SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL INDOLE DERIVATIVES.

Gangadhar B. Gundlewad[1] Bhagwan R. Patil*
[1] *Department of Chemistry, Shri Shivaji Mahavidyalaya, Parbhani, 431 401 (M.S.) India,*
**Department of Chemistry, Sharda Mahavidyalaya, Parbhani 431 401 (M.S.) India.*

Abstract : A novel series of 2-phenylindoles were synthesized starting from substituted anilines with phenacylchloride. The structures of newly synthesized compounds are clearly supported by their 1H NMR spectra studies and microanalysis.

Keywords: Phenacylchloride, substitutedphenylamine, phenacylanilines.

I. INTRODUCTION

Indole is one of the most important nitrogen containing heterocycle found extensively in biological systems playing vital role in biochemical processes. Indole is the commonly used name for the benzopyrrole ring system, consisting of a benzene ring fused to the 2, 3-positions of a pyrrole ring [1, 2]. The interest and development in indole chemistry was started in mid-nineteenth century, when a violet-blue dye, originally derived from Indigofera species in India studied extensively. Today the synthesis of indole is usually performed from non-heterocyclic precursors by cyclization reaction of suitable substituted benzene. Perhaps the most widely used route is the Fischer indole synthesis [3], which also can be used on a large scale, e.g., for production of the stabilizer 2-phenylindole in manufacture of PVC [4, 5].

Indole ring system is found in many natural products, pharmaceuticals agents and polymer materials. The interesting chemical properties of indole have inspired chemists to design and synthesize a variety of indole derivatives [6]. The 2-aryl indole moiety is present in diverse biologically active molecules displaying antiestrogen [7], anti-inflammatory [8, 9] and cytoxic properties [10]. Indole and its derivative have great importance in clinical chemistry. Indole nucleus has various biological activities such as, Analgesic,[11] Antifungal[12] Anticancer[13] Anti HIV[14] Antiviral[15] etc. In addition it was reported that various substituted indole derivatives used as starting material for the synthesis of many alkaloids, pharmaceuticals and perfumes.

The interesting chemical properties of indole inspired chemist to design and synthesize varieties of indole derivatives. Since the first synthesis of indole in 1866[16], a number of synthetic methods for the construction of the indole nucleus have been devised still today. Several substituted indoles were synthesized from N-substituted anilines and Chloroacetyl chlorie[17], from acetophenone and phenylhydrazine using polyphosporic acid [18], from aryl amines and ethylacetoacetate under nitrogen atmosphere [19], the indoles were also synthesized from acetanilide and alkynes using rhodium catalyst [20], by the reaction of tolylhydrazine hydrochloride with isopropyl methyl ketone in acetic acid at room temperature, [21] sulpha substituted anilines and phynacylbromides [22], paladium catalyzed cross coupling of ammonia and alkynes gives indole derivatives [23]. Literature survey however reveals that no work has been done on synthesis of substituted indole and 2-aryl substituted *1H* indoles using α-chloro-hydroxyacetophenones and substituted anilines and their biological activity. Therfore we have interest to synthesize 2-aryl substituted *1H* indoles and to evaluate their biological activity.

II. EXPIRMENTAL

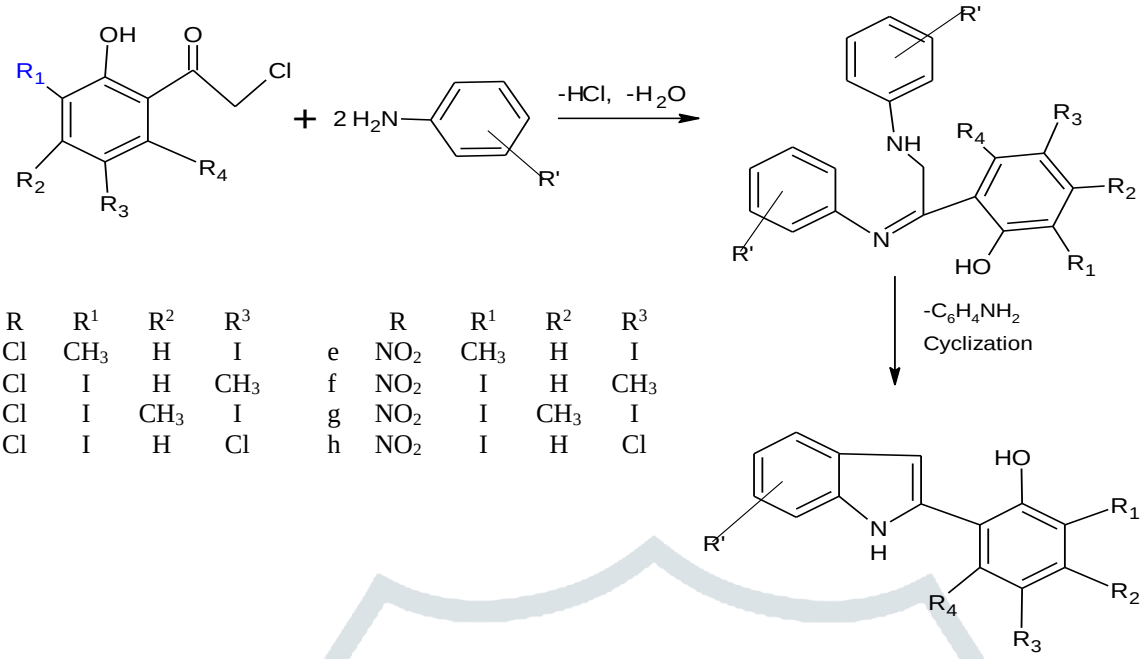
General*:* All the substituted phenyl amine, α-chloroacetophenone, was purchased from Aldrich Chemicals. ethanol, glacial acetic acid and all reagents were used of S. D. Fine Chem. TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

