Dihydropyridines; V*. Synthesis of 4,4-Disubstituted 1,4-Dihydropyridines by Photochemical Cycloaddition of Enaminecarbaldehydes and Alkenes

Lutz-F. TIETZE**, Andreas BERGMANN, Klaus BRÜGGEMANN

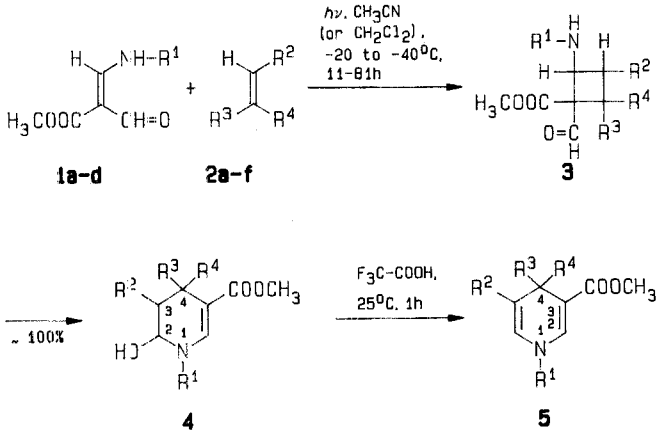
Institut für Organische Chemie der Universität Göttingen, Tammannstraße 2, D-3400 Göttingen, Federal Republic of Germany

Photochemical cycloaddition of the enaminecarbaldehydes **1a–d** and the alkenes **2a–f** leads to the 2-hydroxytetrahydropyridines **4**, which give directly or by treatment with trifluoroacetic acid the 1,4-dihydropyridines **5aa–5df** in nearly quantitative yields.

1,4-Dihydropyridines are highly effective calcium antagonists[1], they act as coenzymes in different dehydrogenases[2], and they are valuable intermediates in the preparation of alkaloids[3]. The synthesis of 1,4-dihydropyridines is most commonly accomplished by condensation of 1,3-dicarbonyl-compounds with aldehydes and amines (Hantzsch reaction)[4] as well as by intermolecular nucleophilic addition of carbanions to pyridinium salts[5]. However, in general, these methods are not suitable for the preparation of 4,4-disubstituted 1,4-dihydropyridines. In some special cases, however, it has been shown[6] that 4,4-disubstituted 1,4-dihydropyridines can be obtained by an intramolecular nucleophilic addition of carbanions to pyridinium salts or by a rearrangement of 1,2-dihydropyridines.

Recently, we have shown that 1,4-dihydropyridines can be prepared efficiently and regioselectively by a photochemical cycloaddition of enaminecarbaldehydes (vinylogous formamides) and alkenes[7]. This method is especially valuable since it has broad scope and gives access to 1,4-dihydropyridines, which cannot be synthesised by other procedures.

In this paper we describe the use of this method for the synthesis of 4,4-disubstituted 1,4-dihydropyridines. Thus irradiating a solution of the enaminecarbaldehydes **1a–1d** and the alkenes **2a–2f** in acetonitrile or dichloromethane at −20 to −40 °C with a mercury high-pressure lamp gives the 2-hydroxytetrahydropyridines **4** in almost quantitative yield. Without isolation, compounds **4** can be transformed into the 1,4-dihydropyridines **5** almost quantitatively by treatment with catalytic amounts of trifluoroacetic acid for 1 h at 25 °C (Table).



1, 3–5	R^1
a	t-C_4H_9
b	CH_3
c	
d	$-(CH_2)_4-COOCH_3$

2, 3–5	R^2	R^3	R^4
a	CH_3	$COOCH_3$	$COOCH_3$
b	H	CH_3	$COOCH_3$
c	i-C_3H_7	$COOCH_3$	$COOCH_3$
d	i-C_3H_7	CN	$COOCH_3$
e	$-(CH_2)_4-$		$COOCH_3$
f	CH_3	CH_3	CH_3

In many cases purification of the products is not necessary, and may be even deleterious because column chromatography on silica gel can cause decomposition (Table). The

