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Eu(fod)3 and SnCl4-Catalyzed Heterocycloadditions of O-Silyl Enol Ethers deriving from Cyclic Ketones

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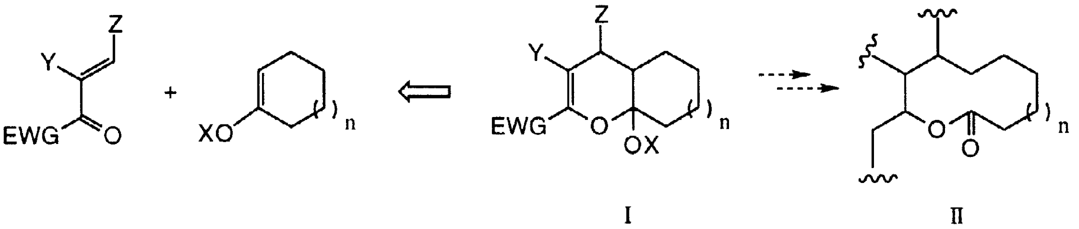
Abstract : *O-t*-Butyldimethylsilyl enol ethers deriving from simple cyclic ketones acted as efficient dienophiles in the Lewis acid-catalyzed heterocycloadditions with methyl benzylidenepyruvate **1**. Good selectivities were observed with cyclohexanone derivatives. Using Eu(fod)$_3$, the dienophile **2b** led to the expected *endo* adduct **3b** (93-97%). When using $SnCl_4$, the major product (89-95%) was found to be the "abnormal" adduct **5b** with a *trans* ring junction. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The polyselective dihydropyran synthesis *via* hetero Diels-Alder reactions of 1-oxabutadienes with electron-rich olefins is well documented and has been widely applied to natural product synthesis.[1] Asymmetric pathways in this area have emerged, first by heterodiene- or dienophile-chirality transfer,[1,2] and very recently *via* asymmetric catalysis.[1,3] We focused our attention on the heterocycloaddition of homocyclic dienophiles, leading to bicyclic adducts (Scheme 1, *eg* I) which are of specific synthetic potential : ring-opening to macrolactones[4] (*eg* II), new stereocontrolled approaches to 1,4- or 1,5 dicarbonyl compounds and subsequent access to annulation products. The sole examples in this field have been reported in thermal conditions and almost without any significant stereocontrol.[1c,d]



Scheme 1

We describe here our first results on the Lewis acid catalyzed-heterocycloadditions of enol ethers derived from cyclic ketones with a representative heterodiene , methyl benzylidenepyruvate **1**, using either Eu(fod)3 or $SnCl_4$ as the catalyst (Scheme 2).

When applied to 1-methoxycyclohexene **2a** (entry 1), Eu(fod)3 catalysis proved efficient and "classically" *endo*-selective in favor of adduct **3a**. A high reactivity occurred also when using $SnCl_4$ at -78°C (entry 2), but led to an unexpected selectivity : the major isomer was the C-8a epimer **5a** of the *endo* product **3a**, this "abnormal" configuration being consistent with the high value of $J_{4\text{-}4a}$ exhibited in ^1H NMR which shows a *trans*-pseudoaxial relationship of both these protons.

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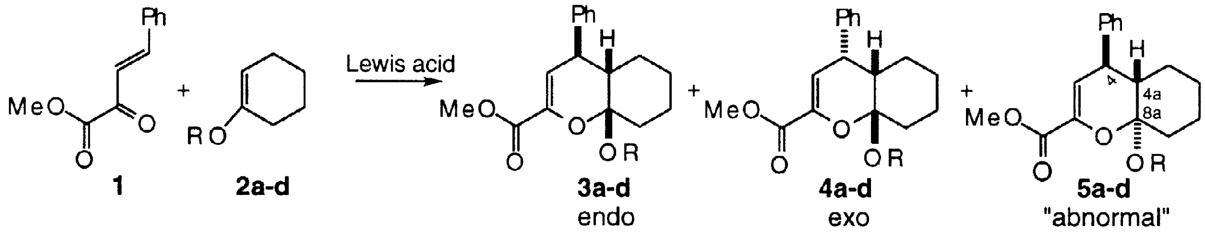
Scheme 2 . Heterocycloadditions of methyl benzylidenepyruvate **1** with enol ethers **2a-d** derived from cyclohexanone.



