

Catalytic Methylaluminum Dichloride: An Efficient Method for Accelerating the Intramolecular Diels-Alder Reaction of the Furan Diene

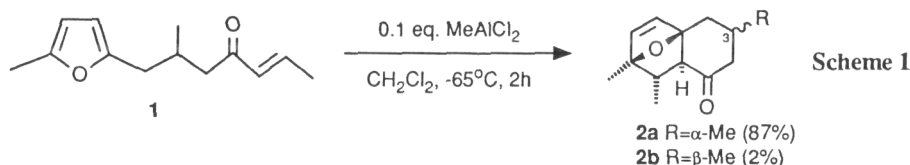
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Abstract: Catalytic (10 mol%) methylaluminum dichloride was found to be an efficient catalyst for the intramolecular Diels-Alder reaction of the furan diene providing oxatricyclo adducts at -65°C within two hours in yields ranging from good to excellent.

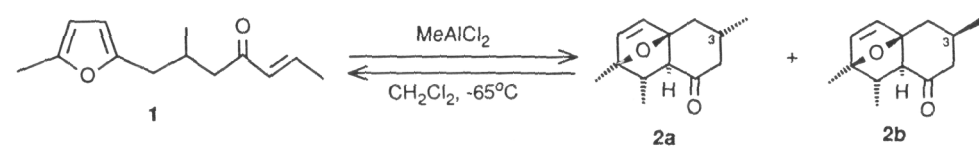
We recently reported that MeAlCl_2 was effective in mediating intramolecular Diels-Alder reactions involving a furan (IMDAF) diene connected to the dienophile by a four carbon atom side arm.¹ In all the examples reported, 1.1 equivalents of the Lewis acid was employed to effect the IMDAF reaction. Systems having no substituents on the dienophile provided adducts in excellent yields (90-97%). Substitution of the dienophile and/or C-5 position of the furan ring with methyl groups, however, lead to starting material:adduct (SM:A) ratios in favour of starting material (SM:A ratios varied from 73:27 to 82:18). During a study of the kinetics of the IMDAF reaction of furan **1** using 0.1 equivalents of MeAlCl_2 , it was observed by ^1H NMR that



after 2 hours at -65°C the ratio of **1:2** was 11:89 (Scheme 1). This ratio was initially surprising since a SM:A ratio of 72:28 was obtained when 1.1 equivalent of MeAlCl_2 was used with compound **1** at -65°C after 2 hours. It is well known that Lewis acids can accelerate the intramolecular Diels-Alder reaction,² however, the literature indicates that there has been only limited success in accelerating the intramolecular Diels-Alder reaction using catalytic quantities of Lewis acids;³ most reports employ ≥ 0.95 equivalents of Lewis acid.⁴ We therefore investigated this observation in more detail and herein report our results.

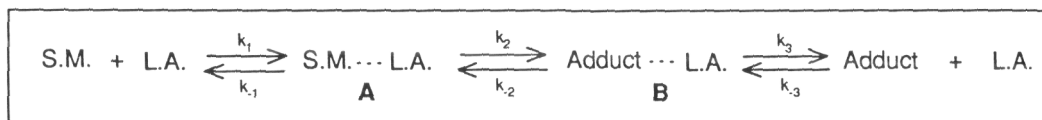
Table 1 summarizes two time studies on the IMDAF reaction of compound **1** employing 1.1 and 0.1 equivalents of MeAlCl_2 . A few points are noteworthy. The Diels-Alder reaction is reversible under both conditions since the quantity of adduct **2a** decreased (relative to **1**) with time when 1.1 equivalents of MeAlCl_2 were used, while the amount of **2a** increased (relative to **2b**) when 0.1 equivalents of MeAlCl_2 was employed. The use of 1.1 equivalents of MeAlCl_2 resulted in a higher amount of adduct **2a** (39%) after 5 min (relative to 0.1 equiv.) which then equilibrated to a lower **1:2a** ratio of 70:30 after 4 hours. The minor isomer

Table 1: Time Studies of the IMDAF Reaction of Compound 1 Employing 1.1 and 0.1 Equivalents of MeAlCl₂.

		
Time	1.1 equiv. MeAlCl ₂ (1:2a)	0.1 equiv. MeAlCl ₂ (1:2a:2b)
5 min	61:39	72:14:14
15 min	81:19	55:27:18
30 min	78:22	32:41:27
1 h	67:33	29:58:13
2 h	72:28	11:87:2
4 h	70:30	17:77:6

2b was neither detected (by ¹H NMR) nor isolated with 1.1 equivalents of MeAlCl₂. Using 0.1 equivalents of MeAlCl₂ provided after 5 minutes 28% of adduct which was a 1:1 mixture of **2a** and **2b**. The amount of adduct increased to 89% after 2 hours with the more thermodynamically stable product **2a** (C-3 equatorial methyl) formed in a 87:2 ratio relative to **2b** (C-3 axial methyl).

A possible explanation for these observations can be deduced by considering the following equilibria.