Table. Reaction of Enaminecorbaldehydes **1** with Alkenes **2**

Reactants (quantity)	Reaction Time	Product[a]	Yield [%]		Appearance
			A[b]	B[c]	
1a (3 mmol) + **2a** (150 mmol)	11 h	**5aa**	≥90	90	yellow oil
1a (3 mmol) + **2b** (150 mmol)	23 h	**5ab**	≥90	70	colourless oil
1a (1 mmol) + **2c** (55 mmol)	16 h	**5ac**	≥90	65	colourless oil
1a (1.6 mmol) + **2d** (82 mmol)	25 h	**5ad**	≥90	43	colourless crystals, m.p. 166 °C
1a (1 mmol) + **2e** (37 mmol)	81 h[d]	**5ae**[e]	≥90	66	yellow oil
1b (1.4 mmol) + **2f** (50 mmol)	22 h	**5bf**	≥90	62	colourless oil
1c (1 mmol) + **2f** (53 mmol)	25 h	**5cf**	≥90	81	colourless oil
1d (0.8 mmol) + **2f** (60 mmol)	25 h	**5df**	≥90	58	yellow oil

[a] It was not possible to obtain correct combustion analysis data for the oily 1,4-dihydropyridines **5aa–5ac**, **5ae**, and **5bf** because of fast decomposition.
[b] Yield determined by ^{1}H.-N.M.R. and U.V.-spectroscopy.
[c] Yield after chromatography on silica gel with ethyl acetate/petroleum ether (1:1).
[d] High pressure mercury lamp 150 Watt.
[e] The photodimer of **2e** was formed as a byproduct.

stability of the products depends on the substituents at the nitrogen and the carbons. Thus, the presence of electron-withdrawing groups at C-3 and C-5, electron-donating groups at C-2 and C-6, and also bulky groups at the nitrogen stabilize the 1,4-dihydropyridines.

The photoaddition takes place completely regioselectively giving only one final compound **5**, but the intermediate tetrahydropyridines **4** are mixtures of diastereomers. Sometimes a separation of these isomers is possible, but often only with low yields because of fast decomposition. In the reactions of the alkyl-substituted alkene **2f**, the photoadducts **4** eliminate water to give the 1,4-dihydropyridines **5** even without the addition of acid. In the photoaddition process, the cyclobutane derivatives **3** are assumed to be formed as the first intermediates, from which the dihydropyridines **5** are obtained through cleavage, recyclisation, and dehydration[8]. Quenching experiments have shown that the reactions involve a triplet excited state of the enaminecarbaldehydes in the 70 kcal/mol range[9]. The apparatus used for the photoaddition is a newly developed photo ring reactor made of pyrex, which, in this reaction, is far superior to the usual reactors since no decomposition occurs[10].

Trimethyl 1-*t*-Butyl-5-methyl-1,4-dihydropyridine-3,4,4-tricarboxylate (5aa):

A solution of methyl 3-*t*-butylamino-2-formyl-2-propenoate (**1a**; 566 mg, 3.00 mmol) and dimethyl ethylidenemalonate[11] (**2a**; 23.7 g, 150 mmol) in absolute acetonitrile (200 ml) is cooled to −33 °C, purged for 30 min with argon, and irradiated with a 500 watt Hanau high pressure mercury lamp through Pyrex for 11 h. Thin layer chromatography on silicia gel with ethyl acetate/petroleum ether (1/1) shows two fractions (R_F = 0.05 and 0.12), which correspond to two isomeric tetrahydropyridines **4aa**. Without isolation of **4aa**, the solution is stirred for 1 h at 25 °C after adding three drops of trifluoroacetic acid. Addition of ten drops of triethylamine, concentration in vacuum, and chromatography on silica gel 60 with hexane (250 ml) and afterwards with ethyl acetate/petroleum ether (1/1) gives the dihydropyridine **5aa** as a light yellow oil; yield: 880 mg (90%).

H.R.M.S.: *m/e* = 325.1525 (M^+); calc. for $C_{16}H_{23}NO_6$: 325.1519.

U.V. (CH_3CN): λ_{max} (lg ε) = 326 (3.80); 245 nm (3.56).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): δ = 1.33 (s, 9H, *t*-C_4H_9); 1.83 (d, *J* = 1.3 Hz, 3H, 5-CH_3); 3.69 (s, 6H, 4-$COOCH_3$); 3.73 (s, 3H, 3-$COOCH_3$); 6.17 (dq, *J* = 1.8 Hz, *J* = 1.3 Hz, 1H, 6-H); 7.59 ppm (d, *J* = 1.8 Hz, 1H, 2-H).

