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Hetero-Diels-Alder Reaction of Enaminecarbaldehydes An Entry to Branched Aminosugars **

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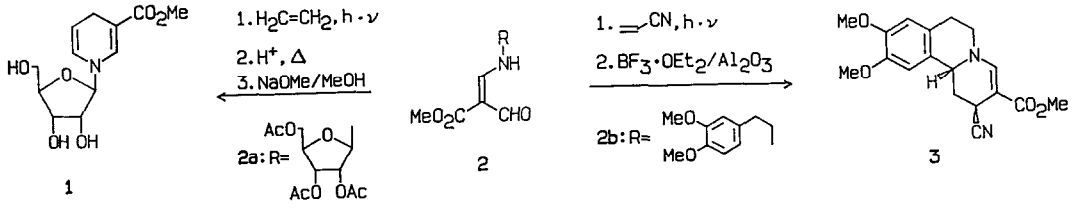
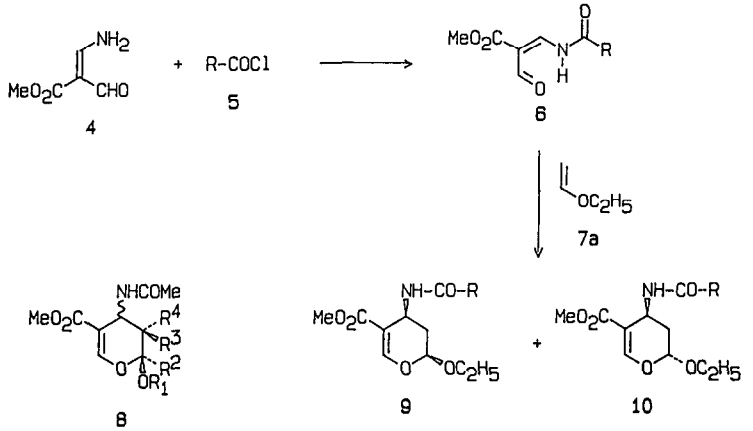
Abstract. N-acyl-enaminecarbaldehydes **6a - g** with an electron accepting group in the α-position react in a hetero-Diels-Alder cycloaddition with enolethers **7a - g** to 4-amino-dihydropyrans **8a - g**, **9a - g** and **10a - g**. This reaction represents a convenient entry to branched aminosugars of the garosamine-type. The rate of the cycloaddition depends strongly on the N-acyl group in **6**. However, the phthalimide **11** does not react because of deconjugation of the electron accepting function in the α-position.

Enaminecarbaldehydes are valuable precursors in the synthesis of 2-tetrahydropyridines and 1,4-dihydropyridines. Thus the photochemical cycloaddition of **2a** and ethylene gives the dihydropyridine nucleoside **1** in almost quantitative yield[1] . On the other hand, the photochemical reaction of **2b** and acrylonitrile leads to the skeleton of the ipecacuanha alkaloids **3** after acid catalysed work up, again in excellent yield [2] . In these transformations a [2 + 2] cycloaddition takes place to a cyclobutane-system, which subsequently undergoes ring-opening and ring-closure to 2-hydroxy-tetrahydropyridines as the first detectable products. Loss of water may follow yielding iminium salts, which can give 1,4-dihydropyridines or can undergo a Mannich-type reaction.



Enaminecarbaldehydes should also be able to undergo a [4 + 2] cycloaddition with inverse electron demand, since they possess a heterodiene-moiety [3]. However, **4** does not give any cycloadducts with enolethers. This is due to the electron donating amino-function at C-3, which raises the LUMO-energy of the heterodiene [4]. In this paper we show that N-acyl-derivatives of enaminecarbaldehydes **6** are excellent educts for hetero-Diels-Alder reactions with enolethers, leading to pyran-derivatives **9/10** with the skeleton of branched amino sugars of the garosamine-type. Garosamine [5] is a component of the gentamicin C antibiotics, which are important in therapy because of their broad antibiotic spectra [6].



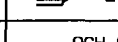
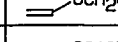
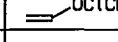
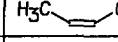
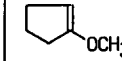
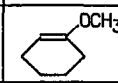
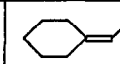
N-acyl-enaminecarbaldehydes **6a - f** can easily be obtained by acylation of **4**[7] with 1.5 mol acylchlorides **5a - f** in ether/dichloromethane (1:2) and 1.5 mol pyridine (addition at 0°C, then 2 h at room temperature, 66 - 85% yield). **7a** can also be prepared by condensation of diformylacetate[8] with acetamide (2d, 70°C, 65%). **7g** was synthesized by addition of **4** to phenylisocyanate in chloroform (reflux, 3 h, 59% yield). The cycloaddition of **6** and **7a** (1 : 5-10) which was performed in toluene or excess enolether (sealed glass tube, if necessary) leads to a diastereomeric mixture of the dihydropyrans **9** and **10** (Tab. 1).