Melting points were determined using an open-ended capillary tube method and are uncorrected. The purity of the synthesized compounds was checked by TLC. FT-IR spectra were recorded on a Perkin-Elmer 1605 series FT-IR in a KBr disc. 1H NMR spectra were recorded at 300 MHz on a Bruker FT-NMR spectrophotometer using TMS as internal standard.

Synthesis of 2-phenylsulpha/substituted indole: A mixture of α-chloroacetophenone and substitutedphenylamine in 1:2 ratio was dissolved in glacial acetic acid and refluxed on water bath for half an hour. On cooling a crystalline solid compound separated out, which is recrystllized from ethyl alcohol as shining crystals (Scheme.1).

2-(5-chloro-1H-indol-2-yl)-4-iodo-6-methylphenol (a) A white crystalline powder, mp 170-172 °C, Yield 73%, IR (KBr) *v*max, 670, 760, 1250, 1550, 3035, 3350, ^{1}NMR (CDCl3) δ in ppm, 10.1 (s 1H), 7.6 (s 1H), 7.3 (d 1H), 7.23 (s 1H), 7.15 (s 1H), 7.1(d 1H) 6.4 (s 1H), 5.0 (s 1H), 2.35 (s 3H), anal. Calcd for $C_{15}H_{11}ClINO$ (382.95): C, 46.96; H, 2.89; Cl, 9.24; I, 33.08; N, 3.65; O, 4.17. Found: C, 46.92; H, 2.88; Cl, 9.22; I, 33.10; N, 3.68; O, 4.18.

2-(5-chloro-1H-indol-2-yl)-6-iodo-4-methylphenol(b) A white crystalline powder, mp 140-142 °C, Yield 70%, IR (KBr) *v*max, 670, 760, 1250, 1550, 3035, 3350, ^{1}NMR (CDCl3) δ in ppm, 10.15 (s 1H), 7.6 (s 1H), 7.3 (d 1H), 7.23 (s 1H), 7.18 (s 1H), 7.11(d 1H) 6.45 (s 1H), 5.1 (s 1H), 2.35 (s 3H), anal. Calcd for $C_{15}H_{11}ClINO$ (382.95): C, 46.96; H, 2.89; Cl, 9.24; I, 33.08; N, 3.65; O, 4.17. Found: C, 46.92; H, 2.88; Cl, 9.22; I, 33.10; N, 3.68; O, 4.18.



	R	R^1	R^2	R^3		R	R^1	R^2	R^3
a	Cl	CH_3	H	I	e	NO_2	CH_3	H	I
b	Cl	I	H	CH_3	f	NO_2	I	H	CH_3
c	Cl	I	CH_3	I	g	NO_2	I	CH_3	I
d	Cl	I	H	Cl	h	NO_2	I	H	Cl

Scheme 1

6-(5-chloro-1H-indol-2-yl)-2,4-diiodo-3-methylphenol (c) A white crystalline powder, mp 149-150 ºC, Yield 75%, IR (KBr) *v*max, 671, 780, 1255, 1552, 3036, 3355, ^{1}NMR (CDCl3) δ in ppm, 9.99 (s 1H), 7.6 (s 1H), 7.3 (d 1H),7.18 (s 1H), 7.11(d 1H) 6.42 (s 1H), 5.08 (s 1H), 2.38 (s 3H), anal. Calcd for $C_{15}H_{10}ClI_2NO$ (509.50) C, 35.36; H, 1.98; Cl, 6.96; I, 49.81; N, 2.75; O, 3.14 Found: C, 35.37; H, 1.96; Cl, 6.98; I, 49.83; N, 2.76; O, 3.15.

