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ACETOXYLATION OF PIPERIDINE DERIVATIVES AT THE 3-POSITION. STEREOSELECTIVE SYNTHESIS OF PSEUDOCONHYDRINE AND N-METHYLPSEUDOCONHYDRINE[1)]

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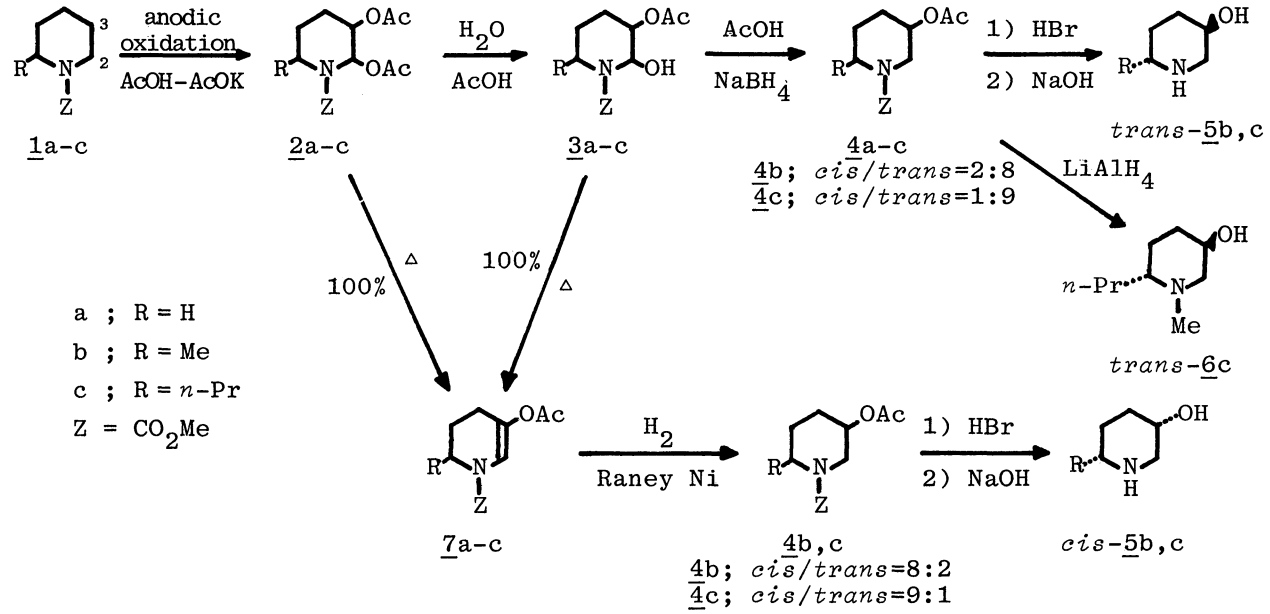
Anodic oxidation of N-methoxycarbonylpiperidine derivatives in AcOH gave 2,3-diacetoxylated products, which were shown to be useful intermediates for the stereoselective synthesis of 3-hydroxypiperidine derivatives including pseudoconhydrine and N-methylpseudoconhydrine, the *Conium* alkaloids.

Functionalization of a methylene group remote from an active site is one of the important subjects in organic synthesis, though only few methods have been known to be practically useful so far.[2)] We report herein a new method convenient for introducing an acetoxyl group to 3-position of piperidines (1).

Scheme 1 illustrates our method applied to the stereoselective synthesis of pseudoconhydrine, *trans*-5c and N-methylpseudoconhydrine, *trans*-6c, the *Conium* alkaloids.[3)]

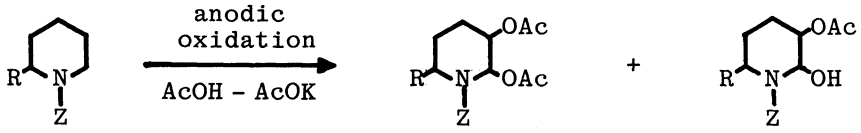


Scheme 1.

