188. Thermal Valence Rearrangements of Heterocycles

Part 2

A New Synthetic Approach Towards the Indole Ring System

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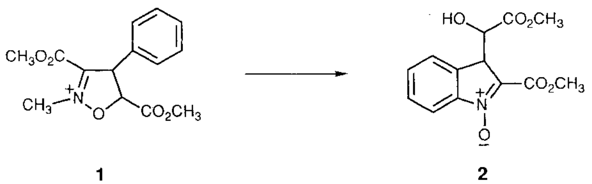
A new synthetic approach towards the indole ring system is described. When dimethyl 1-methyl-2-oxa-1-azaspiro[4.5]dec-3-ene-3,4-dicarboxylate (**6**) was refluxed in toluene, the previously known dimethyl 4,5,6,7-tetrahydro-1-methyl-1*H*-indole-2,3-dicarboxylate (**7**) was obtained in 71% yield, *via* a 2,3-dihydroisoxazole-pyrrole rearrangement. After treatment with DDQ, the tetrahydro analogue **7** was converted to the corresponding dimethyl 1-methyl-1*H*-indole-2,3-dicarboxylate (**8**).

Introduction. – The ability of oxazoles and isoxazoles to undergo chemical transformations to other heterocyclic rings has been studied extensively [1]. Isoxazoles and dihydroisoxazoles have been known to convert to a variety of four- and five-membered rings such as Δ^1-azirines [2], pyrroles [3], pyrazoles [4], imidazoles [5], oxazoles [2a–c][6], thiazoles and isothiazoles [7], 1,2,3- and 1,2,4-triazoles [8], and furazanes [9], as well as a number of six-membered heterocycles [1]. Furthermore, other ring transformations of isoxazole derivatives may prove to be of considerable synthetic value in obtaining some fused heterocyclic rings which otherwise would be difficult to prepare. One such example is the 4,5-dihydro-3,5-bis(methoxycarbonyl)-4-phenyl-2-isoxazolium (**1**) [10] which, in the presence of *Lewis* acid ($TiCl_4$, $BF_3 \cdot Et_2O$), was found to rearrange to an indole, the 1-oxido-3*H*-indole-3-acetate **2** [11] *(Scheme 1)*.

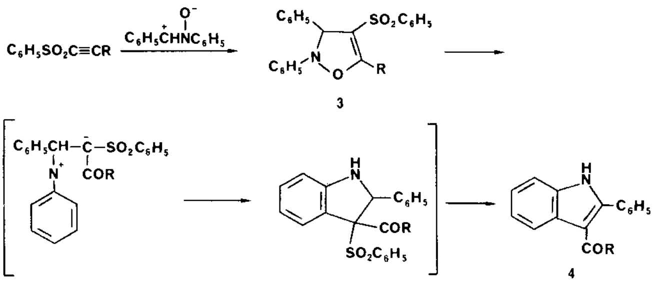
Scheme 1



1 **2**

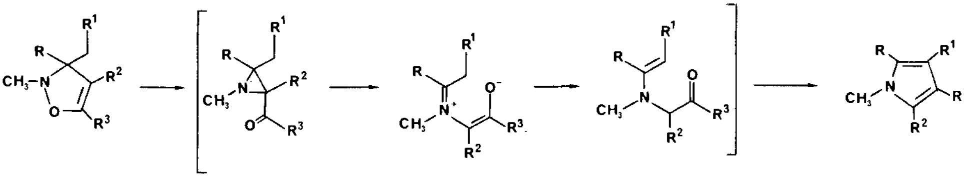
In the same vein, *Parpani* and *Zecchi* [12] reported the preparation of 3-acylindoles (**4**) by 1,3-dipolar cycloaddition reaction of (phenylsulfonyl)alkynes and *C*,*N*-diphenylnitrones *via* the intermediate 2,3-dihydroisoxazole cycloadducts **3** *(Scheme 2)*.

Scheme 2



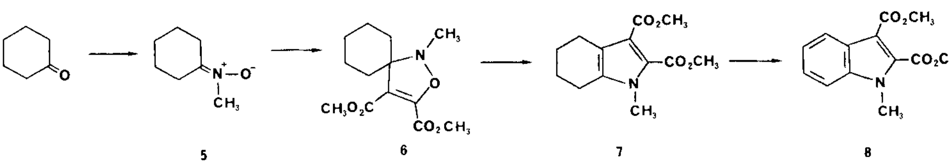
Chemistry. – Previously [13], we have studied the preparation of a series of 2,3,4,5-tetrahydro- and 2,3-dihydroisoxazoles *via* 1,3-dipolar cycloadditions of α-substituted keto-nitrones with appropriate dipolarophiles. In this communication, we describe a new synthetic approach towards the indole ring system utilizing 2,3-dihydroisoxazole-pyrrole rearrangement of a cyclohexylspiro-2,3-dihydroisoxazole precursor. As reported earlier [14], 2,3-dihydroisoxazoles are known to transform readily to the corresponding pyrrole derivatives *(Scheme 3)*.