4-chloro-2-(5-chloro-1H-indol-2-yl)-6-iodophenol (d) A white crystalline powder, mp 129-131 ºC, Yield 72%, IR (KBr) *v*max, 677, 786, 1255, 1556, 3038, 3359, ^{1}NMR (CDCl3) δ in ppm, 10.11 (s 1H), 7.6 (s 1H), 7.3 (d 1H), 7.25 (s 1H) 7.18 (s 1H), 7.1(d 1H) 6.4 (s 1H), 5.0 (s 1H), anal. Calcd for $C_{14}H_8Cl_2INO$ (404.02) C, 41.62; H, 2.00; Cl, 17.55; I, 31.41; N, 3.47; O, 3.96 Found: C, 41.60; H, 2.01; Cl, 17.54; I, 31.42; N, 3.48; O, 3.96.

4-iodo-2-methyl-6-(5-nitro-1H-indol-2-yl)phenol (e) A white crystalline powder, mp 129-131 ºC, Yield 72%, IR (KBr) *v*max, 677, 786, 1255, 1556, 3038, 3359, ^{1}NMR (CDCl3) δ in ppm, 10.1 (s 1H), 7.6 (s 1H), 7.3 (d 1H), 7.23 (s 1H), 7.15 (s 1H), 7.1(d 1H) 6.4 (s 1H), 5.0 (s 1H), 2.35 (s 3H), anal. Calcd for $C_{15}H_{11}IN_2O_3$ (394.16) C, 45.71; H, 2.81; I, 32.20; N, 7.11; O, 12.18 Found: C, 45.73; H, 2.80; I, 32.21; N, 7.10; O, 12.19.

2-iodo-4-methyl-6-(5-nitro-1H-indol-2-yl)phenol(f) A light yellow crystalline powder mp 139-141 ºC, Yield 71%, IR (KBr) *v*max, 677, 788, 1258, 1557, 1620, 3034, 3358, ^{1}NMR (CDCl3) δ in ppm, 10.1 (s 1H), 7.10 (s 1H), 7.6 (s 1H), 7.3 (d 1H), 7.23 (s 1H), 7.1(d 1H) 6.4 (s 1H), 5.0 (s 1H), 2.35 (s 3H); anal. Calcd for $C_{15}H_{11}IN_2O_3$ (394.16) C, 45.71; H, 2.81; I, 32.20; N, 7.11; O, 12.18 Found: C, 45.73; H, 2.80; I, 32.21; N, 7.10; O, 12.19.

2,4-diiodo-3-methyl-6-(5-nitro-1H-indol-2-yl)phenol(g) A light yellow crystalline powder mp 139-141 ºC, Yield 71%, IR (KBr) *v*max, 677, 788, 1254, 1553, 1622, 3034, 3356, ^{1}NMR (CDCl3) δ in ppm, 9.98 (s 1H), 7.6 (s 1H), 7.3 (d 1H), 7.18 (s 1H), 7.1(d 1H) 6.4 (s 1H), 5.0 (s 1H), 2.35 (s 3H), anal. Calcd for $C_{15}H_{10}I_2N_2O_3$ (394.16) C, 34.64; H, 1.94; I, 48.80; N, 5.39; O, 9.23 Found: C, 34.65; H, 1.93; I, 48.81; N, 5.38; O, 9.25.

4-chloro-2-iodo-6-(5-nitro-1H-indol-2-yl)phenol (h) A light yellow crystalline powder mp 139-141 ºC, Yield 71%, IR (KBr) *v*max, 670, 781, 1255, 1554, 1624, 3036, 3354, ^{1}NMR (CDCl3) δ in ppm, 10.1 (s 1H), 7.65 (s 1H), 7.32 (d 1H), 7.24 (s 1H) 7.19 (s 1H), 7.1(d 1H) 6.42 (s 1H), 5.2 (s 1H), anal. Calcd for $C_{14}H_8ClIN_2O_3$ (414.58) C, 40.56; H, 1.94; Cl, 8.55; I, 30.61; N, 6.76; O, 11.58.

III. RESULT AND DISCUSSION

The present studies consist, of synthesis of substituted anilines with phenacylchloride to give phenacylanilines efficiently which were synthesized by simple mixing with 1:2 molar ratio of both reagents in glacial acetic acid and refluxed on water bath for half an hours, the phenacylaniline underwent rapid cyclisation to from 2-phenylsubstitutedindole and a trace of anilinium halide. The structures of newly synthesized compounds are clearly supported by their 1H NMR spectra studies and microanalysis.

IV. CONCLUSION

In conclusion, there is simple and convenient methods for the synthesis of 2-phenylindoles starting from substituted anilines with phenacylchloride were demonstrated. The synthesized compounds were well characterized by Spectral data.

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