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Selective Complexation of 2-Hydroxyethyl Esters Using Lewis Acids

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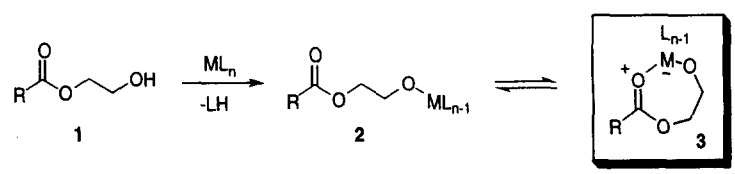
Abstract: Competitive Diels-Alder reactions between ethyl acrylate and 2-hydroxyethyl acrylate (1,3-cyclopentadiene, CH_2Cl_2, 0°C) in the presence of a variety of Lewis acids indicate that selective complexation of the 2-hydroxyethyl ester can be accomplished, most notably using $EtAlCl_2$. Further Diels-Alder reactions using ethyl 2-hydroxyethyl fumarate support these findings. ^{13}C NMR studies provide direct evidence for the nature of the interactions between 2-hydroxyethyl esters and $EtAlCl_2$.

Practitioners of organic synthesis often resort to the use of protecting groups to mask reactive functionality such that selective manipulations can be accomplished in complex systems.[1] However, a seemingly more elegant solution to this problem is to develop reagents and protocols which enable highly chemoselective reactions to be performed without recourse to protective groups. To date, a number of efforts have been made to determine if the selective activation of one basic site within a molecule containing two or more such centres can be accomplished using Lewis acids. In pioneering studies, Yamamoto has demonstrated that the highly sterically hindered Lewis acid, methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), can be used to selectively complex to the least hindered ester carbonyl group of unsymmetrical fumarates.[2] In other studies, Brown has shown that either the ester or the thionoester group of dimethyl monothionofumarate can be activated by use of either a hard or soft Lewis acid.[3] A series of related studies using (*E*)-MeO_2C-CH=CH-COSMe[4] and (*E*)-RCO-CH=CH-COSMe[5] have also been described. In a recent development, Westwell and Williams have selectively activated (2-pyridyl)methyl esters in the presence of benzyl esters using transition metal salts.[6]

We hoped to complex and hence activate 2-hydroxyethyl esters **1** in the presence of other types of esters by forming 7-membered chelated structure **3** as depicted in Scheme 1. Importantly, we anticipated that the formation of an initial covalent bond between the Lewis acid and the hydroxyl group (*ie* **2**) by ligand exchange would allow us to discriminate between 2-hydroxyethyl esters and other types of alkyl and aryl esters. These studies were inspired, in part, by the work of Roush *et al* who had examined the Lewis acid mediated intramolecular Diels-Alder reactions of highly sensitive triene substrates bearing 2-hydroxyethyl esters albeit with only limited success.[7] In this Letter, we disclose our initial findings on the selective complexation and activation of 2-hydroxyethyl esters by Lewis acids.



Scheme 1

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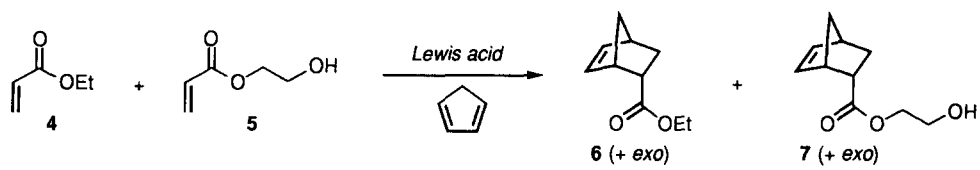
PII: S0040-4039(99)01051-5

