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N-ACYL-1,4-DIHYDROPYRIDINES BY ACID CATALYZED CONDENSATIONS

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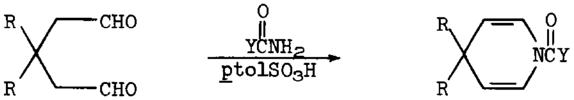
Dihydropyridines have been prepared via the Hantzsch synthesis[1], by reduction of pyridines[2] and condensation reactions using glutaraldehydes.[3] These procedures are often plagued by low yields and unwanted side-products.

We have used N-acyl-1,4-dihydropyridines 1 as precursors of dihydropyridine anions, 2, in studies of electronic structure and charge distribution in, 2.

1 2

It has therefore become necessary to produce compounds, 1, efficiently and this communication reports precisely such a result.

We reasoned that the condensation of glutaraldehyde with a weakly basic amino compound (a carboxamide) could be acid catalyzed. Also, water formed in the reaction could be azeotroped out with benzene. In fact when a glutaraldehyde is refluxed with a carboxamide in benzene in the presence of catalytic amounts of p-toluenesulfonic acid there is observed (by nmr) almost quantitative conversion to the N-acyl-1,4-dihydropyridine, with isolated yields of 40 to 75%, see TABLE 1.

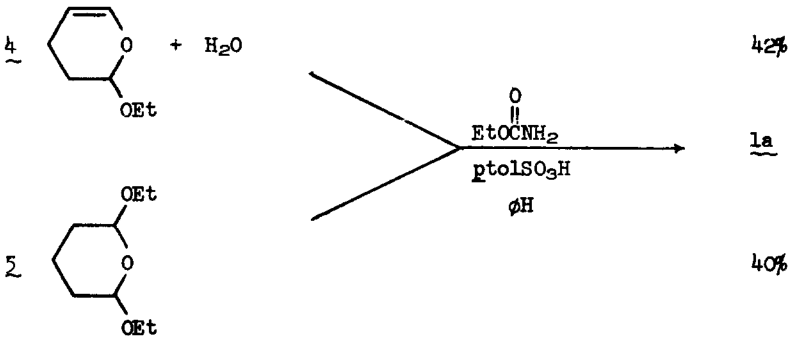


3 1

TABLE 1 N-Acyl-1,4-dihydropyridines from 3 → 1

	R	Y	Yield %	bp°/torr
1a	H	OEt	42	52/0.12
1b	H	CH_3	75	63/0.3
1c	CH_3	CH_3	76	47/0.2
1d	CH_3	∅	75	165-170/0.2

These reactions also proceed readily with glutaraldehyde acetal and even 3,4-dihydro-2-ethoxy-2H-pyran, 4; the latter compound requires an equivalent of water in addition to urethane and acid to give 1a.



Pyrans are reported to undergo similar condensations in acetic acid.[6]

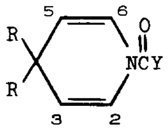
These dihydropyridines are stable indefinitely at -10°. Note, however, that compounds with hydrogen at the 4-position oxidize easily in air and must be stored under argon.

Nmr data[5], both proton and ^{13}C, for the compounds reported here are recorded in TABLES 2 and 3. The results confirm the assigned structures as well as reveal that in the case of 1b and 1c rotation about the nitrogen carbonyl carbon bond is slow on the nmr time scale. Also notice how the gem dimethyl substituents at C-4 cause the shifts of C-3 and C-5 to move downfield by 10 ppm. while C-4 moves upfield by 8-10 ppm.

Procedure

3,3-Dimethylglutaraldehyde (6 g, 0.046 mole), benzamide (5.6 g, 0.046 mole) and 200 mg of p-toluenesulfonic acid were refluxed together in an apparatus equipped with a Dean Stark trap. When no more water collected in the trap, 2 hrs, benzene was removed under reduced

TABLE 2 Pmr shift Data for 1, tau scale



Compound	2,6	3,5	R	Y
1a[2]	3.36	5.23	8.18	4.88 8.72
1b	2.90 3.50	5.00	7.13	7.86
1c	2.90 3.52	5.15	8.92	7.83
1d	3.28	5.17	8.89	2.65

TABLE 3 Cmr shifts in 1, ppm/TMS

Compound	2,6	3,5	4	R	Y	C=O
1a	123.7	105.9	22.5		62.3 14.5	151.5
1b	124.5 122.5	107.6 107.2	21.2		23.0	165.9
1c	121.0 118.9	117.9 117.3	29.1	32.1	21.3	166.1
1d	121.1	117.6	31.6	32.1	*	167.0

*134.2 (α), 128.2 (*o*), 128.4 (*m*), 130.7 (*p*)

pressure and the residue distilled, b.p. 165-170/0.4 torr to give 7.2 g of N-benzoyl-4,4-dimethyl-1,4-dihydropyridine, 1d, in 75% yield.

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