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Regioselective Photochemical Cycloaddition of Enamine-carbaldehydes and Alkenes; Synthesis of 1,4-Dihydropyridines and 2-Hydroxy-1,2,3,4-tetrahydropyridines[1)]

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Summary: Photocycloaddition of enamine-carbaldehydes **1** and alkenes **2** with an electron-withdrawing or an electron-donating group **2 a-f** and **2 g-h** regioselectively yields the 4-substituted and the 3-substituted 2-hydroxy-1,2,3,4-tetrahydropyridines **3** respectively. Dehydratisation of **3** with electron-withdrawing groups at C-4 gives the 1,4-dihydropyridines **4**.

1,4-Dihydropyridines are of great interest because of their biological and chemical properties[2)]. Compounds of this type are used with great success in the treatment of coronary disorders[2)]. Besides they are components of the oxidoreductases, and they also are valuable intermediates in the synthesis of complex nitrogen containing compounds[3)]. Symmetrically substituted 1,4-dihydropyridines with electron-donating substituents at C-2 and C-6 as well as electron-withdrawing substituents at C-3 and C-5 are easily prepared by the method of Hantzsch reacting ß-ketoesters with aldehydes and ammonia or primary amines. Modern variations of this reaction also give access to unsymmetrically substituted 1,4-dihydropyridines[4)].

The synthesis of 1,4-dihydropyridines with other substitution-patterns is difficult and in

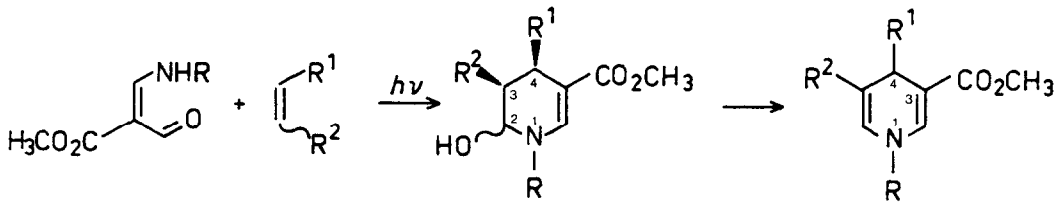
many cases proceeds with only low yields leading to mixtures of products [5]. In the last years, we have developed a novel method to synthesize 1,4-dihydropyridines in good yields which are not available via the Hantzsch reaction [6]. In our synthesis, the key step is a photoaddition of enamine-carbaldehydes **1** and alkenes **2**. The photoreaction probably proceeds via a cyclobutane derivative which undergoes hetero-retro-aldol cleav age followed by recyclisation to give the 2-hydroxy-tetrahydropyridines **3** [6].

In this paper we describe the influence of electron-donating and electron-withdrawing substituents at the olefinic double bond on the regioselectivity of the photochemical cycloaddition. For our investigations, we used the vinylogous formamides **1 a-c** which can be prepared by condensation of methyl diformylacetate [8] with ammonia, methylamine, and tert-butylamine (toluene, Na_2SO_4, 20°C, 1-4 h; yields: 94%, 81%, 81%). A solution of the enamine-carbaldehydes **1** and the alkenes **2** (molar ratio 1:50) in diethyl-ether or acetonitrilewas irradiated with a mercury high-pressure-lamp (TQ 718, Fa. Orig. Hanau) under inert gas atmosphere (scheme 1). A tubular-cylinder (duran glass) with the Hg-lamp placed inside was used as reaction vessel [9]. The whole apparatus was immersed in a cooling-bath at -30°C, thus thermal side reactions were effectively suppressed.

The cycloaddition proceeds with 100% regioselectivity and almost quantitative yields (tab.1). Alkenes with electron-donating substituents **2 g-h** give 2-hydroxy-tetrahydropyridines **3 c-f** with the donor substituent at C-3 exclusively, whereas alkenes with electron-withdrawing groups e.g. **2 b** lead to 2-hydroxy-tetrahydropyridines **3 a,b** with the functionality at C-4. In all cases, the reaction gives mixtures of diastereoisomers.

During isolation and purification of the very sensitive hydroxytetrahydropyridines notable decomposition occurs. The 2-hydroxy-tetrahydropyridines obtained from alkenes **2 a-f** can easily be transformed without isolation into the 1,4-dihydropyridines **4** in almost quantitative yield, by treatment with catalytic amounts of trifluoracetic acid in the presence of molecular sieves (20°C, 2 h) (tab.1). Purification of **4** by chromatography can cause decomposition depending on the stability of the 1,4-dihydropyridines **4**. Thus, a tert-butyl group at the nitrogen as in **4 h-l** stabilizes the 1,4-dihydropyridines whereas compounds without an alkylgroup at the nitrogen as **4 a-e** decompose quite rapidly. The 2-hydroxy-tetrahydropyridines **3 c-f** obtained by photoaddition of **1** and **2 g-h** can not be transformed into the corresponding 1,4-dihydropyridines. This is due to a destabilisation of 1,4-dihydropyridines by an ether function at C-5.

