H, CH_3), 2.77 (s, 2H, CH_2), 4.09-4.11 (q, *J* 21 Hz, 2H, -CH_2), 5.23 (s, 2H, CH_2), 6.44 (s, 2H, CH_2); **^{13}C NMR** (200 MHz, $CDCl_3$) : δ 13.5, 152.5, 53.1, 58.6, 76.4, 78.0, 127.5, 132.1, 168.3, 174.4; m/z : 194 (M^+-18).

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