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Synthesis of Highly Functionalized 3,4-dihydro-2H-pyrans by High Pressure Lewis Acid Catalyzed Cycloaddition of Enol Ethers and α,β–unsaturated Aldehydes.

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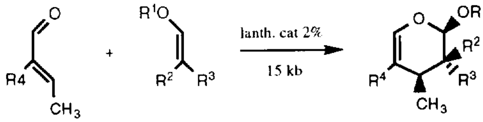
***Abstract*:** New highly substituted 3,4-dihydro-2H-pyrans were synthesized with high ENDO selectivity by high pressure hetero Diels Alder reactions of α,β–unsaturated aldehydes and enol ethers in the presence of lanthanide-catalysts. Chiral induction was studied using chiral catalysts, a chiral enol ether and a combination of these chiralities.

The inverse electron-demand hetero Diels Alder reaction between enol ethers and α,β–unsaturated carbonyl compounds is a short and attractive route to dihydropyrans [1-5] which are useful intermediates for a variety of biologically interesting compounds[1,5]. Without a catalyst, high temperatures are needed (>160°C) to obtain good yields in the reaction of alkyl vinyl ethers and acrolein[1]. Application of lanthanide catalysts enables the reaction of ethyl vinyl ether and crotonaldehyde to occur at room temperature[2]. The use of high pressure extended the scope to mono substituted enol ethers (e.g. 1-ethoxy propene) and mono-substituted α,β–unsaturated aldehydes (crotonaldehyde)[3,6]. No conversion was reported between higher substituted reactants: 1-ethoxy-2-methyl propene did not react with crotonaldehyde at 100°C and 15 kbar pressure[3].

RESULTS AND DISCUSSION

We found that the combination of high pressure and lanthanide catalysts allowed an extension[7] of the applicability of this cycloaddition toward the synthesis of highly functionalized 3,4-dihydro-2H-pyrans. The scope of this method appears from the selected examples of new 3,4-dihydro-2H-pyrans described in table 1. The reaction of crotonaldehyde **1** with two sterically hindered enol ethers **A**, **B** (fig.1) gave the corresponding dihydropyrans **1A** and **1B** in high yields (table 1). The more substituted tiglic aldehyde **2** appeared to be less reactive toward these enol ethers. Nevertheless, moderate yields of the highly substituted products **2A** and **2B** were obtained. Dihydropyran **C**, considered to be unreactive towards dienes in Diels Alder reactions, combined with crotonaldehyde **1** to give the Diels Alder product **1C**, although in modest yield.

No conversions were found for these reactions after keeping the reaction mixtures at normal pressure in the presence of Lewis acids for 48 hours at temperatures up to 50°.



α,β-unsat. aldehyde	enol ether	R^1	R^2	R^3	R^4	3,4-dihydro-2*H*-pyran
1	**A**	i-Pr	Me	H	H	**1A**
1	**B**	Et	Me	Me	H	**1B**
2	**A**	i-Pr	Me	H	Me	**2A**
2	**B**	Et	Me	Me	Me	**2B**
1	**C**	$-CH_2-CH_2-CH_2-$		H	H	**1C**

Fig.1

Table 1. Reaction conditions and Yields of the Synthesis from **1A**, **1B**, **2A**, **2B** and **1C**.

compound	cat	T	t	yield (%)*
1A	Eu(fod)$_3$	r.t.	16 h	85
1A	Eu(tfc)$_3$	r.t.	16 h	75
1B	Eu(fod)$_3$	r.t.	16 h	65
1B	Eu(fod)$_3$	r.t.	2 d	85
1B	Eu(tfc)$_3$	r.t.	3 d	71
2A	Eu(fod)$_3$	50°C#	3 d	37
2B	Eu(fod)$_3$	50°C#	3 d	36
1C	Eu(fod)$_3$	50°C#	3 d	23