The typical procedures are shown below. The anodic oxidation of N-methoxycarbonylpiperidine 1a (15 mmol) in AcOH (40 ml) containing AcOK (40 mmol) without

using diaphragm yielded 2,3-diacetoxylated compound 2a, which was unstable and easily converted into 2-hydroxy-3-acetoxypiperidine 3a in workup. The treatment of the electrolyzed solution with water (method A; r.t., 6 h) gave only 3a, while a mixture of 2a and 3a was obtained under weakly basic conditions using cold aq. $NaHCO_3$ (method B). The yields of 2 and 3 are shown in Table 1.[4)]

Table 1. Anodic Oxidation of Piperidine Carbamates and Amides 1a-f in AcOH[a)]



1a-f 2a,b,d-f 3a-e

Entry	Compound	R	Z	Electricity passed (F/mol)	Method[b)]	Isolated yield/% 2a,b,d-f	3a-e
1	1a	H	CO_2Me	20	A		3a (88)
2	1a	H	CO_2Me	12	B	2a (61)	3a (20)
3	1b	Me	CO_2Me	20	A		3b (92)
4	1b	Me	CO_2Me	20	B	2b (34)	3b (45)
5	1c	*n*-Pr	CO_2Me	21	A		3c (93)
6	1d	Et	CO_2Me	20	A		3d (84)
7	1d	Et	CO_2Me	20	B	2d (35)	3d (30)
8	1e	H	COPh	50	A		3e (69)
9	1e	H	COPh	25	B	2e (77)	
10	1f	H	CO_2CH_2Ph	17	B	2f (50)	

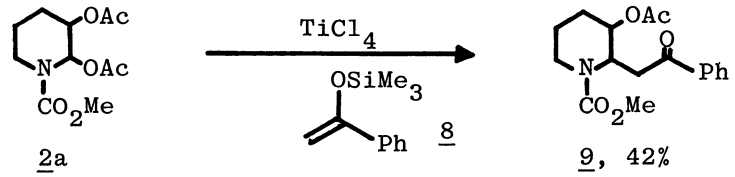
a) Anode, Pt; Cathode, Carbon. b) Method A; Workup with water (r.t., 6 h). Method B; Workup with cold aq. $NaHCO_3$.

The transformation of 2a-c or 3a-c to 3-acetoxypiperidines 4a-c was easily achieved by treating 2a-c or 3a-c (5 mmol) with $NaBH_4$ (5 equiv. mol) in AcOH (20 ml). Isolated yields of 4a-c[4)] were as follows: 4a, 92% from 2a, 59% from 3a; 4b, 84% from 2b, 78% from 3b; 4c, 78% from 3c. Stereoisomers of products 4b and 4c were separable by GLC, and the ratios of *trans*-4 to *cis*-4 were 8:2 in b series and 9:1 in c series.[5)] The stereochemistry between 3-acetoxyl group and 6-alkyl substituent was confirmed at the stage of final products 5b,c.[6)] Hydrolysis of 4b with 47% HBr followed by treatment with aq. NaOH gave *trans*-3-hydroxy-6-methylpiperidine, *trans*-5b[6a)] (59%). Similar hydrolysis of 4c gave pseudoconhydrine, *trans*-5c[6a,e)] (58%). Also, reduction of *trans*-4c with $LiAlH_4$ gave N-methylpseudoconhydrine, *trans*-6c[3b)] (93%).

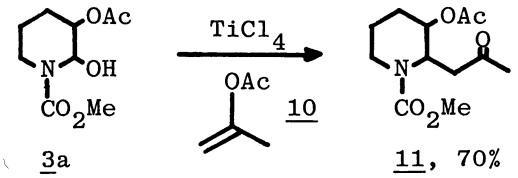
On the other hand, *cis*-5b and *cis*-5c could be prepared almost exclusively from

2b,c or 3b,c. Namely, heating 2b,c or 3b,c in AcOH for a short period (5-10 min) quantitatively gave 7b,c,[4] which were then hydrogenated (10 atm) over Raney Ni to yield 4b (81%, *cis/trans*=8:2)[5] and 4c (76%, *cis/trans*=9:1).[5] The *cis*-configuration of the major isomers of 4b,c was deduced from the fact that *cis*-5b,c[6b-d] were obtained as the major products from 4b,c upon hydrolysis with 47% HBr.

