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Synthesis of γ -Methoxy Carboxylic Acids via Nucleophilic Additions to Oxycarbenium Ions derived from 5-Methoxy-2(3H)-dihydrofuranones.

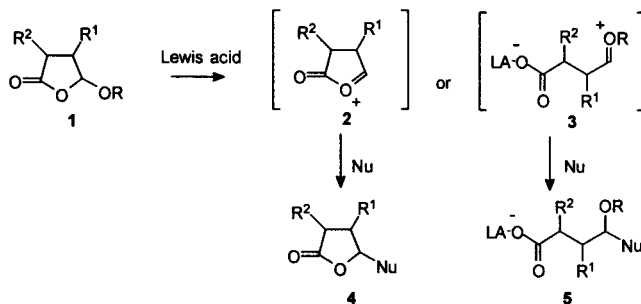
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Abstract: The Lewis acid induced addition of silylated nucleophiles to 5-methoxy-2(3H)-dihydrofuranones was studied. The methodology gives access to α,β -substituted- γ -alkoxy carboxylic acids with modest to high levels of acyclic diastereocontrol in the addition reaction.

α,β -Substituted- γ -alkoxy carboxylic acids are important building blocks in natural products synthesis and as a consequence the stereoselective preparation of this type of compounds has drawn a lot of attention.^{1,2} Some derivatives have shown to be hydroxy dipeptide isosteres³ while structurally related 5-substituted γ -lactones and several 4,5-disubstituted γ -lactones are natural products by themselves.⁴

As part of our research program towards developing new methodology based on 5-alkoxy-2(3H)-dihydrofuranones **1**⁵ we have investigated the chemistry of oxycarbenium ions **2** or **3** derived from these lactones (scheme 1). The Lewis acid mediated nucleophilic additions to oxycarbenium ions derived from cyclic O,O-acetals has been extensively studied.⁶ In most cases however the acetals used sofar have a general structure with both acetal oxygen atoms being part of a ring. In the case of mixed acyloxy-alkoxy acetals, treatment with a Lewis acid leads to the formation of the alkoxy substituted oxycarbenium ion due to the better leaving group ability of the acyloxy group and products derived from the acyloxy-substituted oxycarbenium ion are not found.^{7,8}

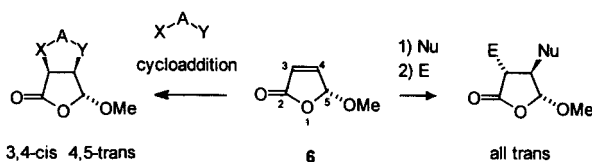


scheme 1

In the case of 5-alkoxy-2(3H)-dihydrofuranones **1** there is also a mixed acyloxy-alkoxy acetal moiety present, but in contrast only the acyloxy moiety is part of the ring. Upon treatment with strong Lewis acids 5-alkoxy-2(3H)-dihydrofuranones can form two types of oxycarbenium ions **2** or **3** as depicted in scheme 1. Quenching of these intermediates with a nucleophile might lead to two possible adducts **4** or **5** depending on the intermediate oxycarbenium ion.

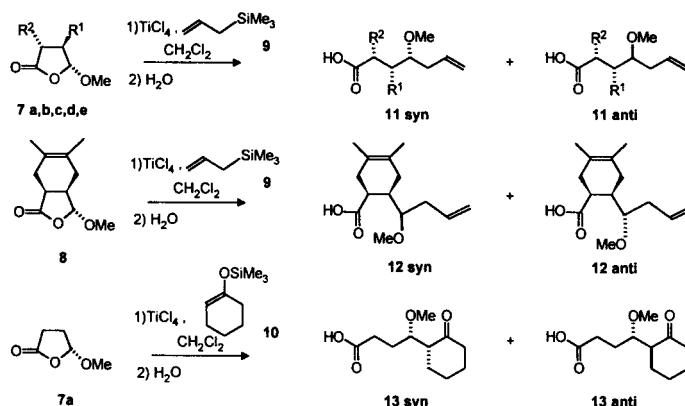
We report here preliminary results of the TiCl₄ induced nucleophilic addition of silylated nucleophiles to oxycarbenium ions derived from (3,4-disubstituted)-5-methoxy-2(3H)dihydrofuranones **1**. The synthesis of substrates

1 has been described by us previously⁹ and is outlined in scheme 2. A large variety of substituents can be readily introduced at the 3 and 4 positions of **1** by tandem Michael additions-enolate alkylations or cycloadditions to 5-methoxy-2(5H)-furanone **6**.



scheme 2

The addition reactions of allyltrimethylsilane **9** and 1-trimethylsilyloxyhexene **10** to 5-methoxy-2(3H)dihydrofuranones **7** or **8** were examined (scheme 3). The oxycarbenium ions were generated in all cases by treatment with an excess of TiCl_4 as the Lewis acid. The results are summarized in table 1.¹⁰ Alkyl or hydrogen



scheme 3

Table 1: Additions of Silylated Nucleophiles to Various Substituted 5-Methoxy-2(3H)-dihydrofuranones **7** and **8**.