*: isolated yields #: no conversion at room temperature

All 3,4-dihydro-2H-pyrans were formed with high ENDO selectivity. The assignment of the cis-configuration of the protons at C-3 and C-4 of **1A** is based[8] on the value of the inter-proton coupling constant of H-3 and H-4 ($J_{3,4}$= 6.0 Hz). The structure of **1B** was determined by ^{1}H-NMR-NOE studies, showing that the anomeric proton and H-4 are cis, thus indicating an ENDO-product. **2A** was identified as the ENDO-product in the same way as **1A** ($J_{3,4}$= 6.1 Hz). The structure of **2B** was also determined as ENDO, using the same NMR-NOE method as for **1B**. Finally, **1C** also proved to be the ENDO-product ($J_{3,4}$ = 5.9 Hz).The effect of the chiral lanthanide catalyst Eu(tfc)$_3$ was studied in the cyclo additions of **1** with enol ethers **A** and **B** (table 1). The isolated products showed very low e.e. as appeared from the absence of optical rotation and from e.e. determinations by NMR studies using chiral shift reagents.

Upon trying to achieve chiral induction, we studied the catalyzed cyclo-addition of crotonaldehyde (**1**) with an enol ether bearing a chiral auxiliary[9] (**D**, fig. 2). The reactions, leading to **1D**, were accelerated with an achiral lanthanide catalyst as well as with a series of chiral lanthanide catalysts (table 2).

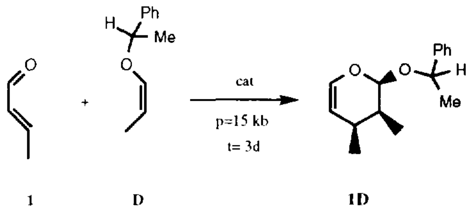


Fig. 2

Table 2: Reaction conditions and Results from the Synthesis of **1D**.

catalyst	T	d.e. (%)	yield (%)
Eu(fod)$_3$	r.t.	19	34*
Eu(tfc)$_3$	r.t.	38	35*
Eu(tfc)$_3$	50°C	30	60#
Eu(hfc)$_3$	r.t.	24	25*
Pr(tfc)$_3$	r.t.	29	30*
Yb(tfc)$_3$	r.t.	45	38*

*: starting material present. #: all starting material disappeared.

The isolated products were diastereomeric ENDO-forms of **1D**, as appeared from NMR studies ($J_{3,4}$: 6.1 and 6.2 Hz). The d.e. was easily determined, as the diastereomers have different GC retention times. Interestingly, a **synergistic effect**[10] was found for the chiral catalysts, increasing the d.e. from 19 to 45%. It is worthwhile to investigate this synergistic effect in other cycloaddition reactions with enol ethers bearing a chiral auxiliary, for example in the reactions reported by G. Dujardin et al.[5].

EXPERIMENTAL

G. C. analysis were carried out with a Hewlett Packard 5890 Series II equipped with a HP1 column. ^{1}H-NMR spectra were recorded on a Bruker AM-400 spectrometer. Chemical shifts are reported in ppm relative to TMS. The solvent was $CDCl_3$. Mass spectra were obtained using a VG 7070E spectrometer. General procedure for the synthesis of the 3,4-dihydro-2H-pyrans: An enol ether (**A-C**; 10 mmol) and an α,β–unsaturated carbonyl compound (**1,2**; 10 mmol), both freshly distilled by bulb-to-bulb distillation, were mixed and put in a high pressure ampule[11] without solvent. Subsequently, 0.2 mmol catalyst and a trace of radical inhibitor (3-tert-butyl-4-hydroxy-5-methylphenyl sulfide) were introduced. Before closing the ampule it was checked that the catalyst is fully dissolved in the reaction-mixture. The closed ampule is kept under a pressure of 15 kbar for the time and temperature indicated in table 1 and table 2. The high pressure apparatus used has been described before[12]. After depressurizing, the product was isolated by bulb-to-bulb distillation. The purity of the oily products was over 95%, as was shown by G.C.. The analytical properties of the products are given below.

