

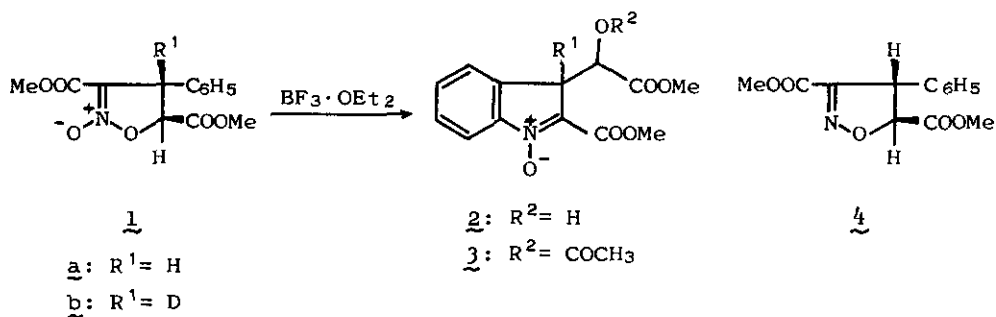
BORON TRIFLUORIDE-PROMOTED TRANSFORMATION OF 3,5-BIS(METHOXY-CARBONYL)-4-PHENYLISOXAZOLINE N-OXIDE INTO 3H-INDOLE N-OXIDE DERIVATIVE¹

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Abstract — 3,5-Bis(methoxycarbonyl)-4-phenylisoxazoline N-oxide (1a) was readily transformed into 3H-indole N-oxide derivative (2a) by the reaction with boron trifluoride etherate in reasonable yield. Mechanism of the transformation was found to involve an ionic intermediate (5), generated by rupture of the nitrogen-oxygen bond, which cyclizes to 3H-indole N-oxide through an intramolecular aromatic substitution. Evidence for the proposed mechanism was obtained by the reaction of 4-phenylisoxazoline-4-d N-oxide (1b) with boron trifluoride to form the expected 3H-indole-3-d N-oxide (2b), as well as by stereochemical consideration.

Synthetic utility of isoxazolines as a vehicle to construct functionalized carbon skeletons has recently been described by Jäger, *et al.*² Despite the analogous structure with isoxazolines, isoxazoline N-oxides would be expected to give rise to unique transformations, inasmuch as they serve as cyclic nitronic esters.³ To our knowledge, however, there have been only few reports^{3,4} of cases in which isoxazoline N-oxides were converted into isoxazoles, γ-amino alcohols, and cyclic oxides by the action of several bases, zinc-acetic acid, and Grignard reagent, respectively. No example of an efficient reaction of isoxazoline N-oxides with acids has appeared. In connection with our current interest in isoxazoline N-oxides,⁵ action of several kinds of acid, *e.g.* mineral acids and Lewis acids, on *trans*-3,5-bis(methoxycarbonyl)-4-phenylisoxazoline N-oxide⁶ (1a) was examined. We wish to report here a new type of transformation of 4-phenylisoxazoline N-oxide (1a) into 3H-indole N-oxide derivative (2a) by the action of boron