^{13}C-N.M.R.[12] ($CDCl_3$, 25 MHz): δ = 18.1 (C-8); 29.0 [C($\underline{C}H_3)_3$]; 51.0 [3-$COO\underline{C}H_3$]; 52.3 [4-$COO\underline{C}H_3$]; 56.9 [$\underline{C}(CH_3)_3$]; 57.4 (C-4); 97.2 (C-3); 110.2 (C-5); 122.2 (C-6); 135.8 (C-2); 167.5 (3-ester-CO); 170.9 ppm (4-ester-CO).

Dimethyl 1-*t*-Butyl-4-methyl-1,4-dihydropyridine-3,4-dicarboxylate (5ab):

Compound **1a** (566 mg, 3.00 mmol) and methyl methacrylate (**2b**; 21.6 g, 150 mmol) are allowed to react as described above for **5aa** to give the 1,4-dihydropyridine **5ab** as a colourless oil after chromatography; yield: 561 mg (70%).

H.R.M.S.: *m/e* = 267.1470 (M^+); calc. for $C_{14}H_{21}NO_4$: 267.1465.

U.V. (CH_3CN): λ_{max} (lg ε) = 340 (3.76); 244 nm (3.63).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): δ = 1.34 (s, 9H, *t*-C_4H_9); 1.46 (s, 3H, 4-CH_3); 3.66 (s, 3H, 3-$COOCH_3$); 3.68 (s, 3H, 4-$COOCH_3$); 4.68 (d, *J* = 8.4 Hz, 1H, 5-H); 6.19 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H, 6-H); 7.54 ppm (d, *J* = 2.0 Hz, 1H, 2-H).

^{13}C-N.M.R. ($CDCl_3$, 20 MHz): δ = 28.0 (4-CH_3); 28.9 [C($\underline{C}H_3)_3$]; 43.0 (C-4); 50.7 (3-$COOCH_3$); 52.2 (4-$COOCH_3$); 56.5 [$\underline{C}(CH_3)_3$]; 102.7 (C-3); 109.0 (C-5); 123.6 (C-6); 136.4 (C-2); 168.0 (3-ester-CO); 175.7 ppm (4-ester-CO).

Trimethyl 1-*t*-Butyl-5-isopropyl-1,4-dihydropyridine-3,4,4-tricarboxylate (5ac):

Compound **1a** (185 mg, 1.00 mmol) and dimethyl 2-methylpropylidenemalonate[13] (**2c**; 10.2 g, 55 mmol) are allowed to react as described above for **5aa** to give the 1,4-dihydropyridine **5ac** as a colourless oil after chromatography; yield: 230 mg (65%).

H.R.M.S.: *m/e* = 353.1838 (M^+); calc. for $C_{18}H_{27}NO_6$: 353.1831.

U.V. (CH_3CN): λ_{max} (lg ε) = 331 nm (3.84), 247 nm (3.60).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): δ = 1.12 [d, *J* = 6.4 Hz, 6H, $CH(C\underline{H}_3)_2$]; 1.37 (s, 9H, *t*-C_4H_9), 2.10–2.60 [m, 1H, $C\underline{H}(CH_3)_2$]; 3.67 (s, 3H, 3-$COOCH_3$); 3.70 (s, 6H, 4-$CO\underline{C}H_3$); 6.25 (d, *J* = 1.7 Hz, 1H, 6-H); 7.61 ppm (d, *J* = 1.7 Hz, 1H, 2-H).

^{13}C-N.M.R. ($CDCl_3$, 25 MHz): δ = 25.0 [$CH(\underline{C}H_3)_2$]; 29.1 [$C(\underline{C}H_3)_3$]; 29.8 [$\underline{C}H(CH_3)_2$]; 51.0 (3-$COOCH_3$); 52.3 (4-$COOCH_3$); 57.1 [$\underline{C}(CH_3)_3$]; 60.2 (C-4); 98.1 (C-3); 121.5 (C-6); 121.9 (C-5); 135.9 (C-2); 167.6 (3-ester-CO); 171.1 ppm (4-ester-CO).