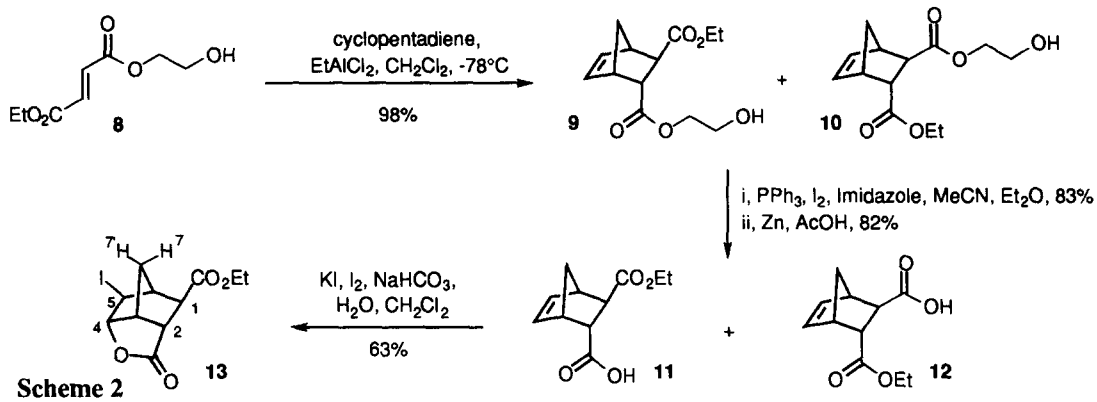
We chose to use the Diels-Alder reaction as a mechanistic probe for Lewis acid complexation because binding of a Lewis acid to a dienophile is known to dramatically accelerate the rate of the subsequent cycloaddition reaction.[8] Thus, by performing a series of competition experiments using acrylates bearing different ester groups and analysing the product mixture, we hoped to determine if selective Lewis acid binding to the 2-hydroxyethyl ester group could be accomplished. Initial experiments to identify suitable Lewis acids focused on intermolecular competition experiments between ethyl acrylate and 2-hydroxyethyl acrylate, a selection of the results are presented in Table 1.[9] Ethyl aluminium dichloride was found to be the most selective Lewis acid (Entry 5) albeit with only low levels of conversion under these reaction conditions. Notably, in the absence of competing ethyl acrylate [$EtAlCl_2$ (1 eq), 1,3-cyclopentadiene (3 eq) -78°C, 12 h], cycloadduct **7** (*endo*:*exo*; 95:5) can be obtained in quantitative yield.



Entry	Reaction Conditions#	Products (Ratio§)	Conversion§
1	CH_2Cl_2, 0°C	**6** : **7** (50 : 50)	<1%
2	$BF_3.Et_2O$, CH_2Cl_2, 0°C	**6** : **7** (43 : 57)	14%
3	$TiCl_4$, $^iPr_2EtN$, CH_2Cl_2, 0°C	**6** : **7** (19 : 81)	43%
4	$SnCl_4$, $^iPr_2EtN$, CH_2Cl_2, 0°C	**6** : **7** (31 : 69)	<3%
5	$EtAlCl_2$, CH_2Cl_2, 0°C	**6** : **7** (17 : 83)	10%

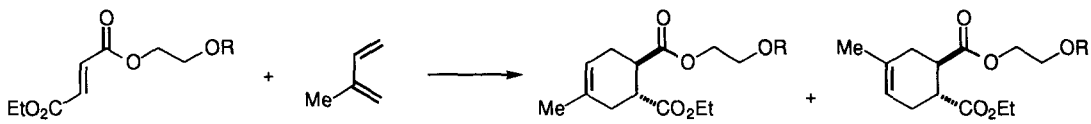
Table 1. # Reactions performed using 1:1:1 molar ratio of the two acrylates and 1,3-cyclopentadiene § Determined by GLC analysis after 1 h, authentic samples were made for comparison purposes.

To further evaluate the selective complexation of Lewis acids to 2-hydroxyethyl esters, we have studied the Diels-Alder reactions of fumarate **8** which contains both an ethyl ester and a 2-hydroxyethyl ester. Treatment of this fumarate with one equivalent of ethyl aluminium dichloride and 1,3-cyclopentadiene at -78°C overnight furnished cycloadducts **9** and **10** in a 75:25 ratio as judged by ^1H NMR spectroscopy (Scheme 2).[10] In contrast, thermolysis of fumarate **8** with excess 1,3-cyclopentadiene (110°C, 3h, 71%) produced essentially equal quantities of these cycloadducts (51:49 ratio). As the cycloadducts **9** and **10** were not separable, the relative stereochemistry of the major adduct could not be determined at this stage. Selective cleavage of the 2-hydroxyethyl ester was accomplished by its conversion into the corresponding 2-iodoethyl ester and subsequent zinc induced β-elimination. Subjection of the resulting 72:28 mixture of carboxylic acids **11** and **12** to iodolactonisation conditions resulted in the isolation of a single lactone **13** in 63% yield. The relatively high yield of this reaction indicates that this lactone must ultimately be derived from the major cycloadduct **9**. The structure and relative stereochemistry of this lactone were unambiguously established using a combination of NMR experiments. ^1H and ^{13}C assignments were made using HETCOR, COSY and HMQC experiments. NOe measurements were then used to establish the relative stereochemistries within lactone **13**. Strong enhancements between H-1→ H-5 (8.3%); H-7→H-2 (2.1%); H-7'→H-4 (2.1%); H-5→H-1 (8.4%) were used in conjunction with other enhancements to determine the relative spatial disposition of H-1, H-2, H-4 and H-5. From these studies, we conclude that Diels-Alder cycloaddition of fumarate **8** yields diester **9** as the major product. These findings suggest that in the presence of the ethyl aluminium dichloride, selective complexation to the 2-hydroxyethyl ester is occurring such that this ester moiety preferentially adopts the *endo* orientation in the subsequent Diels-Alder reaction.



