Tetrahedron Letters No. 36, pp 3473 - 3476.

0040-4039/79/0901-3473$02.00/0

A CARBON-CARBON BOND FORMATION USING ENDOPEROXIDES OF 1,2-DIHYDROPYRIDINES

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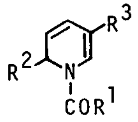
Summary: A novel type of a nucleophilic substitution on the piperidine ring was achieved by a stannous chloride-effected reaction of endoperoxides of N-alkoxycarbonyl-1,2-dihydropyridines with various kinds of carbon nucleophiles.

1,2-Dihydropyridines[1] have been a useful starting material for the synthesis of N-heterocyclic compounds related to natural products.[2-7] Recently, we have investigated the sensitized photooxygenation reaction of 1-acyl-1,2-dihydropyridine derivatives and demonstrated that either N-methoxycarbonyl-1,2-dihydropyridine (1a)[5a] or N-benzoyl-5-cyano-1,2-dihydropyridine derivative (1b)[7a] afforded in almost quantitative yield the corresponding endoperoxides (2), which were susceptible to nucleophilic reaction and produced 3a, 4a, and 5, when they were reacted with a thiol or an alcohol in the presence of both an acid and a reducing reagent.[7b,7c] In this communication, we wish to describe a $SnCl_2$-effected reductive ring-opening reaction of the endoperoxide (2a) in the presence of various kinds of carbon nucleophiles, such as trimethylsilylated ketones, vinyl ethers, enamines, indole, N-methylpyrrole, and furan, establishing a novel type of carbon-carbon bond formation at the α or γ position of piperidine ring in a non-carbanion manner.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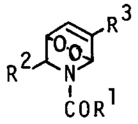
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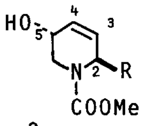
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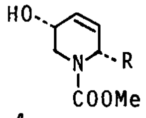
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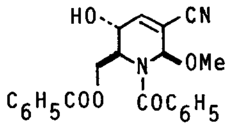
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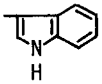
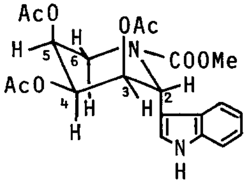
a R^1=OMe R^2=R^3=H

b R^1=Ph R^2=$C_6H_5COOCH_2$-
R^3=CN

a R=-SC_6H_5

b R=

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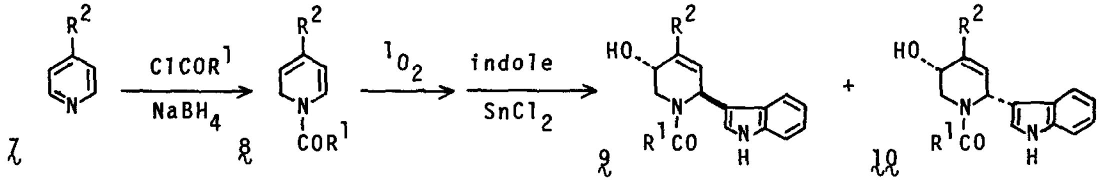
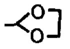
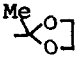
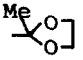
Photooxidation of 1a (2.007 g, 14.4 mmol) was carried out as described before[7b] in CH_2Cl_2 solution (300 ml) with methylene blue (30 mg) under Dry Ice-acetone chilling for 5 hr, using a 500-W halogen lamp. Without isolation of 2a, indole (2.027 g, 17.3 mmol) was added to this solution, and a suspension of well-ground $SnCl_2$ (4.115 g, 21.7 mmol) in AcOEt (240 ml) was added during 40 min, while the mixture was cooled with Dry Ice-acetone. The reaction mixture was allowed to stand overnight[8] and a simple work-up[9] gave in 69% yield a single reaction product (3b), whose PMR spectrum ($CDCl_3$, 60°) exhibited a complex multiplet of three proton signals at 5.88-6.25 δ attributable to H-2, H-3, and H-4, and a 2'-proton signal of indole portion appeared at 7.03 δ (d, J=3 Hz), which coalesced to a singlet by the addition of D_2O.

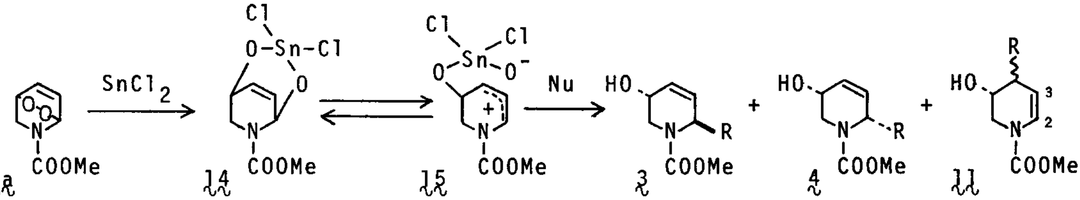
Structure of 3b was further confirmed by examination of PMR spectrum of 6 [δ in $CDCl_3$, 60°: 2.00, 2.08, 2.12 (Ac×3); 2.98 (dd, J=15.5, 1.5 Hz, H-6a); 3.85 (s, COOMe); 4.35 (ddd, J=15.5, 3, 2 Hz, H-6e); 4.92-5.18 (m, H-5); 5.38 (dd, J=3.5, 3.5 Hz, H-3); 5.87 (ddd, J=3.5, 2, 1.5 Hz, H-2); 6.03 (dd, J=3.5, 2 Hz, H-4); 7.03-7.77 (m, arom. H); 8.62-8.85 (br. s, NH)], which was obtained by oxidation of 3b with OsO_4, followed by acetylation with Ac_2O in pyridine in 32% yield. A W-type long-range coupling[10] (2 Hz) between H-2 and H-6e, as well as the small value of coupling constant (1.5 Hz) between H-5 and H-6a, suggested that the indolyl group and the original oxygen function at C-5 were oriented in an axial fashion,[11] and hence situated in the trans relationship.

