REACTIONS WITH CHLOROSULFONYL/CHLOROCARBONYL ISOCYANATES: SYNTHESIS OF PYRROLO[1,2,3-de]-1,2,4-BENZOTHIADIAZIN-3(2H)-ONE 1,1-DIOXIDES AND 1H-PYRROLO[3,2,1-ij]QUINAZOLINE-1,3(2H)-DIONES

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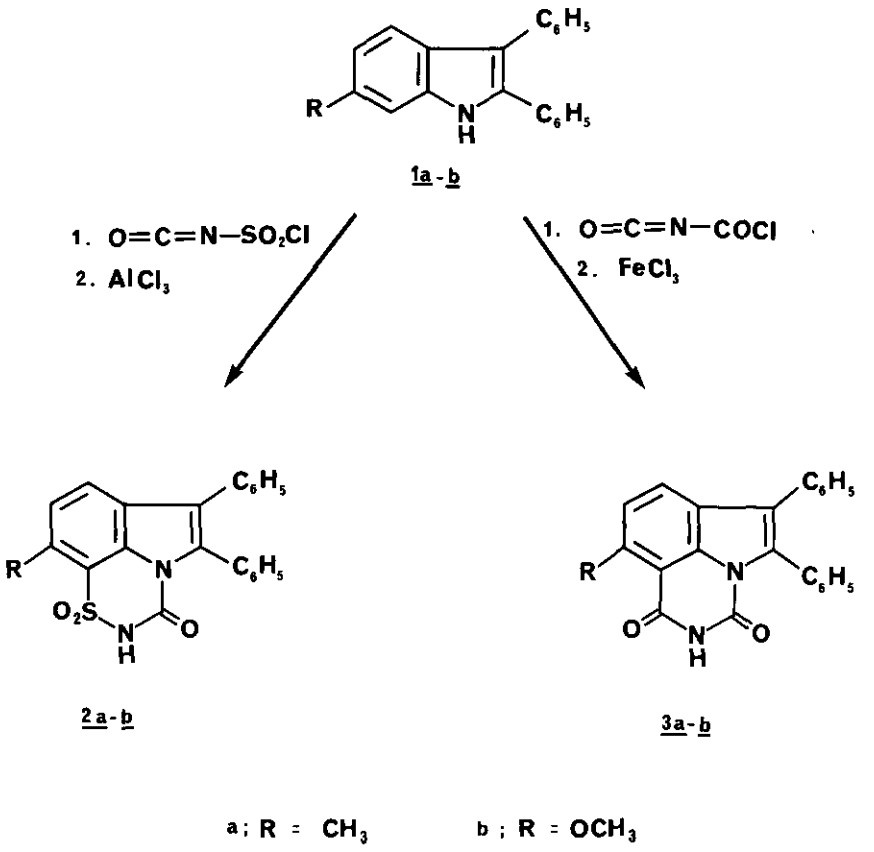
Abstract - 6-Substituted 2,3-diphenylindoles on reaction with chlorosulfonyl/chlorocarbonyl isocyanates, followed by cyclization with aluminium chloride afforded 9-substituted 5,6-diphenylpyrrolo[1,2,3-de]-1,2,4-benzothiadiazin-3(2H)-one, 1,1-dioxides 2 and 9-substituted 5,6-diphenyl-1H-pyrrolo[3,2,1-ij]-quinazoline-1,3(2H)-diones 3 respectively. In these reactions, an electron donating substituent such as methyl group at position 6 in indole is necessary for cyclization.

Recent studies in our laboratory have been concerned with the reactions of chlorosulfonyl isocyanate[1](CSI) and chlorocarbonyl isocyanate[2] (CCI) with bifunctional compounds for the synthesis of a variety of heterocycles[3-5] of biological significance. We have also been interested in the synthesis of fused quinazolines[6] and 1,2,4-benzothiadiazines[7] with a view to explore their biological properties. In continuation of our studies on the applications of CSI and CCI, we investigated the reactions of 2,3-diphenyl-6-substituted indoles[8] with CSI and CCI and found that it leads to the synthesis of pyrrolo[1,2,3-de]-1,2,4-benzothiadiazin and pyrrolo[3,2,1-ij]quinazoline ring systems on cyclization. Reaction of CSI with 2,5-dimethyl indole has been reported[9] to yield N-carbamoylindoles upon hydrolysis of the N-chlorosulfonyl chloride intermediate, but no attempt has been made for the cyclization of the intermediate.

Despite, quinazolines[10] and benzothiadiazines[11] have been investigated intensively, the title ring systems have not been reported previously. Thus, herein, we describe the synthesis of novel class of title compounds and the effect of substituents in cyclizations for these compounds.

Reaction of 2,3-diphenyl-6-methylindole 1a with CSI in nitromethane followed by cyclization with aluminium chloride afforded 9-methyl-5,6-diphenylpyrrolo [1,2,3-de]-1,2,4-benzothiadiazin - 3(2H)-one-1,1-dioxide 2a, whereas reaction of 1a with CCI in nitromethane followed by cyclization with ferric chloride yielded 9-methyl-5,6-diphenyl-1H-pyrrolo[3,2,1-ij]quinazoline-1,3(2H)-dione 3a.