SCHEME 1



1 ≡ 2 ≡ 3 ≡ 4 ≡

1	R
a	H
b	CH_3
c	$C(CH_3)_3$

2	R^1	R^2	
a	CN	H	
b	CO_2CH_3	H	
c	$CO_2C(CH_3)_3$	H	
d	CO_2CH_3	CH_3	(E)
e	CO_2CH_3	CO_2CH_3	(Z)
f	CO_2CH_3	C_6H_5	(E)
g	H	OC_2H_5	
h	H	$OSi(CH_3)_3$	

3	R	R^1	R^2	
a	CH_3	CO_2CH_3	H	ß-OH
b	CH_3	CO_2CH_3	H	α-OH
c	CH_3	H	OC_2H_5	ß-OH
d	CH_3	H	OC_2H_5	α-OH
e	CH_3	H	$OSi(CH_3)_3$	ß-OH
f	CH_3	H	$OSi(CH_3)_3$	α-OH

4	R	R^1	R^2
a	H	CN	H
b	H	CO_2CH_3	H
c	H	CO_2CH_3	CO_2CH_3
d	CH_3	CO_2CH_3	H
e	CH_3	CO_2CH_3	C_6H_5
f	CH_3	CO_2CH_3	CO_2CH_3
g	CH_3	CO_2CH_3	CH_3
h	$C(CH_3)_3$	CO_2CH_3	H
i	$C(CH_3)_3$	$CO_2C(CH_3)_3$	H
j	$C(CH_3)_3$	CO_2CH_3	CH_3
k	$C(CH_3)_3$	CO_2CH_3	CO_2CH_3
l	$C(CH_3)_3$	CO_2CH_3	C_6H_5

Tab. 1: Photoaddition of enamine-carbaldehydes **1** and alkenes **2**

educts	reaction time (h)	solvent	prod.3	yield* a	yield* b	prod.4	yield* a	yield* b	NMR (6-H)**
1a + 2a	4,2	Et_2O	-	-	-	4a	95	25	8.25 (s; 1 H)
1a + 2b	6,3	Et_2O	-	-	-	4b	95	49	6.10 (m; 1 H)
1a + 2e	60,1	Et_2O	-	-	-	4c	93	51	7.33 (s; 1 H)
1b + 2b	4,2	CH_3CN	3a, 3b	96	48	-	-	-	4.61 (t, J=2.6 Hz; 1 H), 4.44 (m; 1 H)
1b + 2b	4,2	CH_3CN	-	-	-	4d	97	48	5.83 (ddd, J_1=7.8 Hz, J_2=J_3=1.6 Hz; 1 H)
1b + 2g	15,0	CH_3CN	3c	19	9	-	-	-	4.65 (dd, J_1=3.0 Hz, J_2=2.0 Hz; 1 H)
			+3d	78	40	-	-	-	4.52 (m, br; 1 H)
1b + 2h	20,3	Et_2O	3e, 3f	95	28	-	-	-	4.40 (m, br; 1 H)
1b + 2f	60,3	CH_3CN	-	-	-	4e	92	65	6.62 (d, J=1.5 Hz; 1 H)
1b + 2e	21,5	CH_3CN	-	-	-	4f	93	66	7.30 (s; 1 H)
1b + 2d	3,9	CH_3CN	-	-	-	4g	95	74	5.72 (m; 1 H)
1c + 2b	2,2	CH_3CN	-	-	-	4h	97	81	6.25 (ddd, J_1=8.5 Hz, J_2=1.5 Hz, J_3=1.5 Hz; 1 H)
1c + 2c	21,5	CH_3CN	-	-	-	4i	93	78	6.22 (ddd, J_1=8.2 Hz, J_2=2.0 Hz, J_3=1.2 Hz; 1 H)
1c + 2d	4,9	CH_3CN	-	-	-	4j	98	79	6.02 (m; 1 H)
1c + 2e	46,0	CH_3CN	-	-	-	4k	92	65	7.53 (s; 1 H)
1c + 2f	93,8	CH_3CN	-	-	-	4l	89	63	7.56 (s; 1 H)

* : yield a: determined by UV-spectroscopy before isolation, yield b: after purification by column chromatography (silica gel, ethyl acetate/petrolether 1:3)

**: Varian EM 360 A, $CDCl_3$, TMS: δ= 0 ppm.

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Literature

1. Dihydropyridines, Part 3. Part 2: Lit. 3.
2. D.M. Stout, A.I. Meyers, Chem. Rev. 82, 223 (1982); E.E. van Tamelen (Ed.), Bioorganic Chemistry Vol. IV, Chapt. 8 and 14; Academic Press, New York 1978.
3. L.F. Tietze, K. Brüggemann, Angew. Chem. 94, 550 (1982); Angew. Chem.,Int. Ed. Engl. 21, 539 (1982).
4. F. Bossert, H. Meyer, E. Wehinger, Angew. Chem. 93, 755 (1981); Angew. Chem., Int. Ed. Engl. 20, 762 (1981).
5. A.I. Meyers, N.R. Natale, Heterocycles 18, 13 (1982).
6. L.F. Tietze, K. Brüggemann, Angew. Chem. 91, 575 (1979); Angew. Chem.,Int. Ed. Engl. 18, 540 (1979).
7. The mechanism has been proved by performing the cycloaddition with ^{13}C - and ^{2}H - labeled compounds. L.F. Tietze, A. Bergmann, unpublished results.
8. G. Büchi, J.A. Carlson, J.E. Powell and L.F. Tietze, J. Am. Chem. Soc. 95, 540 (1973).
9. L.F. Tietze and T. Eicher: Reaktionen und Synthesen im organisch chemischen Praktikum, Thieme, Stuttgart 1981, p. 13.

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