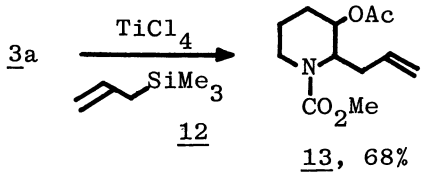
The compounds 2 and 3 were useful intermediates for the synthesis of 2-alkyl-3-acetoxypiperidines. Thus, the reaction of 2a with silyl enol ether 8 in the presence of Lewis acid yielded 9 (Eq. 1).[4] Similarly, 3a gave 11 and 13 upon reaction with enol acetate 10 and allylsilane 12, respectively[4] (Eqs. 2 and 3).



2a 9, 42% (1)

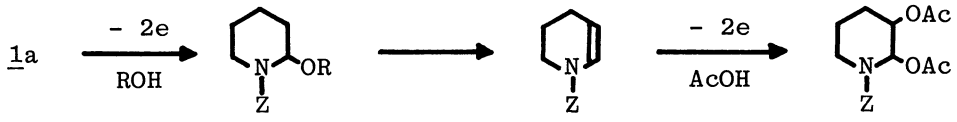


3a 11, 70% (2)



13, 68% (3)

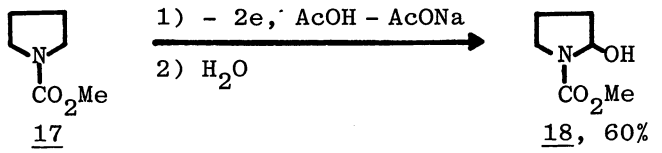
The inactive 3-position of 1 seems to be acetoxylated by the anodic oxidation of an intermediate enecarbamate 15[7] generated *in situ* from the initial product 14 since the anodic oxidation of 15, independently prepared from 1a through 16,[8] in AcOH afforded 2a in 71% yield (Scheme 2).



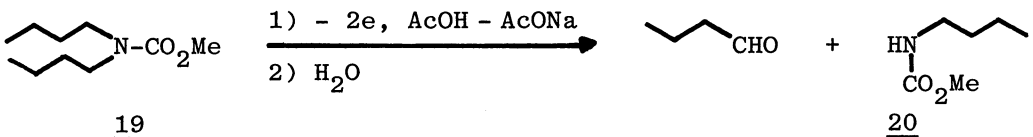
14; R = Ac
16; R = Me
15
2a
Z = CO_2Me

Scheme 2.

On the other hand, carbamates other than 1 showed different patterns of reactions as exemplified in Eqs. 4 and 5. Thus, the anodic oxidation of 17 and 19 in AcOH did not give 2,3-diacetoxylated products 22[9] and 24, but 18 was obtained from 17 and a mixture of butyraldehyde and 20 from 19.

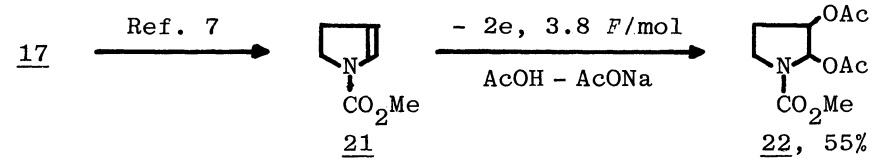


17 18, 60% (4)



19 20 (5)

As suggested in Scheme 2, however, the 3-position of 17 and 19 were successfully acetoxylated by using the corresponding enecarbamates as the starting compounds. Thus, 17 and 19 were converted into enecarbamates 21 and 23 according to our previously reported method[7] and the anodic reaction of 21 and 23 under the conditions similar to the oxidation of 15 yielded 2,3-diacetoxylated products 22 and 24 in 55 and 76% yields, respectively (Eqs. 6 and 7).



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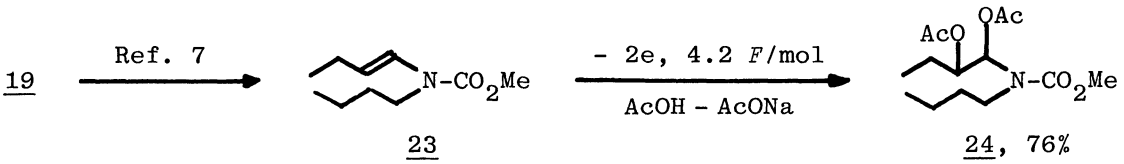

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5) The ratios were determined by GLC.
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