Entry	substrate ^{R1}	R ²	nucleophile	T (°C)	product	Yield ^a %	syn:anti ^b
1	7a	H	9	-70	11a	74	-
2	7a	H	10	-70	13	59	50:50
3	7b	Me	9	-70	11b	87	65:35
4	7c	Et	CH_2Ph	-70	11c	86	85:15
5	8	$\text{CH}_2\text{C}(\text{Me})=\text{C}(\text{Me})\text{CH}_2$	9	-70	12	85	c
6	7d	$\text{C}(\text{Me})_2\text{CO}_2\text{Et}$	Me	9	11d	53	c
7	7e	$\text{CPh}(\text{CO}_2\text{Et})_2$	H	9	11e	34 ^d	<5:>95

^a Yields are of isolated pure products after chromatography

^b Syn:anti ratio determined by ¹³C NMR

^c Only one diastereomer is observed

^d >60 % starting material was recovered as a mixture of cis and trans furanone **7e**

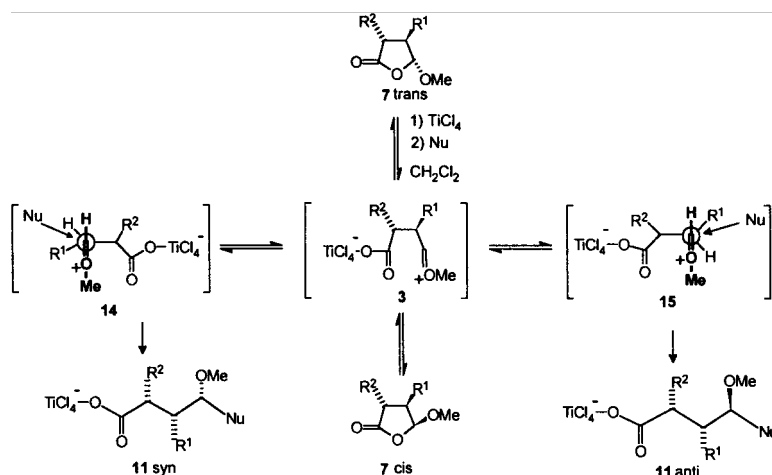
substituted substrates (**7a,b,c,8**, entry 1,2,3,4,5) gave a very clean addition reaction at a temperature of -70°C . The substrates containing an ester group in the substituent R¹ (**7d,e**, entry 6,7) did not react at this temperature, but gave the addition reaction at more elevated temperatures, although in modest yields. This lack of reactivity might be due to stabilization of the oxycarbenium ion by the adjacent ester oxygen atom.

It should be noted that all products are derived from the intermediate oxycarbenium ion **3**, as no lactones **4**

were detected (scheme 1). The yields of these addition reactions to various alkyl substituted lactones **7a,b,c**, **8** were all consistently high, demonstrating the versatility of this method for the synthesis of γ -methoxy (alkoxy) substituted carboxylic acids.

Diastereoselectivities of the nucleophilic additions to oxycarbenium ions derived from lactones **1** depend strongly on the substituents at C₄ (see table 1). The diastereomeric ratio could be easily determined by ¹³C NMR, while the syn or anti configuration could be assigned by comparison of the ¹³C NMR data with those reported by Kunz and co-workers for **11b**.² The relative configuration of adduct **11e** was unequivocally established by a single crystal X-ray analysis.¹¹

