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A CARBON-CARBON BOND FORMATION USING AN ENDOPEROXIDE OF N-METHOXYCARBONYLPYRROLE AND A CONVENIENT SYNTHESIS OF 4-ALKYLINDOLES

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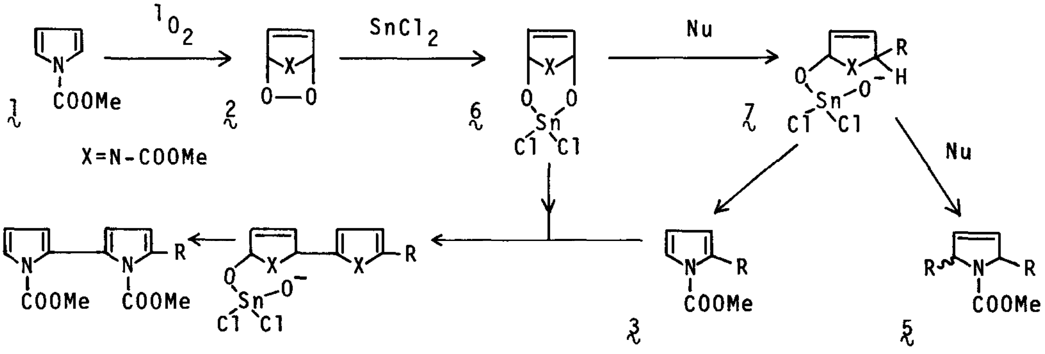
Summary: A convenient synthesis of 4-alkylindoles was attained by utilizing the result of a stannous chloride-effected reaction of endoperoxide of N-methoxycarbonylpyrrole with carbon nucleophiles.

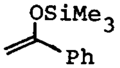
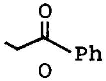
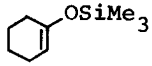
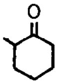
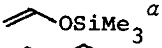
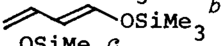
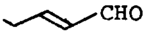
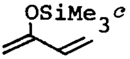
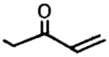
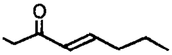
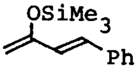
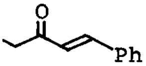
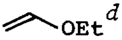
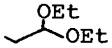
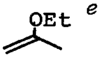
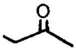
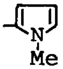
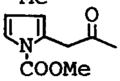
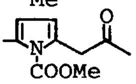
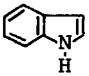
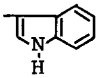
A number of examples of sensitized photooxygenation reaction have been reported in the field of heterocyclic chemistry,[1] but these are mostly concerned with the characterization of direct oxygenation products as well as of their secondary degradation products in individual cases. Our intention is different from these, and we studied utilization of unstable but reactive endoperoxides as useful intermediates for the introduction of various functional groups into the piperidine ring.[2] In this communication, we report an application of our SnCl$_2$-effected reaction of endoperoxide[2c] to a pyrrole derivative and also describe a successful synthesis of 4-alkylindoles in five steps from N-methoxycarbonylpyrrole.

Completely analogous to the experimental condition in the case of 1,2-dihydropyridine derivatives,[2c] N-methoxycarbonylpyrrole (1)[3] was photooxygenated at a low temperature, and the endoperoxide (2)[4,5] thus obtained was condensed with nucleophiles, such as trimethylsilylated ketones, vinyl ethers, N-methylpyrrole, and indole by the help of SnCl$_2$ to afford 2-substituted pyrrole derivatives (3) as major products, accompanied by the formation of 2,2'-bipyrrole derivatives (4) and N-methoxycarbonyl-3-pyrrolines (5) having two substituents



which came from the nucleophiles (Table 1). The reaction is tentatively assumed to proceed through the complex (6),[2c] whose reactive C-O bond is cleaved by the attack of a nucleophile, and predominant path is the subsequent aromatization to afford 3. Contrary to the case of 1,2-dihydropyridine, the second reactive C-O bond exists in 7 and further attack of the nucleophile affords 2,5-disubstituted 3-pyrroline (5), although stereochemical control is missing. The pyrrole product (3) is presumed to be a poor nucleophile due to the presence of N-methoxycarbonyl group but behaves as another nucleophile and attacks the complex (6) in competition with the first nucleophile to produce the minor product (4). This is evidenced by the formation of 3k, when 2-acetonyl-N-methoxycarbonylpyrrole (3i) was independently reacted with endoperoxide (2).