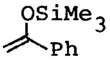
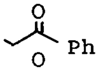
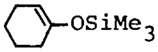
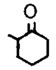
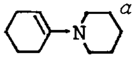
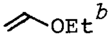
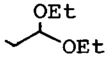
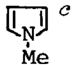
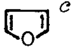
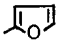
The same reaction proceeded well with dihydropyridines (8) derived from 4-substituted pyridines (7a-7f) and produced highly functionalized indole derivatives (9a-9f) in good yield.



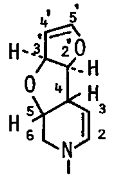
	R^1	R^2	Yield (%) from 7 9	 10
a	OMe	-CN	24	3
b	OMe	-COOMe	62	0
c	OMe	$-COOCH_2Ph$	49	0
d	OMe		69	0
e	OMe		68	0
f	OCH_2Ph		60	0

The reductive condensation of **2a** with other carbon nucleophiles was achieved as shown in the following Table and compounds having trans substituents (**3c**-**3f**) were also major products, whereas in some cases, there were obtained in low yield cis products (**4c**, **4f**, and **10a**), whose characterization was readily possible by the large coupling constant (9-11 Hz) between H-5 and the pseudo-axial proton of C-6 methylene group, compared with those (∿0-3 Hz) of the trans products, the same phenomena being notable in the case of phenylthio derivatives (**3a** and **4a**). Structure of $\Delta^{2,3}$-compounds (**11f**, **11g**, and **12**) was easily deduced from the olefinic proton signals (H-2 at 6.72-7.03 δ and H-3 at 4.49-4.92 δ) of the acylenamine character and the structure of **12** was presumed from the analysis of its PMR spectrum,[12] as well as its transformation into **13** by treatment with $BF_3 \cdot Et_2O$ in $MeOH-CH_2Cl_2$ in 39% yield.

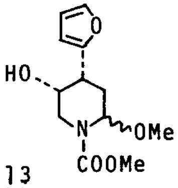


Nucleophile		R	Yield (%) from 1a		
			3	4	11
	c		58	3	0
	d		60	0	0
 a	d	"	21	0	0
 b	e		50	0	0
 c	f		35	7	11
 c	g		0	0	14(trans)+12(10%)

a) Hydrolysis with 50% $AcOH-H_2O$ *b*) Addition of EtOH
c) Addition of $SnCl_2$ first and then a nucleophile



12



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The role of $SnCl_2$ is considered as follows: Two-electron transfer from bivalent metal to the peroxide takes place to form both diol dianion and quadrivalent tin species, which might produce a complex such as **14**. The complex (**14**) is in equilibrium with an allylic cation (**15**), but nucleophiles might mainly attack **14** by the S_{N2} mechanism to afford trans products, whereas **15** might play a part to give cis products and 4-substituted compounds. Mechanistic consideration for the latter, however, must await further accumulation of similar examples.

ACKNOWLEDGEMENT

A part of this work was supported by Grant-in-Aid for Special Project Research, Chemical Research in Development and Utilization of Nitrogen-Organic Resources, from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

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8. During 14 hr, temperature reached -10°.
9. Addition of sat. $NaHCO_3$, filtration of inorganic material, and the following usual work-up afforded a crystalline mass, which was purified by recrystallization (MeOH) and chromatography (silica gel, C_6H_6-EtOAc=2:1).
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11. Alkyl side chain at the position α to the nitrogen of N-acylpiperidines is proved to be stable in the axial configuration. *cf.* J. Quick, C. Mondello, and M. Humora, *J. Org. Chem.*, 43, 2705 (1978).
12. PMR δ (CCl_4, 70°): 2.71-2.83 (m, H-4), 3.17 (dd, J=15, 2 Hz, H-6), 3.69 (s, COOMe), 4.01-4.13 (m, H-5), 4.17 (dd, J=15, 3 Hz, H-6'), 4.49 (ddd, J=8, 3, 2 Hz, H-3), 4.55 (d, J=6 Hz, H-2'), 4.92 (dd, J=3, 3 Hz, H-4'), 5.23 (dd, J=6, 3 Hz, H-3'), 6.43 (d, J=3 Hz, H-5'), 6.72 (br. d, J=8 Hz, H-2).

(Received in Japan 18 May 1979)