In the case of adduct **11b** (entry 3) a mixture of diastereomers was obtained in a syn:anti ratio of 65:35. To obtain further information on the mechanism of the reaction and on the stereodirecting effect of the C₄ substituent (R¹) in **7b** both cis- and trans-substituted 5-methoxy-4-methyl-2(3H)-dihydrofuranone **7b** were tested under the same reaction conditions. The syn:anti ratio of the adducts was independent of the starting material used: cis-lactone **7b** gave the same ratio of diastereomers of the product **11b** as the trans-lactone **7b**. When 5-methoxy-4-methyl-2(3H)-dihydrofuranone **7b** was treated with TiCl₄ in CH₂Cl₂ at 0°C for 2 min. and subsequently quenched with water the product was a mixture of cis- and trans-substituted lactones **7b** in a ratio of 33:67. These results are a strong indication



scheme 4

for the direct formation of the oxycarbenium ion **3** (schemes 1 and 4), which is in equilibrium with the ring closed furanone **7**. After the initial formation of the oxycarbenium ion **3**, it reacts with the nucleophile (either intra- or intermolecular, to **7** or **11** respectively) to give a mixture of diastereomeric products, mainly determined by the size of the R¹-substituent in the substrate. The major diastereomer is the one that is predicted by employing the Felkin-Anh model.¹² The C₄-ethyl substituted substrate **7c** with a somewhat greater steric demand than the methyl substituted **7b** gives preferentially syn adduct **11c** (entry 4). Though not unambiguously determined in this case, the Felkin-Anh model predicts the syn diastereomer as the main product (scheme 4, intermediate **14**). Substrate **8** contains a rigid cyclohexyl structure. The intermediate oxycarbenium ion exists essentially in one conformation and the addition product is formed as a single diastereomer.

The substrates with an ester functional group at C₄, **7d** and **7e**, gave the intermolecular addition products **11** in a lower yield and only at higher temperatures (>0°C). Much to our surprise the nucleophilic addition took place in a completely diastereocontrolled fashion. The oxycarbenium ion derived from trans-**7e** is however formed at temperatures below -50°C. This can be concluded from the reaction of **7e** with more than 2 equivalents of TiCl₄ in

CH₂Cl₂ at -60°C. After aqueous work up a mixture of the starting material and one product was obtained. This compound was characterized by single crystal X-ray analysis¹¹ and by NMR as cis-4-substituted-5-methoxy-2(3H)-dihydrofuranone **7e**. This means that epimerization must have taken place at the acetal center. This epimerization can be explained by the formation of the oxycarbenium ion **3** as depicted in scheme 4. The oxycarbenium ion which is initially formed can undergo a ringclosure reaction to furnish a mixture of cis- and trans-substituted lactones **7e**. The ratio between cis- and trans-substituted furanone **7e** seems to be determined by the size of the substituent R¹, but also the Lewis acid used has an effect on the equilibrium. While TiCl₄ gives cis and trans furanone **7e** in a ratio of 8:1, the use of SnCl₄ results in a cis-trans ratio of 1:17 and these reactions are reversible. This difference in ratio is not clear at present, as cis **7e** is expected from the Felkin Ahn model (scheme 4), but might be explained by the greater oxophilicity of titanium giving a strong chelate with the ester carbonyl oxygen atoms of R¹, inhibiting the stabilization of the oxycarbenium ion by the ester carbonyl oxygen atom. The ester carbonyl oxygen atoms of the R¹ substituent are probably not blocked by SnCl₄, allowing initial complexation to the oxycarbenium ion. Ring closure will in this case be a S_N2 type nucleophilic displacement, resulting predominantly in the trans substituted furanone **7e**.

It should be noted that in case there is a phenyl group in the substrate (entry 7), it does not act as a nucleophile to give a cyclization reaction.¹³

It can be concluded that the Lewis acid mediated addition reaction of silylated nucleophiles to oxycarbenium ions derived from 5-methoxy-2(3H)dihydrofuranones **1** is a versatile method of synthesizing a variety of γ-methoxy substituted carboxylic acids. The diastereoselectivity in the addition reactions to the forementioned oxycarbenium ions is strongly depending on the substituents at the 4-position of the substrates and both high syn and anti selectivities have been found. The stereochemical outcome of the nucleophilic addition to the oxycarbenium ions can be rationalized by the Felkin-Anh model.

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10. A typical experimental procedure is as follows: To a solution of the methoxy furanone **7** (1 mmol) and allyltrimethyl silane (3 mmol) in 5 ml CH₂Cl₂ was added at -70°C a solution of TiCl₄ in CH₂Cl₂ (1 ml, 1.5M). The reaction mixture was stirred at this temperature for 1 h and poured into a mixture of 10 ml water and 20 ml ether. The layers were separated and the water layer extracted with 10 ml ether. The combined organic layers were washed with brine (10 ml) and dried. Evaporation of the solvent gave the crude product which was purified by chromatography over silica gel.
11. Single crystal X-ray analyses were performed by Auke Meetsma from the crystallographic department of the University of Groningen; data will be published separately.
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