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NOTE

Intramolecular Cyclization of N′-Chloroacetylindole Hydrazide¶

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In this paper, some active class of compounds were synthesized, which are linked to indole nucleus. Various ethyl indole-2-carboxylates (**1a-c**) were prepared according to the Fischer method. These esters (**1a-c**) on reaction with hydrazine hydrate in ethanol yielded substituted indole-2-carboxyhydrazides (**2a-c**). Hydrazides (**2a-c**) on reaction with chloroacetyl chloride in dry dioxane at reflux temperature to get N′-chloroacetylindole hydrazide (**3a-c**). The compounds **3a-c** on reaction sodium hydroxide in dimethyl formamide at reflux temperature with constant stirring gave 5,6-dihydro-5-substituted-3-phenylindole-1,3,4-oxadiazin-5-one (**4a-c**).

Key Words: Synthesis, Cyclization, N′-Chloroacetylindole hydrazide.

Indole and its derivatives have attracted immense research interest due to their applications in pharmacology studies[1,2]. They can also be used in anti-HIV activity and varied biodynamic properties of indole analogues as reported in the literature eariler[3]. On continuation of interest in the synthesis of new medium-sized heterocycles[4] related hydrazine as potential psychopharmacological drug with monoaminooxidase inhibitory properties, the synthesis of 5,6-dihydro-5-substituted-3-phenylindole-1,3,4-oxadiazin-5-one (**4a-c**) is reported.

All melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. The reaction was monitored by TLC, IR spectra were recorded in KBr on Perkin-Elmer (one spectrum). ^{1}H NMR spectra were recorded on AMX-400 (in DMSO, using TMS as internal standard) at Sophisticated Instruments Facility, Indian Institute of Science, Bangalore, India. Resonances are assigned in ppm value. 5-substituted 3-phenylindole-2-carboxyhadrazide (**2a-c**) was prepared according to the literature procedure[5].

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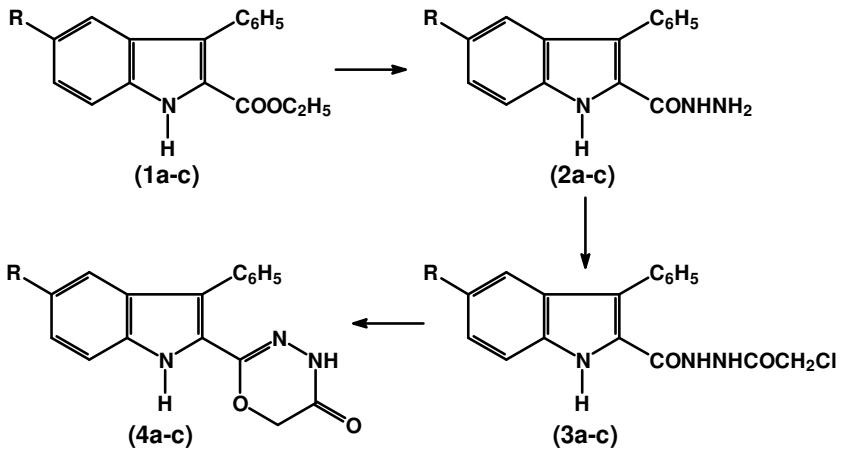
Synthesis of N′-chloroacetylindole hydrazide (3a-c): Mixture of 10 g of indole-2-carboxyaldehyde (**2a-c**), 8.5 g of chloroacetyl chloride in 40 mL of dry dioxane was refluxed for 2 h. After cooling, the crystals were separated and recrystallized from dioxane.

Synthesis of 5,6-dihydro-5-substituted-3-phenylindole-1,3,4-oxadiazin-5-one (4a-c): A mixture of N′-chloroacetylindole hydrazide or N′-substituted-N′-chloroacetylindole hydrazide (**3a-c**), 0.4 g of sodium hydroxide in 25 mL of dimethylformamide was heated at 130 ºC in oil bath for 2 h with stirring and filtered. The solvent was evaporated, the solid obtained was crystallized from ethanol (**Scheme-I**).



Scheme-I

The structures of the synthesized compounds (**3a-c**) were confirmed by their spectral data and elemental analysis (Table-1). IR spectrum of **3a** displayed a peak at 3231 cm^{-1} for indole NH, peak at 3038 cm^{-1} for NH of chloroacetylindole hydrazide and 1684 cm^{-1} for carbonyl functionality. ^1H NMR of **3a** exhibits singlet at 12.2 ppm which can be assigned to NH proton of indole moiety. Resonances at 10.6 ppm and 10.0 ppm can be ascribed to NH/NH of chloroacetyl hydrazide protons.

Compound (**3a-c**) on reaction with NaOH in DMF to yield 5,6-dihydro-5-substituted-3-phenylindole-1,3,4-oxadiazin-5-one (**4a-c**). The compound **4a** exhibited 3312 cm^{-1} for indole NH, 1682 cm^{-1} for cyclic carbonyl group. The ^1H NMR spectrum of compound **4a** exhibits indole NH peak at 12.5 ppm and 11.6 ppm for cyclic NH and 8.3 ppm for cyclic -CH_2, the disappearance of NH group at 10.0 ppm confirms the cyclization of oxadiazine ring.

TABLE-1
ANALYTICAL AND SPECTRAL DATA OF THE COMPOUNDS **3a-c** AND **4a-c**

Compd. (m.f.)	Yield (%) / (m.p. ºC)	Elemental analysis (%): Calcd. (Found)			IR (cm^{-1})	^1H NMR (ppm)
		C	H	N		
3a ($C_{17}H_{13}N_3O_2BrCl$)	62 (240)	50.24 (50.20)	3.20 (3.18)	10.34 (10.32)	3231,NH; 3038,NH; 1684,C=O	12.2, indole NH; 10.6, NH; 10.0, NH; 4.3,CH_2
3b ($C_{17}H_{13}N_3O_2Cl_2$)	55 (260)	56.50 (56.20)	3.60 (3.58)	12.31 (12.30)	3200,NH; 3025,NH; 1690,C=O	12.1, indole NH; 10.4,NH;10.3,NH; 4.3,CH_2
3c ($C_{18}H_{16}N_3O_2Cl$)	64 (232)	59.82 (59.80)	3.81 (3.80)	12.31 (12.30)	3219,NH; 3014,NH; 1684,C=O	12.2, indole NH; 10.5,NH;10.0,NH; 4.3,CH_2
4a ($C_{17}H_{12}N_3O_2Br$)	70 (250)	54.94 (54.92)	3.23 (3.22)	11.31 (11.30)	3212,NH; 1682,C=O cyclic	12.5, indole NH; 11.6,cyclic NH; 8.3, cyclic CH_2
4b ($C_{17}H_{13}N_3O_2Cl$)	54 (262)	62.57 (62.55)	3.68 (3.65)	12.88 (12.86)	3443,NH; 1692,C=O cyclic	12.4, indole NH; 11.6,NH; 8.3, cyclic CH_2
4c ($C_{18}H_{16}N_3O_2$)	68 (258)	66.66 (66.64)	3.92 (3.91)	13.78 (13.76)	3323, NH; 1590, C=O cyclic	12.2, indole NH; 11.2,cyclic NH; 8.6, cyclic CH_2

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