Table 1

Nucleophile		R	Yield (%) from 1 3	4	5
	a		57	7	0
	b		67	0	0
 [a]	c		54	0	0
 [b]	d		62	0	†
 [c]	e		72	0	0
	f		72	5	2 (trans) 5 (cis)
	g		64	0	1.5 (trans) 3 (cis)
 [d]	c		20	0	0
	h		9		
 [e]	i		48	0	0
	j		14	0	0
	k		21	0	0
	l		32	8	0

† Presence of 5d (trans+cis) was detected in PMR spectrum, but isolation from other unknown by-products failed.

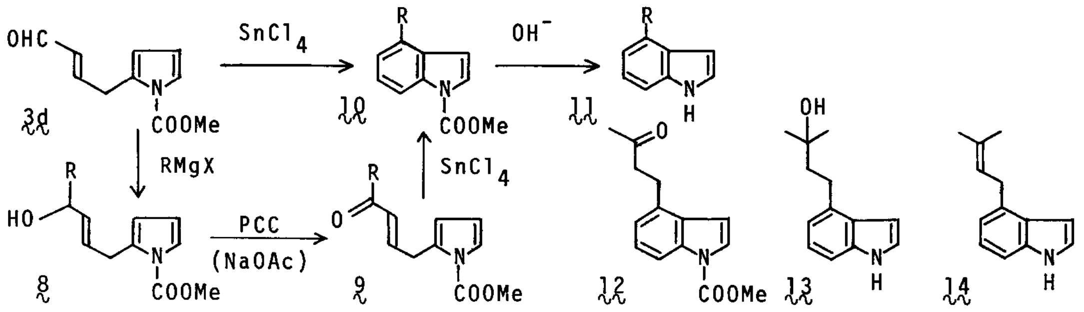
a) M.E. Jung and R.B. Blum, Tetrahedron Lett., 3791 (1977).

b) Sociétè des Usines Chimiques Rhône-Poulenc, Fr. Patent Add. 88,358 (1967) [Chem. Abst., 68, 49733j (1968)].

c) M.E. Jung and C.A. McCombs, Tetrahedron Lett., 2935 (1976).

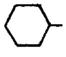
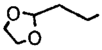
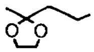
d) Addition of EtOH.

e) W.J. leNoble and P.J. Crean, J. Org. Chem., 27, 3875 (1962).



Acid-catalyzed cyclization of 3d was studied in order to find a novel type of indole synthesis[6] and treatment of 3d with $HClO_4$ in EtOAc (room temperature, 20 hr), $BF_3 \cdot Et_2O$ in CH_2Cl_2 (0°, 20 min), or $SnCl_4$ in CH_2Cl_2 (0°, 8 min) was effective to afford N-methoxycarbonylindole (10a, R=H) in 48%, 59%, or 69% yield, respectively. This knowledge was immediately extended to the synthesis of 4-alkylindoles. The corresponding unsaturated ketones (9b-9h), which were readily obtained from 3d by the Grignard reaction, followed by oxidation with pyridinium chlorochromate,[7] were cyclized to 10b-10h by the catalysis of $SnCl_4$ in dichloroethane under ice-cooling for 10-20 min. Simultaneous cleavage of dioxolane group took place during the cyclization reaction and PMR spectrum of 12 [δ in $CDCl_3$: 2.02 (s, COMe), 2.70 and 2.98 (A_2B_2, J=8 Hz, methylenes), 3.90 (s, COO-Me), 6.57 (d, J=4 Hz, H-3), 6.95 (br. d, J=7.5 Hz, H-5), 7.19 (dd, J=7.5, 7.5 Hz, H-6), 7.54 (d, J=4 Hz, H-2), 8.02 (br. d, J=7.5 Hz, H-7)] represented the common feature of aromatic proton signals of 4-substituted N-methoxycarbonylindoles (10). Synthesis of 4-alkylindoles (11) was completed by alkaline hydrolysis of 10 (10% KOH in MeOH-H_2O, room temperature, 30-40 min) in high yield. All results are summarized in Table 2.