Scheme 3



We reasoned that a precursor such as the cyclohexylspiro-2,3-dihydroisoxazole **6** may undergo, in a similar fashion, a 2,3-dihydroisoxazole-pyrrole rearrangement to furnish the corresponding 4,5,6,7-tetrahydroindole ring system **7**. Indeed, when dimethyl 1-methyl-2-oxa-1-azaspiro[4.5]dec-3-ene-3,4-dicarboxylate (**6**; easily prepared from the known cyclohexanone nitrone **5** [15]) was refluxed in toluene, the previously reported [16] dimethyl 4,5,6,7-tetrahydro-1-methyl-1*H*-indole-2,3-dicarboxylate (**7**) was obtained in 71% yield. After treatment with DDQ, **7** was converted to the known dimethyl 1-methyl-1*H*-indole-2,3-dicarboxylate (**8**) [17] *(Scheme 4)*.

Scheme 4



The preparation of diester **8** represents a novel and efficient approach towards indole heterocycles that may prove beneficial in providing a general access to this ring system because of its simplicity and ready accessibility of starting material.

Experimental Part

General. M.p.: *Thomas-Hoover* cap. melting-point apparatus; uncorrected. IR spectra (KBr): *Nicolet-MX-1-FT* spectrometer. ^{1}H-NMR spectra: *Varian-EM-360-A* (60 MHz) spectrometer; TMS as internal standard. All spectra were consistent with the assigned structures.

Dimethyl 1-Methyl-2-oxa-1-azaspiro[4.5]dec-3-ene-3,4-dicarboxylate (**6**). A mixture of cyclohexanone (12.3 ml, 0.119 mol), *N*-methylhydroxylamine hydrochloride (10.0 g, 0.119 mol), and AcONa (19.5 g, 0.238 mol) in 150 ml of abs. EtOH was stirred at r.t. for 24 h. Following the addition of $NaHCO_3$ (40.0 g, 0.476 mol), the mixture was filtered and the filtrate concentrated, leaving 13.6 g of nitrone **5** as an unstable oily material which was used immediately in the next step. To a stirred soln. of **5** (12.11 g, 0.095 mol) in 100 ml of toluene, dimethyl acetylenedicarboxylate (17.55 ml, 0.143 mol) was added dropwise, while keeping the temp. at 0°. The mixture was stirred an additional 20 min at 0° then allowed to warm to amb. temp. After the removal of the solvent, the resulting dark-colored oil was purified by flash chromatography on neutral silica gel using hexane/AcOEt 8:2, yielding 14.8 g (58%) of **6**. M.p. 54–56° (hexane). Anal. calc. for $C_{13}H_{19}NO_5$: C 57.98, H 7.11, N 5.20; found: C 57.72, H 7.12, N 5.20.

*Dimethyl 4,5,6,7-Tetrahydro-1-methyl-1*H*-indole-2,3-dicarboxylate* (**7**). A soln. of **6** (2.0 g, 7 mmol) in 75 ml of toluene was refluxed for 48 h, then the solvent was evaporated and the resulting orange oil was purified by flash chromatography on neutral silica gel using hexane/AcOEt 8:2. The resulting pure material (1.32 g, 71%) was crystallized from AcOEt/hexane. M.p. 70–73°([16a]: 79–81° (Et_2O/petroleum ether)). Anal. calc. for $C_{13}H_{17}NO_4$: C 62.14, H 6.82, N 5.57; found: C 62.12, H 6.94, N 5.48.

*Dimethyl 1-Methyl-1*H*-indole-2,3-dicarboxylate* (**8**). A soln. of **7** (2.0 g, 8 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 5.42 g, 24 mmol) in 100 ml of benzene was refluxed for 16 h, then filtered and the filtrate evaporated leaving crude **8**, which was purified by flash chromatography on neutral silica gel ($CHCl_3$): 0.92 g (46%) of crystalline **8**. M.p. 37–40° ([17]: 35° (Et_2O/petroleum ether)). Anal. calc. for $C_{13}H_{13}NO_4$: C 63.15, H 5.30, N 5.66; found: C 63.21, H 5.36, N 5.65.

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