Dimethyl 1-*t*-Butyl-4-cyano-5-isopropyl-1,4-dihydropyridine-3,4-dicarboxylate (5ad):

Compound **1a** (302 mg, 1.63 mmol) and methyl 2-cyano-4-methyl-2-pentenoate[14] (2d; 12.5 g, 82.0 mmol) are allowed to react as described above for **5aa** to give the dihydropyridine **5ad** as a colourless oil which crystallises on treatment with diethyl ether; yield: 225 mg (43%); m.p. 166 °C.

$C_{17}H_{24}N_2O_4$	calc.	C 63.73	H 7.55	N 8.74
(320.2)	found	63.80	7.57	8.69

U.V. (CH_3CN): λ_{max} = (lg ε) = 342 nm (3.76); 254 nm (3.40).

^{1}H-N.M.R. ($CDCl_3$, 60 MHz): δ = 1.02 [d, *J* = 7.0 Hz, 3H, $CH(C\underline{H}_3)_2$]; 1.26 [d, *J* = 7.0 Hz, 3H, $CH(C\underline{H}_3)_2$]; 1.36 (s, 9H, *t*-C_4H_9), 2.10–2.80 [m, 1H, $C\underline{H}(CH_3)_2$]; 3.70 (s, 3H, 3-$COOCH_3$); 3.80 (s, 3H, 4-$COOCH_3$); 6.25 (d, *J* = 1.8 Hz, 1H, 6-H), 7.56 ppm (d, *J* = 1.8 Hz, 1H, 2-H).

^{13}C-N.M.R. ($CDCl_3$, 25 MHz): δ = 23.6 [$CH(\underline{C}H_3)_2$]; 24.0 [$CH(\underline{C}H_3)_2$]; 28.9 [$C(\underline{C}H_3)_3$]; 29.5 [$\underline{C}H(CH_3)_2$]; 48.8 (C-4), 51.4 (3-$COOCH_3$); 53.5 (4-$COOCH_3$); 57.8 [$\underline{C}(CH_3)_3$]; 96.1 (C-3); 118.3 (CN); 119.1 (C-5); 122.1 (C-6); 136.6 (C-2); 166.3 (3-ester-CO); 169.1 ppm (4-ester-CO).

Dimethyl 2-*t*-Butyl-2,4a,5,6,7,8-hexahydroisoquinoline-4,4a-dicarboxylate (5ae):

Compound **1a** (185 mg, 1.00 mmol) and methyl cyclohexene-1-carboxylate[15] (**2e**; 5.15 g, 37.0 mmol) are irradiated in a 50 ml ring reactor with a 150 watt mercury high pressure lamp (Hanau) according to the procedure described above for **5aa**. The product **5ae** is obtained as a light yellow oil after chromatography; yield: 200 mg (66%).

H.R.M.S.: *m/e* = 307.1783 (M^+); calc. for $C_{17}H_{25}NO_4$: 307.1777.

U.V. (CH_3CN): λ_{max} (lg ε) = 347 (3.48); 240 nm (3.35).

^{1}H-N.M.R. ($CDCl_3$, 200 MHz): δ = 1.05–2.20 (m, 8H, 5-H, 6-H, 7-H, 8-H); 1.36 (s, 9H, *t*-C_4H_9); 3.73 (s, 3H, 4-$COOCH_3$); 3.77 (s, 3H, 4a-$COOCH_3$); 5.99 (d, *J* = 2 Hz, 1H, 1-H); 7.45 ppm (d, *J* = 2 Hz, 1H, 3-H).

^{13}C-N.M.R. ($CDCl_3$, 50 MHz): δ = 23.7 (C-7), 28.4 [$C(\underline{C}H_3)_3$], 31.3 (C-5), 36.4 (C-8); 47.8 (C-4a); 50.6 (4-$COOCH_3$); 52.1 (4a-$COOCH_3$); 56.3 [$\underline{C}(CH_3)_3$]; 102.0 (C-4); 118.3 (C-1); 120.3 (C-8a); 136.8 (C-3); 168.3 (4-ester-CO); 174.8 ppm (4a-ester-CO).

Methyl 1,4,4,5-Tetramethyl-1,4-dihydropyridine-3-carboxylate (5bf):

Methyl 2-formyl-3-methylamino-2-propenoate (**1b**; 200 mg, 1.40 mmol) in 2-methyl-2-butene (**2f**; 14 ml, 50 mmol) is irradiated for 22 h according to the procedure described above for **5aa**. After column chromatography the 1,4-dihydropyridine **5bf** is obtained as a colourless oil; yield: 164 mg (62%); R_F: 0.3 (ethyl acetate/hexane, 1/3).