Entry	R	2	Catalyst	Major adduct[5]	Diastereomeric ratio 3	/ 4	/ 5	Yield (%)
1	Me	**2a**	5% Eu(fod)$_3$ [a)]	**3a**	**97**	3	0	84
2	Me	**2a**	20% SnCl$_4$ [b)]	**5a**	0	5	**95**	86
3	SiMe$_2$tBu	**2b**	5% Eu(fod)$_3$ [a)]	**3b**	**97**	3	0	62
4	SiMe$_2$tBu	**2b**	5% Eu(fod)$_3$ [c)]	**3b**	**93**	3	4	92
5	SiMe$_2$tBu	**2b**	1% SnCl$_4$ [b)]	**5b**	0	11	**89**	95
6	SiMe$_2$tBu	**2b**	5% SnCl$_4$ [b)]	**5b**	0	11	**89**	99
7	SiMe$_2$tBu	**2b**	1,5eq SnCl$_4$ [b)]	**5b**	0	5	**95**	88
8	SiMe$_2$tBu	**2b**	1% TiCl$_4$ [b)]	**5b**	8	13	**79**	10
9	SiPh$_2$tBu	**2c**	5% Eu(fod)$_3$ [c)]	**3c**	**96**	2	2	80
10	SiPh$_2$tBu	**2c**	1% SnCl$_4$ [b)]	**5c**	0	14	**86**	85
11	SiMe$_3$	**2d**	5% Eu(fod)$_3$ [c)]	**3d**	**89**	4	5	93
12	SiMe$_3$	**2d**	1% SnCl$_4$ [b)]	**5d**	3	30	**67**	30

a) Petrol ether, 60°C, 60h ; b) CH_2Cl_2, -78°C, 1h ; c) Petrol ether / $CHCl_3$ 6/1 , 60°C, 3-7 days.

Alkyl enol ethers derived from simple cyclic ketones are generally difficult to obtain in good yields and in a sufficiently pure state. Therefore, in order to widen the scope of the present heterocycloaddition methodology, we considered using as dienophiles the corresponding O-silyl enol ethers **2b-d** more readily available.[6,7] Under uncatalyzed conditions,[8] a good dienophilicity of the trimethylsilyl enol ether **2d** towards isopropylidene ethylidenemalonate at 20°C was reported by Endo *et al* (selectivity 4/1).[8a] Earlier, Tietze *et al.* [8b] described the uncatalyzed heterocycloaddition of trimethylsiloxy cyclopentene with malondialdehyde (selectivity 6/1). To our knowledge, the only examples of a catalyzed reaction in this area were firstly the obtention of a pyranic adduct from an alkenoyl cyanide and **2d** (or trimethylsilyloxy cyclopentene) when using *ca.* 1.5 equivalent of $TiCl_4$,[9] and secondly the formation of a dihydropyranic adduct from diethyl E-crotonoylphosphonate and the O-trimethylsilyl enol ether of propiophenone, when using *ca.* 0.5 equivalent of $SnCl_4$.[10]

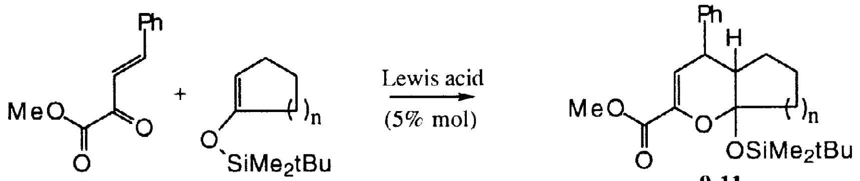
Whereas the heterodiene **1** did not react with the t-butyldimethylsilyl enol ether **2b** in the absence of catalyst, heterocycloaddition smoothly occurred in the presence of catalytic amounts (5% molar) of Eu(fod)$_3$ (entry 3) thus selectively leading to the crystalline *endo* adduct **3b** in 62% yield. Using chloroform as a cosolvent enhanced markedly the yield but brought about some epimerization at C_{8a}, presumably due to the presence of trace amounts of HCl in the cosolvent (entry 4).

Indeed, radiocrystallographic studies[11] have identified this *endo* isomer in a *cis* pseudo-equatorial conformation of both phenyl and silyloxy groups (related to the dihydropyranic ring), thus confirming the veracity of our ^1H NMR assignments.

In another experiment, it was found that the reaction of the heterodiene **1** with the dienophile **2b** was rapid (1 h) in CH_2Cl_2 at -78°C, when using $SnCl_4$ as a catalyst. It could be mentioned that the quantities of $SnCl_4$ required here are unusually low (down to 1%, entry 5) in view of literature precedents.[10,12] Using 5% of this Lewis acid quantitatively led to the "abnormal" crystalline adduct **5b**, together with small amounts of the *exo* adduct **4b** (entry 6). Radiocrystallographic studies[11] have shown that the phenyl substituent is *pseudo*-equatorial and the silyloxy group axial in the abnormal adduct **5b**. The ^1H NMR signal of the H_4 proton of **5b** appears at δ 3.22 ppm, as a *dd* having $J_{3\text{-}4}$ = 2.2 Hz and $J_{4\text{-}4a}$ = 11.2 Hz. This latter value confirms that the H_4 and H_{4a} protons of **5b** are *trans* diaxal. On the other hand, the ^1H NMR signal of the minor *exo* adduct **4b** shows up at δ 4.20 ppm as a *dd* having $J_{3\text{-}4}$ = 2.5 Hz and $J_{4\text{-}4a}$ = 5.9 Hz. The existence of a ^4J coupling between H_{4a} and the vinylic proton H_3 in the spectrum of the *exo* adduct **4b** implies that H_{4a} is *pseudo*-equatorial.