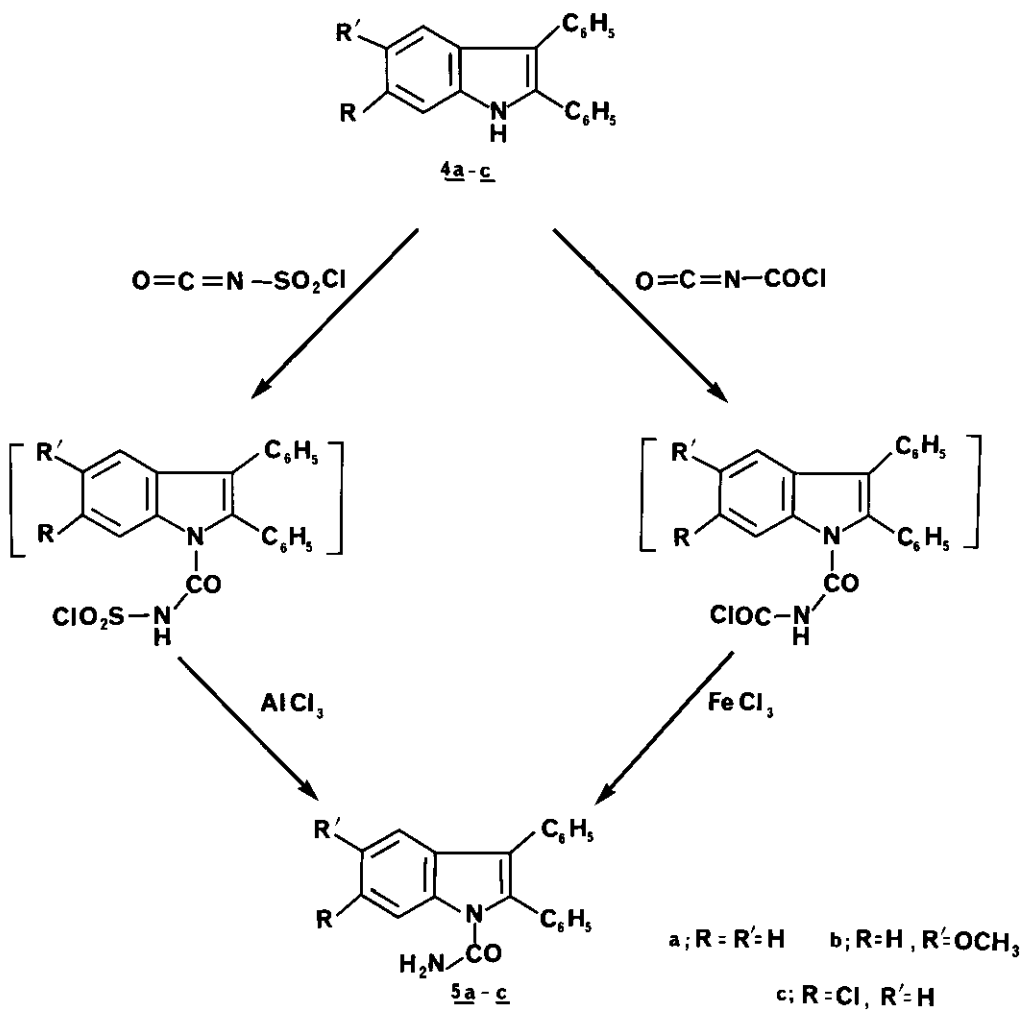


a; R = CH_3 b ; R = OCH_3

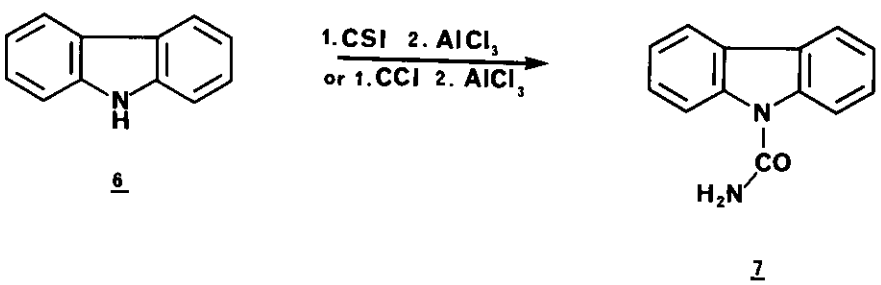
In the similar manner, 2,3-diphenyl-6-methoxyindole 1b on reaction with CSI and CCI gave the corresponding cyclized products 2b and 3b.

With a view to explore the generality of these reactions, unsubstituted 2,3-diphenylindole 4a was reacted with CSI in nitromethane followed by the cyclization step with aluminium chloride. On work-up of the reaction it was observed that the desired cyclized product was not obtained. One of the products thus isolated was characterized as N-carbamoyl-2,3-diphenyl indole 5a. Similarly, the reaction of 4a with CCI also did not afford the desired cyclized product[12].