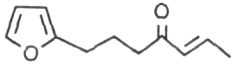
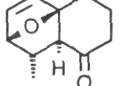
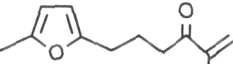
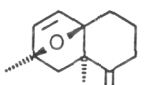
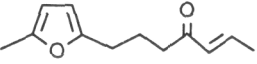
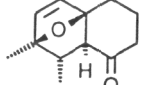
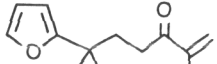
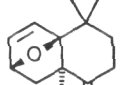
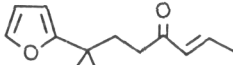
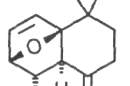
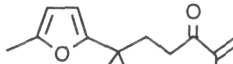
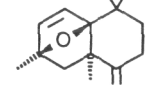
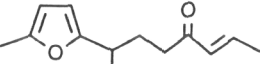
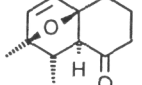
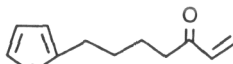
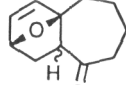


In the presence of excess MeAlCl₂ (1.1 equiv.) the starting material and adduct are essentially complexed with Lewis Acid (i.e. k_{-1} and k_{-3} are small relative to k_1 and k_3), therefore both the forward and reverse Diels-Alder reactions (k_2 and k_{-2}) are accelerated, eventually leading to a thermodynamic ratio of Lewis acid complexed starting material **A** and adduct **B** which on workup provides a 70:30 ratio of **1:2a**. The decrease in the amount of **2a** initially formed with 1.1 equivalents of MeAlCl₂ after 5 minutes may be due to complex **B** being kinetically formed at short reaction times (< 5 min) and then equilibrating (as the concentration of **B** increases) to a thermodynamic ratio.

In the case where catalytic amounts of MeAlCl₂ are employed the Lewis acid should preferentially coordinate with the more basic enone in the starting material than with the saturated ketone in the adduct (i.e. $k_1 \gg k_{-1}$ and $k_3 \gg k_{-3}$). The decomplexing of the Lewis acid of the adduct becomes faster than the reverse Diels-Alder reaction (i.e. $k_3 \gg k_{-2}$), therefore the equilibrium of the reaction is between the complexed starting material **A** and the uncomplexed adducts **2a** and **2b**. The equilibrium is therefore shifted to provide more adduct (relative to 1.1 equiv. of MeAlCl₂). Further studies are underway to verify this hypothesis.

The above observations were not limited to compound **1** since a variety of compounds (**3-10**, Table

Table 2: IMDAF Results Using 10 Mol% MeAlCl₂

Starting Material	SM:A Ratios (% Yield) ^a		Adduct
	1.1 equiv. MeAlCl ₂ (8h, -78°C)	0.1 equiv. MeAlCl ₂ (2h, -65°C)	
3 	78:22 (11)	31:69 (66)	11 
4 	19:81 (80)	0:100 (98)	12 
5 	82:18 (18)	24:76 (73)	13 
6 	68:32 (31)	40:60 (58)	14 
7 	73:27 (22)	27:73 (70)	15 
8 	78:22 (18)	23:77 (75)	16 
9 	78:22 (15) (eq.:axial ratio 2.5:1)	17:83 (81) (eq.:axial ratio 20:1)	17 
10 	---	8:92 (91) ^b (endo:exo 91:9)	18 

a) isolated yields; b) at -78°C

2)^{1,5,6} provided superior SM:A ratios when treated with 10 mol% MeAlCl₂ when compared to the ratios obtained with 1.1 equivalents of MeAlCl₂. The adducts are easily separated from the starting material by flash chromatography, thereby allowing a recycling of starting material. Adducts **11-17** had the side arm orientated *exo* with respect to the oxygen bridge. Furan **9** provided adducts **17** (81%) in a 20:1 ratio in favour of the methyl group equatorially positioned on the side arm. Interestingly, compound **10**, which had been previously reported to provide the oxatricyclo adducts **18** only at 12 kbar (endo:exo; 1:1),⁶ provided adducts **18** (91%) with greatly improved stereoselectivity in favour of the endo isomer (91:9).⁷

We have therefore shown that 10 mol % MeAlCl₂ is an effective catalyst for the IMDAF reaction in which the diene and dienophile are connected by 4 or 5 carbon atoms. Synthetic applications of this work are currently in progress.

Experimental

To a solution of compound **1** (0.4 mmol, freshly distilled) in CH₂Cl₂ (10 mL, dry, distilled) under argon (at -65°C) was added 0.1 equivalents of MeAlCl₂ (1.0 M in hexanes, Aldrich). The solution was stirred for the appropriate time and quenched with cold sodium bicarbonate (10%) and extracted with CH₂Cl₂. The solvent was removed *in vacuo* (no external heating) and the product(s) purified by flash chromatography. The ratios obtained for the time studies were determined by integrating the crude ¹H NMR spectra.

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References and Notes

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