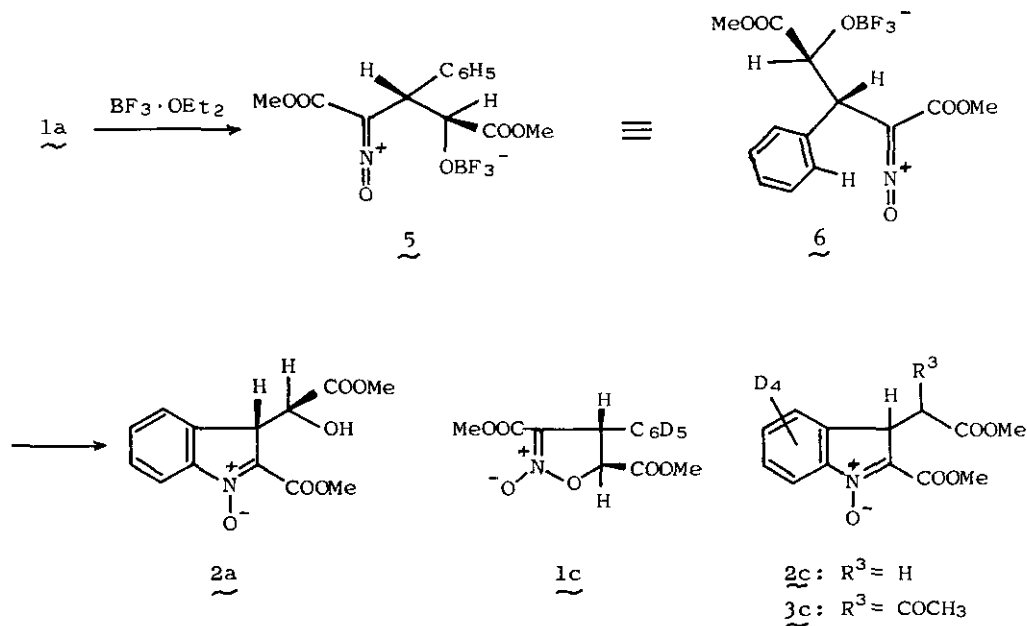


Scheme 1

trifluoride etherate as shown in Scheme 1 and the reaction mechanism thereof. Compound 1a, readily obtained from benzaldehyde and methyl nitroacetate, was treated with excess boron trifluoride etherate in benzene at 0-5°C for 0.5 h. After stirring at room temperature for additional 1 h, the mixture was quenched with 10 % aqueous sodium carbonate and extracted with benzene. The extract was concentrated and purified through a column of silica gel with ethyl acetate-chloroform (1:4) as eluant, affording 3-hydroxymethyl-2,1'-bis(methoxycarbonyl)-3H-indole N-oxide (2a) in 48 % yield: mp 84-85°C (ethyl acetate-hexane); IR (KBr) cm^{-1} : 3400 (OH), 1750-1700 (ester C=O), 1615 (C=N); UVmax (MeOH) nm (log ϵ): 282 (3.62); ^{13}C -NMR (CDCl₃) δ : 37.7 (C-3), 53.0 and 53.3 (ester Me), 73.2 (C-1'), 115.2 (C-2), 147.9 (C-8), 152.3 (C-9), 163.1 and 172.3 (ester C=O), 114.2, 125.4, 128.2 and 129.2 (C-4,5,6 and 7); MS m/e : 279 (M^+). Elemental analysis gave satisfactory results.

^{13}C - and 1H -NMR spectra of 2a (summarized above and in Table I, respectively) clearly confirmed its structure comprising a single diastereomer. 2a was readily acetylated with acetic anhydride in pyridine, giving 3a in 86 % yield; mp 109-110°C (ethyl acetate-hexane), which was characterized by its spectral and elemental analysis.

Transformation of 1a into 2a is specified from isoxazoline N-oxide, while the same treatment of the corresponding isoxazoline (4), prepared from 1a by deoxygenation with triethyl phosphite, resulted in quantitative recovery of 4. A possible reaction mechanism of the transformation is illustrated in Scheme 2; the initial electrophilic attack of boron trifluoride to 1a causes the cleavage of nitrogen-oxygen bond to give the intermediate (5), and subsequent intramolecular displacement of an aromatic proton at ortho-position by the nitrosonium



Scheme 2

species in a rotamer (6) furnishes 3H-indole N-oxide (2a). This mechanism is supported by the following facts. A selectively deuterated isoxazoline-4-d N-oxide⁵ (1b), prepared from benzaldehyde-1-d⁷ and methyl nitroacetate, was used for this reaction. Treatment of 1b with boron trifluoride exclusively gave the expected 2b which, as well as its O-acetate (3b), was manifestly characterized by its ¹H-NMR spectra as shown in Table I. Additional evidence is given by stereochemical considerations. The route of Scheme 2 progresses with retention of the relative configuration of the starting material (1a), trans-configuration of which gives the intermediates (5 and 6) with erythro-configuration, and subsequently defined the product (2a) uniformly as shown in Scheme 2. This would agree well with spectral data (¹³C- and ¹H-NMR) of 2a described above, in which no other isomers of 2a was detected. Furthermore, the formation of 2c from 1c may suggest that the transformation involved no concerted proton rearrangement.

It should be noted that this transformation appears to be a facile and efficient way of obtaining substituted 3H-indole N-oxides from readily available starting materials. Application of this reaction to other isoxazoline N-oxides possessing a substituted phenyl group are now in progress.

Table I. $^1\text{H-NMR}$ Data of 3H-Indole N-Oxides: 6 in CDCl_3

Compd.	OH	ester Me	H-3	H-1'	H-4,5,6,7
2a	3.05(m)	3.71, 3.96(s)	4.31 ~ 4.44(m)	—	7.0~7.4(m)
2b	3.12(d)	3.75, 3.95(s)	—	4.40(d)	7.0~7.4(m)
2c	3.02(m)	3.70, 3.92(s)	4.25 ~ 4.43(m)	—	—
3a	2.06(s) ^{a)}	3.72, 3.94(s)	4.61(d)	5.08(d)	7.0~7.4(m)
3b	2.07(s) ^{a)}	3.73, 3.95(s)	—	5.09(s)	7.0~7.4(m)
3c	2.05(s) ^{a)}	3.70, 3.93(s)	4.61(d)	5.08(d)	—

a) A signal for COCH_3 .

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Received, 1st October, 1979