CYCLIZATION OF β-KETOSULFOXIDE. IV. SYNTHESIS OF INDOLE, BENZOTHIOPHENE AND CARBAZOLE DERIVATIVES

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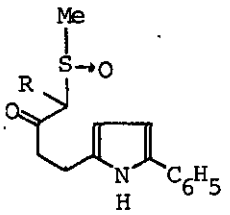
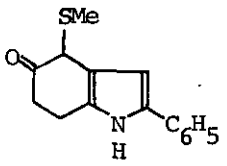
On acid-treatment, β-ketosulfoxides having pyrrole, thiophene and indole nuclei were converted to indoles, benzothiophenes and carbazoles, respectively, through intramolecular nucleophilic substitution.

In previous papers we reported the acid-catalyzed cyclization of β-ketosulfoxides having electron-rich aromatic nuclei to naphthalene and phenanthrene derivatives.[1-3] We now wish to report a further work designed to extend the utility of the cyclization reaction for a new synthesis of condensed heterocycles such as indole, benzothiophene and carbazole derivatives.

On heating under reflux with p-toluenesulfonic acid in tetrahydrofuran for 1 hr, 1 cyclized easily to 3 in good yield. The use of methanol and ethanol as a solvent, instead of tetrahydrofuran, gave aromatized indoles 4 and 5, respectively. Similarly, compound 2, readily synthesized from 1 and phenylisocyanate, gave a 4-substituted indole 6 in high yield. The results are summarized in Table I.



1, R=H
2, R=CONHC$_6$H$_5$



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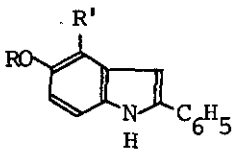


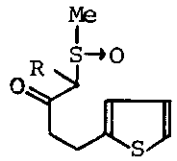
4, R=Me, R'=H
5, R=Et, R'=H
6, R=H, R'=CONHC$_6$H$_5$

Table I. Cyclization of 1 and 2 to indole derivatives

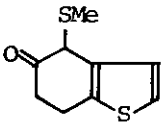
compd	acid	solvent	product[4]	yield(%)	mp°C
1	TsOH	THF	3	63	139-141
1	TsOH	MeOH	4	80	164-166[5]
1	TsOH	EtOH	5	72	136-137[5]
2	TsOH	i-PrOH	6	91	106-108

Under similar conditions, β-ketosulfoxides having thiophene nuclei (7, 8, 9 and 17) gave the corresponding benzothiophene derivatives (Table II), though the yields were lower than those of indole derivatives (Table I) in all cases. The results, together with the failure of the cyclization of furan β-ketosulfoxide, indicate that the product yields reflect the reactivities of pyrrole, thiophene and furan nuclei toward the electrophilic species.

Indole β-ketosulfoxides (19-21) gave similarly carbazole derivatives in good yields (Table III). Tryptophan derivative 22, as well as thiophene amino acid derivative 17, under the aromatization conditions gave an oxazole



7, R=H
8, R=CONHC$_6$H$_5$
9, R=CH$_2$CO$_2$Me



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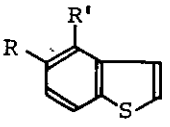
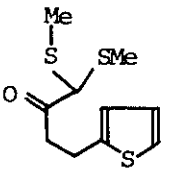


11, R=OH, R'=H
12, R=SMe, R'=H
13, R=OMe, R'=H
14, R=OH, R'=CONHC$_6$H$_5$



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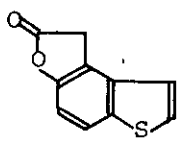

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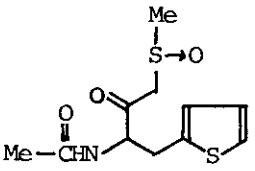

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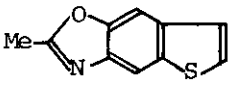

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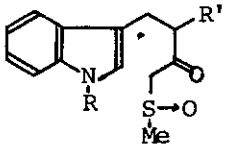
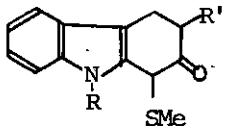
Table II. Cyclization of thiophene β-ketosulfoxides to benzothiophenes

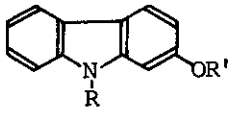
compd	acid	solvent	product[4]	yield(%)	mp°C
7	CF_3CO_2H	C_6H_6	10	50	oil
7	TsOH	MeCN	11	56	104-105[6]
			12	14	41-42
			15	7	oil
7	CCl_3CO_2H	MeCN-MeOH	13	22	38-40[7]
8	TsOH	C_6H_6	14	55	190-192
9	TsOH	C_6H_6	16	25	121-123
17	TsOH	MeCN	18	53	76-77



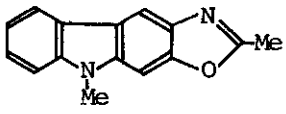
19, R=Me, R'=H
20, R=$CH_2C_6H_5$, R'=H
21, R=H, R'=H
22, R=Me, R'=NHAc



23, R=Me, R'=H
24, R=$CH_2C_6H_5$, R'=H



25, R=Me, R'=H
26, R=Me, R'=Me
27, R=Me, R'=Et
28, R=H, R'=H



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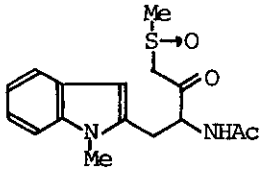

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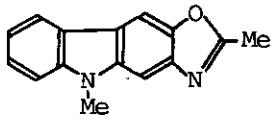

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Table III. Cyclization of indole β-ketosulfoxides to carbazoles

compd	acid	solvent	product[4]	yield(%)	mp°C
19	TsOH	THF	23	82	147-148
20	TsOH	THF	24	60	132-133
19	TsOH	dioxane	25	54	161-164[8]
19	TsOH	acetone-MeOH	26	47	97-98[8]
19	TsOH	acetone-EtOH	27	40	76-78
21	TsOH	MeCN	28	40	255-261[8]
22	TsOH	MeCN	29	80	180-181
30	TsOH	MeCN	31	trace	200-202

derivative 29. Isotryptophan derivative 30 gave an isomeric oxazole 31, though in very poor yield.

It is believed that formation of 2,3-disubstituted indoles by electrophilic substitution in 3-substituted indoles involves initial formation of 3,3-disubstituted indolenines, followed by rearrangement, rather than direct substitution at the 2-position.[9] This may also be the mechanism in the cyclization of β-ketosulfoxides, because we recently isolated an initially formed indolenine as an intramolecular trapping product, of which will report soon.

There are many useful synthetic methods of condensed heterocycles such as indoles and benzothiophenes, which consist of building up of pyrrole and thiophene rings, not benzene ring. Nevertheless the cyclization of β-ketosulfoxides presented here may provide a potential new method in the area of heterocyclic chemistry for the following reasons. 1) The starting materials, β-ketosulfoxides, are easily synthesized from the corresponding esters and dimsyl sodium.[10] 2) Two types of compounds, cyclic β-ketosulfides (3, 10, 23 and 24) and aromatized compounds are obtained separately by the choice of the reaction conditions. 3) Since this synthetic method is characterized with regard to building up of phenyl nucleus different from the conventional methods, it is facilitated to introduce certain substituents on the phenyl nucleus, because they can be introduced prior to cyclization; e. g., syntheses of 6, 14 and 16.

Further synthetic application of this reaction is in progress.

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