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SYNTHESIS OF DIHYDRO- AND TETRAHYDROISOXAZOLO[3',4':3,4]PYRROLO[1,2-a]INDOLES VIA INTRAMOLECULAR CYCLOADDITIONS. A NOVEL CLASS OF MITOMYCIN ANALOGUES[1]

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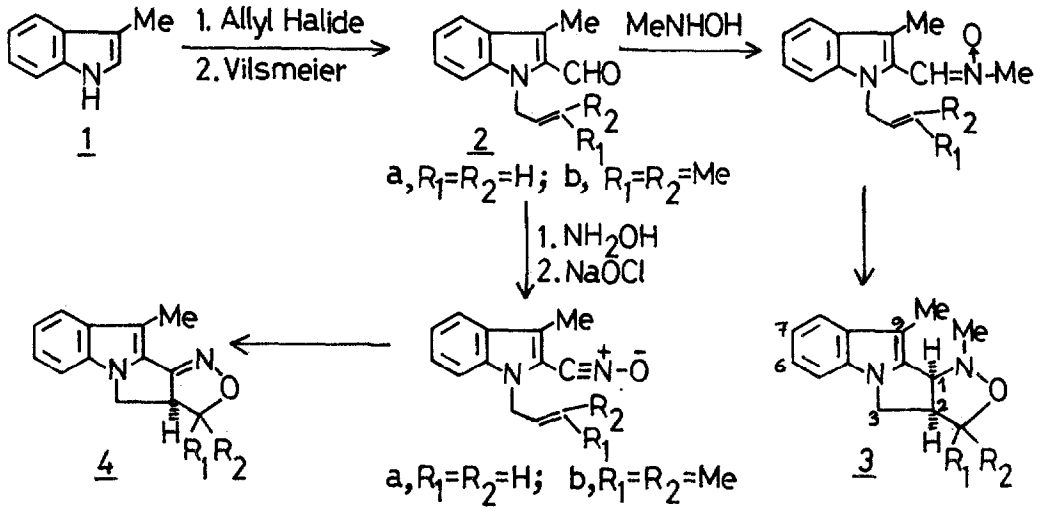
Abstract: *A novel class of dihydro- and tetrahydroisoxazolo[3',4':3,4]pyrrolo[1,2-a]indoles are synthesized via intramolecular nitrone and nitrile oxide cycloaddition reactions.*

The potent antitumour antibiotic Mitomycins[2] have attracted a great deal of interest and a variety of molecular manipulations have been reported without loss of any significant biological activities[3]. Although numerous C_1-fused furan, thiophen and pyridine annelated Mitomycins are reported they have their limitations due to the fact that these heterocycles are not prone to ring transformations. The dihydro- and tetrahydroisoxazoles have rich chemistry because of their ready reductive cleavage[5] and susceptibility to ring transformations[6]. Therefore, we envisioned[7,8] the syntheses of C_1-fused dihydro- and tetrahydroisoxazoles analogues of Mitomycins using cycloaddition strategy. Undoubtedly intramolecular cycloaddition reactions have emerged as single powerful methodology for the construction of bicyclic and polycyclic ring system. Our approaches for the synthesis of these target molecules involve intramolecular nitrone and nitrile oxide cycloaddition reactions.



2-Formyl-3-methyl-N-allylindoles (2) are obtained from 3-methylindole by condensation with allyl halide under phase transfer catalysis followed by Vilsmeier reactions (88%). Treatment of 2a with methylhydroxylamine yielded nitrone which underwent intramolecular cycloaddition to give 9-methyl-tetrahydroisoxazolo[3',4':3,4]pyrrolo[1,2-a]indole(3a), in excellent yield[9a]. Similar treatment of hydroxylamine with 2a followed by hypochlorite oxidation generated the nitrile oxide which cycloadded with the N-allyl group to afford 9-methyl-dihydroisoxazolo[3',4':3,4]pyrrolo[1,2-a]indole

(4a) in 75% yield[10a].

Table : Preparation of 3 and 4 intramolecular cycloaddition reactions[11]

Compound	R_1	R_2	Yield %	M.p. °C	Ms(M^+) m/e
3a	H	H	82	160	228
3b	CH_3	CH_3	80	102	256
4a	H	H	75	118	212
4b	CH_3	CH_3	72	98	240

These compounds 3 and 4 possessing suitably pliable heterocycles have tremendous potentiality as a precursor to various Mitomycin analogues. In addition to this the presence of the C-9 methyl group also enhances its importance due to possibility of side chain manipulations at the C-10 nucleophilic bio-reductive site.

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9. (a) 3a: ^{1}H NMR (200 MHz, $CDCl_3$), δ2.36 (s,3H), 2.84 (s,3H) 3.90 (m,1H), 4.05 (m,2H), 4.20 (d,1H), 4.35 (m,2H), 7.06-7.26 (m,3H), 7.60 (d,1H).
   (b) 3b: ^{1}H NMR (200 MHz, $CDCl_3$), δ1.45 (s,3H), 1.50 (s,3H), 2.35 (s, 3H), 2.80 (s,3H), 3.45 (m,1H), 3.95 (m,2H), 4.15 (d,1H), 7.02-7.33 (m,3H), 7.55 (d,1H).
10. (a) 4a: ^{1}H NMR (200 MHz, $CDCl_3$), δ2.33 (s,3H), 4.10 (d,2H), 4.40 (d,2H), 4.65 (m,1H), 7.15-7.35 (m,3H), 7.55 (d,1H).
    (b) 4b: ^{1}H NMR (200 MHz, $CDCl_3$), δ1.73 (s,3H), 1.80 (s,3H), 2.33 (s,3H), 4.46 (d,2H), 4.70 (t,1H), 7.00-7.33 (m,3H), 7.53 (d,1H).
11. All new compounds reported here gave satisfactory elemental analysis.

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