2-isopropoxy-3,4-dimethyl-3,4-dihydro-2*H*-pyran (1A)

Bp. 40^{o}C/1.3mmHg. ^{1}H-NMR: δ= 0.91 (3H, CH_3-3, d; 7.1 Hz), 0.97 (3H, CH_3-4, d; 7.4 Hz), 1.15 (3H, CH_3 (i-Pr), d; 6.2 Hz), 1.21 (3H, CH_3 (i-Pr), d; 6.2 Hz), 1.7-2.1 (1H, H-3, m), 2.4-2.6 (1H, H-4, m), 3.94 (1H, CH (i-Pr), h), 4.50 (1H, H-5, dd; 2.9 & 6.1 Hz), 4.92 (1H, H-2, d; 2.2 Hz), 6.18 (1H, H-6, dd; 2.3 Hz). MS(EI): m/e (%)= 170 (6; M^+), 111 (13), 100 (28), 71 (36), 58 (100).peak match: M^+= 170.13068 (calculated: 170.1307).

2-ethoxy-3,3,4-trimethyl-3,4-dihydro-2*H*-pyran (1B)

Bp. 40^o/1.3mmHg. ^{1}H-NMR: δ= 0.81(3H, CH_3-3, s), 0.90 (3H, CH_3-4, d; 7.4 Hz), 0.93 (3H, CH_3-3, s), 1.21 (3H, CH_3 (Et), t; 7.0 Hz), 2.0-2.1 (1H, H-4, m), 3.52 (1H, CH_2(Et), dq; 9.7 Hz), 3.89 (1H, CH_2(Et), dq), 4.43 (1H, H-5, dd; 2.4 Hz), 4.43 (1H, H-2, s), 6.19 (1H, H-6, dd; 2.3 & 5.8 Hz). MS(EI): m/e (%) = 170 (11; M^+), 125 (11), 109 (8), 100 (100). peak match: M^+= 170.13068 (calculated: 170.1307).

2-isopropoxy-3,4,5-trimethyl-3,4-dihydro-2*H*-pyran (2A)

Bp. 40^o/1.0mmHg. ^{1}H-NMR: δ= 0.95 (3H, CH_3-3, d; 7.1 Hz), 1.02 (3H, CH_3-4, d; 7.3 Hz), 1.12 (3H, CH_3 (i-Pr), d; 6.1 Hz), 1.18 (3H, CH_3 (i-Pr), d; 6.1 Hz), 1.54 (3H, CH_3-5, s), 1.97 (1H, H-3, ddq), 2.15 (1H, H-4, dq; 6.1 Hz), 3.89 (1H, CH (i-Pr), h), 4.84 (1H, H-2, d; 2.3 Hz), 5.98 (1H, H-6, s). MS(EI): m/e (%)= 184 (33; M^+), 125 (46), 109 (19), 100 (100). peak match: M^+= 184.14635 (calculated: 184.1463).

2-ethoxy-3,3,4,5-tetramethyl-3,4-dihydro-2*H*-pyran (2B)

Bp. 50^{o}/0.3mmHg. ^{1}H-NMR: δ= 0.87 (3H, CH_3-3, s), 0.94 (3H, CH_3-3, s), 0.98 (3H, CH_3-4, d; 7.2 Hz), 1.20 (3H, CH_3 (Et), t; 7.1 Hz), 1.52 (3H, CH_3-5, s), 1.82 (1H, H-4, q), 3.48 (1H, CH_2 (Et), dq; 9.7 Hz), 3.85 (1H, CH_2 (Et), dq), 4.35 (1H, H-2, s), 6.00 (1H, H-6, s). MS(EI): m/e (%)= 184 (5; M^{+}), 183 (6), 139 (47), 123 (80), 100 (100). peak match: M^{+}= 184.14635 (calculated: 184.14633).