Tab.1. Hetero-Diels-Alder reactions of N-acyl-enaminecarbaldehydes **6** and ethylvinylether **7a**

								^{1}H-NMR(TMS, δ= 0 ppm)	
5,6 9,10	R	educts	products	conditions (°C/h)	yield (%)	ratio (9/10)	mp. (°C) 9/10	9/10 2-H	9/10 4-H
a	CH_3	7a/6a	9a/10a	90/12	93	1:1.9	102/167	5.33/5.02	5.06/4.82
b	$C(CH_3)_3$	6b	9b/10b	120/20	72	1:1.2	92/227	5.30/4.98	5.02/4.76
c	CCl_3	6c	9c/10c	22/20	37	1:1.3	78/143	5.38/5.07	4.99/4.82
d		6d	9d/10d	70/25	86	1:1.7	80/170	5.39/5.10	5.30/5.02
e		6e	9e/10e	22/72	63	1:2.0	147/200	5.39/5.13	5.27/5.02
f	CO_2CH_3	6f	9f/10f	90/12	59	1:1.1	87/147	5.36/5.06	5.04/4.88
g		6g	9g/10g	95/96	71	1:1.1	143/201	5.27/5.12	4.68/4.70

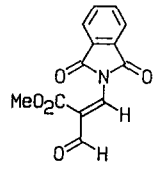
Isomerisation experiments show that the cis-substituted compound **9** is more stable because of an intramolecular hydrogen bond. Thus, treatment of the resulting 1:1.9 mixture of **9a** and **10a** with boron trifluoride etherate yields the two compounds in a 7:1 ratio. The reaction temperature and reaction time strongly depend on the nature of the acyl-group. Thus the trichloroacetamide **6c** and the p-nitrobenzamide **6e** react completely at room temperature within 20 resp. 72 h. For the cycloaddition of the trimethylacetamide **6b** with the acylgroup of smallest electron accepting ability a reaction temperature of 120°C is necessary. The best results are obtained with the acetamide **6a** since this compound is quite stable and most easy to prepare. In contrast **6c** tends to decompose. Besides ethylvinylether **7a**, other acylic enolethers **7b - d** and more complex compounds **7e - g** were used in the cycloaddition with **6a**. In most cases the dihydropyrans **8** are obtained in excellent yield. *Thus even annulated and spiro systems can be synthesized in this way (Tab. 2).*

Tab. 2. Hetero-Diels-Alder reactions of N-acetyl-enaminecarbaldehydes **6a** and enolethers **7**

7	enolether	products	R^1	R^2	R^3	R^4	conditions (°C/h)	yield (%)	ratio (4β/4α)	mp. (°C) (4β/4α)
a		8a=9a/10a								
b		8b	$CH_2C_6H_5$	H	H	H	100/48	95	1:1.3	120/176
c		8c	$C(CH_3)_3$	H	H	H	105/24	96	1:1.1	124/163
d		8d	CH_3	H	CH_3	H	100/20	88	2.7:1	- /123
e		8e	CH_3	$-(CH_2)_3-$		H	120/12	76	1:2.5	200/126
f		8f	CH_3	$-(CH_2)_4-$		H	130/50	48	1:2.3	169/123
g		8g	CH_3	H	$-(CH_2)_5-$		140/15	63	1:1.3	91/219

Interestingly, the phthalimide **11** does not react although it can be assumed that the imide moiety has no electron donating effect. X-ray crystallography shows that the methoxycarbonyl-group stands nearly orthogonally to the heterodiene-moiety. Thus, the LUMO-energy of the system is lifted, resulting in a higher ΔG^{+}-value. This is an excellent proof for the rate acceleration in the hetero-Diels-Alder reaction with inverse electron demand by introduction of a conjugated electron accepting group in the α-position of the heterodiene[3a].

Crystals of **11** *are triclinic, space group* $P\bar{1}$, *with two molecules in a cell of dimensions* a=7.578(1), b=7.829(1), c=10.151(1) A, α=77.18(1), ß=87.42(1), γ=88.75(1)°. The structure was solved by multisolution direct methods [9] and refined with anisotropic C, N, and O and isotropic riding H to R=0.039, R_w=0.050 *for 1895 reflections with* $F > 4\sigma$ *(F) measured on a* Stoe-Siemens 4-circle diffractometer with MoK_α radiation by a profile-fitting procedure[10].
Selected torsional angles : C(3)-C(2)-C(1)-O(17) -172.9(1)°
C(3)-C(2)-C(4)-O(16) -117.4(2)°



11

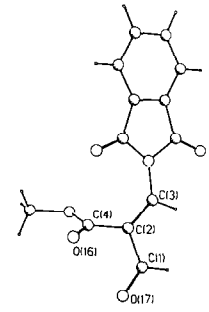


Figure 1. Formula and X-ray structure of **11**

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