The *endo* adduct **3b** was treated with 5% molar $SnCl_4$ in the very conditions used for the above cycloaddition reaction and this afforded the abnormal adduct **5b**, clearly resulting from epimerization of **3b** at C_{8a}. Thus, contrary to some previous observations with other types of cycloreactants,[12] $SnCl_4$ does not act as an *exo*-directing catalyst in the present cases. The almost exclusive formation of the abnormal adduct **5b** implies that either the process is concerted and *endo*-selective, first leading to **3b** with ultimate epimerization at C-8a into **5b**, or more likely stepwise, as previously suggested in relevant cases,[10,13] the first step being a Mukaiyama-Michael addition of the O-silyl vinylether **2b** to the Michael acceptor **1**. It should be mentioned that using stoechiometric amounts of $SnCl_4$ markedly enhanced this unique stereocontrol (entry 7). Attempts to effect the cycloaddition of **1** with **2b** using $TiCl_4$ as a catalyst led to very low yields (ca. 10%, entry 8) of mixtures of four products which were not further examined.

Scheme 3 . Heterocycloadditions of methyl benzylidenepyruvate **1** with enol ethers **6-8** deriving from cyclic ketones.



1 **6-8** **9-11**

Entry	n	Enol ether[5]	Catalyst	Adduct[5]	Product ratio	Yield (%)
1	1	**6**	Eu(fod)$_3$ [a)]	**9**	84 / 10 / 6	92
2	1	**6**	$SnCl_4$ [b)]	**9**	50 / 32 / 18	67
3	4	**7**	Eu(fod)$_3$ [c)]	**10**	49 / 36 / 15	88
4	4	**7**	$SnCl_4$ [b)]	**10**	89 / 11 / 0	81
5	8	**8**	Eu(fod)$_3$ [a)]	**11**	76 / 13 / 11	83
6	8	**8**	$SnCl_4$ [b)]	**11**	54/ 46 / 0	94

a) Petrol ether / $CHCl_3$ 6/1, 60°C, 2.5-4.5 days; b) CH_2Cl_2, -78°C, 1h; c) petrol ether / $CHCl_3$ 9/1, 60°C, 2.5 days.

Some variations of the dienophile were next studied. The *t*-butyldiphenylsilyl derivative **2d**[6] reacted slowly and gave no substantial improvement over its *t*-butyldimethyl analogue **2b** when $Eu(fod)_3$ or $SnCl_4$ was used as the catalyst (entries 9,10). The *O*-trimethylsilyl vinylether **2c**, similarly treated with the heterodiene **1**, gave poorer results, especially in $SnCl_4$-catalytic conditions (entry 12), the main products being acyclic adducts in this particular case. Thus, we must conclude that a *t*-butyldimethylsilyl enol ether is so far the best dienophile (or nucleophile) for these types of reactions.[14]

We next considered using as new dienophiles the *O*-*t*-butyldimethylsilyl enol ethers **6-8**, easily derived from the corresponding cyclic ketones by the standard procedure used for the preparation of **2b**.[6] These enol ethers were treated with the heterodiene **1** in the presence of either Eu $(fod)_3$ or $SnCl_4$ in the usual conditions (Scheme 3). This gave mixtures of two or even three isomeric adducts in yields higher than 67%. The diastereoselectivity of the cycloaddition reaction was generally poor, except in the case of **7**/$SnCl_4$ which led to a mixture of two adducts **10**, one of which being largely predominant (entry 4). On the basis of the ^1H NMR spectra, tentative structures were ascribed to the different adducts **9-11** thus obtained, but those require further confirmation.

Conclusion

We have demonstrated that the readily available *O*-*t*-butyldimethylsilyl enol ethers deriving from simple cyclic ketones can act as electron rich dienophiles (or nucleophiles) in the $Eu(fod)_3$ (or $SnCl_4$) catalysed heterocycloaddition with the electrodeficient heterodiene **1**. High yields and selectivities were observed in the case of the dienophile **2b** deriving from cyclohexanone. Using $Eu(fod)_3$, the expected *endo* adduct **3b** was largely preponderant. Using $SnCl_4$ as the catalyst, we found that the major product was the "abnormal" adduct **5b** in which the ring junction is *trans*.[15] Asymmetric access to such bicyclic adducts and their use as intermediates for macrocyclic lactones[16] are under progress in our laboratory.

References and notes

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