This observation was further confirmed by reacting CSI and CCI with 5-methoxy and 6-chloro substituted indole 4b and 4c, wherein the desired cyclized products were not obtained. For comparison purpose, 5a was also obtained by the treatment of reaction intermediate of 4a with water.



Reaction of carbazole 6 with CSI and CCI also did not afford the desired cyclized compound, instead N-carbamoylcarbazole 7 was obtained.



Hence, it can be summarized that the presence of an electron donating group at 6-position in 2,3-diphenyl indoles is necessary for the synthesis of title ring systems by the method described here employing CSI and CCI.

EXPERIMENTAL

Melting points were taken using Buchi melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 283B Spectrophotometer in a KBr pellet. ^{1}H NMR spectra were measured with a JEOL FX-90 Fourier transform spectrometer from $CDCl_3$ solution using internal TMS. Mass spectra were recorded on a VG 7070H mass spectrometer at 40 eV.

9-Methyl-5,6-diphenyl Pyrrolo[1,2,3-de]-1,2,4-benzothiadiazin -3(2H)-one 1,1-Dioxide, 2a

General Procedure:

To a solution of 1a (6.49 g, 2.3 mmol) in nitromethane (150 ml), a solution of CSI (2 ml, 2.3 mmol) in nitromethane (5 ml) was added dropwise with stirring at 5-10°C. After the completion of the addition the stirring was continued for 30 min at room temperature. To the reaction mixture was then added anhydrous aluminium chloride (5 g) and refluxed for 1 h. The reaction mixture was poured into cold water (500 ml). The solid precipitated was filtered and washed twice with water (200 ml). It was recrystallized from ethanol and decolourized by animal charcoal to give 4.6 g (52%) of 2a; mp 197-198°C; IR, 3400, 1715, 1600, 1440, 1160 cm^{-1}; ^{1}H NMR: 2.16 s, 6.5-7.7 m, 8.1-9.3 (D_2O exchangeable).

MS, m/z 388 (M^+), 345 (M^+-HNCO), 280 [(M^+-HNCO)-$HSO^{\bullet}_2$].

2b: yield 32%, mp 193-194°C; IR, 3405, 1710, 1605, 1445, 1160 cm^{-1}; MS, m/z 404 (M^+).

9-Methyl-5,6-diphenyl-1H-pyrrolo[3,2,1-ij]quinazoline-1,3(2H)-dione, 3a

General Procedure:

To a solution of 1a (7.04 g, 2.5 mmol) in nitromethane (150 ml), a solution of CCI (2 ml, 2.5 mmol) in nitromethane (8 ml) was added dropwise with stirring at 0-5°C. On completion of the addition the stirring was continued for 1 h at room temperature. To the reaction mixture was then added anhydrous ferric chloride (4 g) and refluxed for 1 h. The reaction mixture was poured into cold water (250 ml). The solid separated was filtered and washed twice with water (150 ml). It was recrystallized from ethanol and decolourized by animal charcoal to give 4.2 g (48%) of 3a; mp 222-225°C; IR, 3480, 1710, 1680, 1605 cm^{-1}; MS, m/z 352 (M^+), 309 (M^+-HNCO), 280 [(M^+-HNCO)-$HCO^{\bullet}$].

3b: yield, 38%; mp 210-214°C; IR, 3475, 1710, 1675, 1600 cm^{-1}; MS, m/z 368 (M^+).

N-Carbamoyl-2,3-diphenyl Indoles, 5

5a: yield, 27%; mp 165-168°C; IR, 3390, 3365, 1675, 1620 cm^{-1}; MS, m/z 312 (M^+).

5b: yield 22%, mp 156-157°C; IR, 3385, 3360, 1680, 1610 cm^{-1}; MS, m/z 342 (M^+).

5c: yield 25%, mp 171-173°C; IR, 3380, 3365, 1675, 1620 cm^{-1}; MS, m/z 346 (M^+).

N-Carbamoylcarbazole, 7

General Procedure:

To a solution of 6 (1.91 g, 1.1 mmol) in nitromethane (150 ml), a solution of CSI (1 ml, 1.1 mmol)/ CCl (0.9 ml, 1.1 mmol) in nitromethane (5 ml) was added dropwise with stirring at 45-50°C. The stirring was further continued after the completion of the addition for 30 min at the same temperature. Then anhydrous aluminium chloride (2 g) was added to the reaction mixture and refluxed for 1 h. On pouring the reaction mixture to the ice cold water (400 ml) the solid separated was filtered and washed twice with water (200 ml). It was recrystallized from ethanol and decolourized by animal charcoal to give 0.8 g (33%) of 7; mp 225-228°C; IR, 3350, 3190, 1670, 1620 cm^{-1}; MS, m/z 210 (M^+), 167 (M^+-HNCO).

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12. These findings suggest that the presence of an electron donating group such as methyl or methoxy at 6-position of indole are essential for the cyclization of chlorosulfonyl/chlorocarbonyl intermediates, whereas, in the absence of such a group the electron density is decreased due to the high degree of resonance in 2,3-diphenyl indole at the site of cyclization.

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