H.R.M.S.: *m/e* = 195.1259 (M^+); calc. for $C_{11}H_{17}NO_2$: 195.1259.

U.V. (CH_3OH): λ_{max} (lg ε) = 356 (3.71); 280 (3.11); 240 nm (3.45).

^{1}H-N.M.R. ($CDCl_3$, 100 MHz): δ = 1.50 (s, 6H, 4-CH_3); 1.68 (d, *J* = 1.6 Hz, 3H, 5-CH_3); 2.94 (s, 3H, N—CH_3); 3.66 (s, 3H, OCH_3); 5.43 (m, 1H, 6-H); 7.04 ppm (d, *J* = 2 Hz, 1H, 2-H).

Methyl 1-(1-Phenethyl)-4,4,5-trimethyl-1,4-dihydropyridine-3-carboxylate (5cf):

Methyl 2-formyl-3-(1-phenethylamino)-2-pentenoate (**1c**; 233 mg, 1.00 mmol) and 2-methyl-2-butene (**2f**; 15 ml, 53 mmol) are allowed to react as described above for **5aa** to give the 1,4-dihydropyridine **5cf** as a colourless oil after chromatography; yield: 231 mg (81%).

H.R.M.S.: *m/e* = 285.1729 (M^+); calc. for $C_{18}H_{23}NO_2$: 285.1729.

U.V. (ether): λ_{max} (lg ε) = 348 (3.65); 278 nm (3.54).

^{1}H-N.M.R. ($CDCl_3$, 100 MHz): δ = 1.48 (s, 6H, 4-CH_3); 1.58 (d, *J* = 7.5 Hz, 3H, 2′-H); 1.60 (d, *J* = 1.1 Hz, 3H, 5-CH_3); 3.60 (s, 3H, OCH_3); 4.37 (q, *J* = 7.5 Hz, 1′-H); 5.40 (m, 1H, 6-H); 7.27 ppm (m, 6H, 2-H and aromatic H).

Methyl 1-(4-Methoxycarbonylbut-1-yl)-4,4,5-trimethyl-1,4-dihydropyridine-3-carboxylate (5df):

Dimethyl 2-formyl-4-azanon-2-ene-1,9-dioate (**1d**; 194 mg, 0.8 mmol) and 2-methyl-2-butene (**2f**; 16 ml, 60 mmol) are allowed to react as described above for **5aa** to give the 1,4-dihydropyridine **5df** as a yellow oil after chromatography; yield: 137 mg (58%).

H.R.M.S.: *m/e* = 295.1784 (M^+); calc. for $C_{16}H_{25}NO_4$: 295.1784.

U.V. (CH_3CN): λ_{max} (lg ε) = 350 (3.83); 287 nm (3.17).

^{1}H-N.M.R. ($CDCl_3$, 200 MHz): δ = 1.46 (s, 6H, 4-CH_3); 1.64 (d, *J* = 1.5 Hz, 3H, 5-CH_3); 1.74–1.56 (m, 4H, 2′-H_2, 3′-H_2); 2.35 (t, *J* = 6.5 Hz, 2H, 4′-H); 3.10 (t, *J* = 6.5 Hz, 2H, N—CH_2); 3.66 (s, 3H, OCH_3); 3.70 (s, 3H, 4′-OCH_3); 5.44 (dq, $J_{H\text{-}6,H\text{-}2}$ = 1.8 Hz, $J_{H\text{-}6,5\text{-}CH_3}$ = 1.5 Hz, 1H, 6-H); 7.06 ppm (d, *J* = 1.8 Hz, 1H, 2-H).

^{13}C-N.M.R. ($CDCl_3$, 50 MHz): δ = 15.6 (5-CH_3); 21.8 (C-3′); 27.2 (4-CH_3); 29.4 (C-2′); 33.5 (C-4′); 35.3 (C-4); 50.3 (3-$COOCH_3$); 51.6 (4′-$COOCH_3$); 53.7 (C-1′); 103.6 (C-3); 121.2 (C-5); 121.3 (C-6); 141.0 (C-2); 168.5 (3-ester-CO); 173.6 ppm (4′-ester-CO).

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