Scheme 2

The reactions of fumarate **8** with isoprene under both thermal and Lewis acid mediated conditions have also been examined (Table 2). In this case, an appreciable level of regiochemical control was achieved in the presence of one equivalent of ethyl aluminium dichloride. Significantly, when the hydroxyl group is blocked as the corresponding methyl ether (*ie* **14**) no regiochemical control was observed.



8 (R = H); **14** (R = Me)

Entry	Acrylate	Reaction Conditions	Product (Ratio)§	Yield¶
1	**8** (R = H)	toluene, 110°C, 12h	R = H (48 : 52)	95%
2	**8** (R = H)	$EtAlCl_2$, CH_2Cl_2, 0°C, 12h	R = H (76 : 24)	81%
3	**14** (R = Me)	toluene, 110°C, 12h	R = Me (48 : 52)	99%
4	**14** (R = Me)	$EtAlCl_2$, CH_2Cl_2, 0°C, 12h	R = Me (52 : 48)	76%

Table 2. ¶ Yield of isolated material after column chromatography. § Determined by ^1H NMR analysis.

In order to directly probe the complexation phenomena associated with these 2-hydroxyethyl esters, we have studied the ^{13}C NMR spectrum of 2-hydroxyethyl acrylate **5** in dideuteriodichloromethane (75 MHz, 25°C). Upon addition of one equivalent of ethyl aluminium dichloride (1.0 M in hexanes), significant downfield shifts of the carbonyl group (δ 166.1 → 171.1, 173.1), one of the olefinics (δ 128.2, 130.6 → 125.1, 125.8, 140.8, 141.7) and one of the ether carbons atoms (δ 61.0, 66.1 → 62.9, 63.4, 74.0, 74.7) were observed. These observations are consistent with the formation of a complex such as **3** (Scheme 1). Intriguingly, we recorded two sets of signal in near equal amounts which may suggest that we are observing both *s-cis* and *s-trans* conformations of the acrylate system on the NMR timescale. While other interpretations of this data can be envisaged,[11] we do not believe that monomeric, non-chelated structure **2** would be consistent with the observed ^{13}C NMR spectrum as no downfield shift of the C=O carbon would be anticipated. In summary, we believe we have obtained experimental evidence which lends us to conclude that using ethyl aluminium dichloride, selective activation of 2-hydroxyethyl esters can be accomplished in accordance with Scheme 1. Further work to improve the selectivity of this process and to explore its applications in synthesis are currently under investigation. This work will be disclosed in due course.

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8. For a discussion on this topic, see Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*, pp 161-165, Wiley, New York, 1976.
9. All new compounds gave satisfactory spectroscopic and high resolution mass spectral data.
10. ***Typical procedure:*** To a solution of fumarate **8** (3.76 g, 20.0 mmol) in CH_2Cl_2 (40 ml) was added ethyl aluminium dichloride (1.0 M in hexanes, 20.0 ml, 20.0 mmol) and the solution stirred for 15 min, then cooled to -78°C. 1,3-Cyclopentadiene (3.40 ml, 41.2 mmol) was added and the solution was stirred overnight and allowed to slowly warm to room temperature. Sodium bicarbonate solution (30 ml) was added cautiously and the aqueous layer extracted with CH_2Cl_2 (2 x 100 ml). The organic layers were combined, dried (Na_2SO_4) and the solvent removed *in vacuo* to give the crude product. Column chromatography (40% ethyl acetate / 60% light petroleum) gave an inseparable 75:25 mixture of **9** and **10** (4.97 g, 98% yield) as a colourless oil. ν_{max} 3447, 2982, 1728, 1456, 1333, 1267, 1185, 1080, 1033, 851 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.29-6.26 (1H, m), 6.10-6.07 (1H, m), 4.24-4.08 (4H, m), 3.82-3.75 (2H, m), 3.41 (0.75H, t, J = 4.1 Hz), 3.35 (0.25H, t, J = 4.1 Hz), 3.28 (1H, br s), 3.19-3.01 (2H, m), 2.70 (0.25H, dd, J = 4.5, 1.4 Hz), 2.66 (0.75H, dd, J = 4.4, 1.4 Hz), 1.62-1.61 (1H, overlapping singlets), 1.47-1.44 (1H, overlapping singlets), 1.27 (2.25H, t, 7.1 Hz), 1.26 (0.75H, t, 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (major compound) 174.4 (s, C=O), 173.5 (s, C=O), 137.5 (d, =CH), 135.0 (d, =CH), 66.0 (t, CH_2), 60.8 (t, CH_2), 60.7 (t, CH_2), 47.8 (d, CH), 47.6 (d, CH), 47.22 (d, CH), 47.17 (t, CH_2), 45.6 (d, CH), 14.1 (q, CH_3); *m/z* 254 (M^+), 237 (MH^+-H_2O); Found (M^+): 254.1149; $C_{13}H_{18}O_5$ requires 254.1154.
11. For example, it is conceivable that the NMR data could be interpreted in terms of an equilibrium whereby we observe the desired monomeric species in equilibrium with a symmetrical dimer.