5-methyl-2,3,4,4a,5,8a-hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyran (1C)

Bp. 50^{o}/1.5mmHg. ^{1}H-NMR: δ= 0.92 (3H, Me, d; 7.4 Hz), 1.0-2.0 (5H, H-3; H-3'; H-4 ; H4' & H-4^{a}, m), 2.6-2.7 (1H, H-5, m), 3.69 (1H, H-2, ddt; 1.4 & 4.9 & 11.2 Hz), 3.90 (1H, H-2', td; 3.3 & 11.9 Hz), 4.33 (1H, H-6, dd; 1.6 Hz), 5.21 (1H, H-8^{a}, d; 1.9 Hz), 6.24 (1H, H-7, dd; 2.7 & 6.1 Hz). MS(EI): m/e (%)= 154 (100; M^{+}), 139 (94), 111 (71), 95 (62), 85 (83). peak match: M^{+}= 154.09941 (calculated: 154.0994).

3,4-dimethyl-2-(1-phenyl-ethoxy)-3,4-dihydro-2*H*-pyran (1D)

Bp. 70-85^{o}/3.0mmHg (mixture of diastereomers).

Major isomer: ^{1}H-NMR: δ= 0.94 (3H, CH_3-3, d; 7.0 Hz), 0.99 (3H, CH_3-4, d; 7.3 Hz), 1.46 (3H, CH_3 (CHMePh), d; 6.6 Hz), 1.7-2.1 (1H, H-3, m), 2.2-2.4 (1H, H-4, m), 4.51 (1H, H-5, dd; 3.1 Hz), 4.67 (1H, H-2, d; 2.1 Hz), 4.88 (1H, CH (CHMePh), q), 6.20 (1H, H-6, dd; 2.1 & 6.1 Hz), 7.2-7.4 (5H, Ph, m). MS(EI): m/e (%)= 232 (4; M^{+}), 128 (46), 112 (28), 105 (100). peak match: M^{+}= 232.14610 (calculated: 232.1463).

Minor isomer: ^{1}H-NMR: δ= 1.01 (3H, CH_3-3, d; 6.2 Hz), 1.03 (3H, CH_3-4, d; 7.6 Hz), 1.45 (3H, CH_3 (CHMePh), d; 5.7 Hz), 2.0-2.2 (1H, H-3, m), 2.3-2.5 (1H, H-4, m), 4.54 (1H, H-5, dd; 3.4 & 6.2 Hz), 4.81 (1H, CH (CHMePh), q), 5.03 (1H, H-2, d; 2.2 Hz), 6.03 (1H, H-6, dd; 2.1 Hz), 7.2-7.4 (5H, Ph, m). MS(EI): m/e (%)= 232 (1; M^{+}), 128 (15), 112 (10), 105 (100). peak match: M^{+}= 232.14610 (calculated: 232.1463).

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8. **1A** has a similar structure as compounds reported by Desimoni et al.. The ENDO-products of these compounds have a typical $J_{3,4}$-value close to 6 Hz. For the EXO-products the $J_{3,4}$-value was found to be around 10 Hz, see Desimoni G., Colombo G., Righetti P. P. and Tacconi G. *Tetrahedron*, **1973,** *29*, 2635.
9. The chiral enol ether was applied as a racemic mixture.
10. This effect is also reported by Danishefsky and Bernardsky, on combining chiral dienes and aldehydes with the aid of Eu(hfc)$_3$: *J. Am. Chem. Soc.*, **1986,** *108*, 7060.
11. The reactions were carried out on 10 mmol scale in ampules of about 2.5 ml. It is possible to perform the reaction on a larger scale, as the high pressure apparatus can contain two 8 ml ampules.
12. Aben, R.W.M., Scheeren, J.W. *J. Org. Chem.*, **1987,** *52*, 365.

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