Table 2

	R	8	9	10	Recovery of 9	11
				Yield (%)		
b	Me	82	75	51	27	quant.[a]
c	n-Bu	91	83	44	23	quant.
d	i-Am	91	83	46	15	quant.
e		87	68	14	0	-
f		58	71	trace	61	-
g		90	73	44[b,c]	0	-
h		90	70	12:52	22[b]	-

[a] Identical with the authentic sample of 4-methylindole.
[b] Simultaneous cleavage of dioxolane form to the ketone group.
[c] Isolated in the form of dioxolane derivative by treatment with methyl ethyl ketone ethylene ketal and p-toluenesulfonic acid.

The compound (**12**) was hydrolyzed with alkali as above to **11i** ($R=CH_2CH_2COMe$) in 93% yield and the reaction of **11i** with methylmagnesium iodide afforded **13** in 84% yield. Dehydration of **13** was effected by refluxing a benzene solution of **13** in the presence of p-toluenesulfonic acid and purification of the resulting mixture through crystalline picrate gave in 40% yield 4-(3-methyl-2-butenyl)indole (**14**);[8] picrate, mp 143-145°, whose derivative, 4-(3-methyl-2-butenyl)tryptophan is proved to be an important precursor in the biogenesis of ergot alkaloids.[9]

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REFERENCES AND NOTES

1. T. Matsuura and I. Saito, "Phtochemistry of Heterocyclic Compounds," edited by O. Buchardt, John Wiley & Sons Inc., New York, 1976, p.456.
2. (a) M. Natsume, Y. Sekine, and H. Soyagimi, *Chem. Pharm. Bull. (Tokyo)*, 26, 2188 (1978). (b) M. Natsume, M. Wada, and M. Ogawa, *ibid.*, 26, 3364 (1978). (c) M. Natsume, Y. Sekine, M. Ogawa, H. Soyagimi, and Y. Kitagawa, *Tetrahedron Lett.*, preceding paper.
3. N.W. Gabel, *J. Org. Chem.*, 27, 301 (1962).
4. Rf value of **2** on the TLC plate of Merck Silica Gel $60F_{254}$ was 0.17, compared to Rf 0.93 of **1** (CH_2Cl_2:AcOEt=1:1).
5. Low-temperature PMR spectrum of **2** in $CDCl_3$ at -20°, δ: 3.72 (s, COOMe), 6.37 (dif. t, J=1.5 Hz) and 6.45 (dif. t, J=1.5 Hz)(diffused A_2B_2). At room temperature, these signals were no longer observed and signals of **1** appeared at 4.02 (s, COOMe), 6.33 (t, J=2 Hz) and 7.38 ppm (t, J=2 Hz)(A_2B_2).
6. During the preparation of this manuscript, we noticed that a new synthetic method for 4-substituted indoles from N-methylpyrrole was reported. B.M. Trost, M. Reiffen, and M. Crimmin, *J. Am. Chem. Soc.*, 101, 257 (1979).
7. E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
8. H. Plieninger, M. Hobel, and V. Liede, *Chem. Ber.*, 96, 1618 (1963).
9. H. Plieninger, E. Meyer, W. Maier, and D. Gröger, *Liebigs Ann. Chem.*, 813 (1978), and references cited therein.

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