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A NEW METHOD FOR THE SYNTHESIS OF 1-ARYL PHTHALAZINES+

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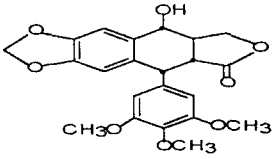
Abstract: A simple versatile method for the conversion of 1-aroyl-2-(substituted benzylidene)-hydrazines to 1-aryl-phthalazines using polyphosphate ester (PPE) is described .

Podophyllotoxin (**1**), a cytotoxic constituent of the plant species podophyllum peltatum has attracted considerable research activities, which culminated in the synthesis of tenoposides, and etoposides, which are now clinically used as antitumor agents[1].



1

Recently some of the aza analogs of **1** have been synthesized by several groups and attract much attention since they retain potent antitumor activity[2].
In our effort to synthesize some of the diaza analogs of **1** for the investigation of their anticancer activity, 1-aryl phthalazines **5(a-c)** were required as intermediates. Barghash reported the synthesis of 1-aryl phthalazines, however in relatively low yield[3]. We now report the cyclodehydration of 1-aroyl-2 substituted benzylidene hydrazines **4**

+ Previous paper: S.Shashikanth and C. Anjanamurthy, Indian *Journal of Chemistry, 1997*, 36B, 572.

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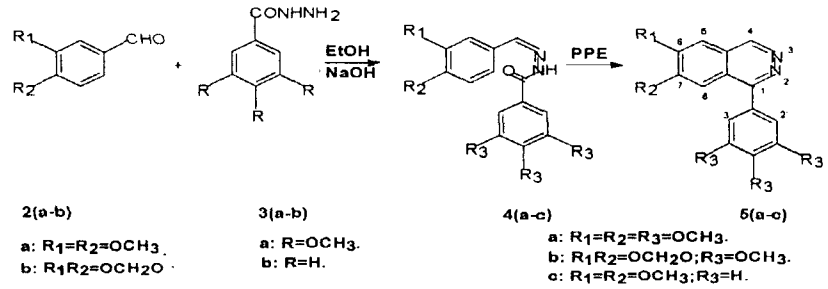
Scheme 1.



(**a-c**) using polyphosphate ester[4] to obtain the corresponding 1-aryl phthalazines **5(a-c)** in excellent yield (scheme 1).

The hydrazines **4(a-c)**, required for the synthesis of **5(a-c)**, were obtained by the condensation of the corresponding benzaldehydes **2(a-b)** and aryl acid hydrazides **3(a-b)** in sodium hydroxide and ethanol[5]. In a typical experiment a solution of 1-(3′,4′,5′-trimethoxy)-benzoyl-2-(3,4-dimethoxy)benzylidene hydrazine (**4a**) in chloroform and polyphosphate ester[4] was refluxed for 3-4 hr. After workup 1-(3′,4′,5′–trimethoxy phenyl)–6,7–dimethoxy phthalazine (**5a**) was obtained as pale yellow crystalline compound in 61 % yield . Structural proof for compounds 5(a-c) were provided by **IR** , **^{1}H NMR** and mass spectral data. The **IR** spectra of substituted benzylidene hydrazine **4(a-c)** showed absorption in the region 3240 to 3140 cm^{-1} and at 1650 cm^{-1} assigned to N-H and amide carbonyl group respectively. In the cyclised product **5(a-c)** the peaks due to amide group was absent but it showed strong **IR** absorption in the region 1622-1630 cm^{-1} assigned to C=N stretching and 1610-1615 cm^{-1} due to N=N stretching frequencies. **^{1}H NMR** spectra of **5(a-c)** showed singlets at δ 7.25 , 7.4 and 9.3 assigned to C_8–H and C_5–H and C_4–H respectively . C_8–H was relatively up field when compared to C_5–H because of the shielding effect of the pendent 3,4,5-trimethoxyphenyl ring . The benzylidene proton of compound **4(a-c)** which showed singlets at δ 8.3 has been converted in to C_4–H in phthalazine **5(a-c)** with δ 9.3 . The down field absorptions of C_4–H in **5(a-c)** was in agreement with the earlier observation[6] .The mass spectra of the compounds **5(a-c)** showed the molecular ion peaks as their base peaks at m\z 356 , 340 and 266 respectively. The mass spectral fragmentation is in accordance with the earlier studies of the mass spectra of phthalazine derivatives[7]

Experimental section:

The Thomas Hoover capillary melting point apparatus determined melting points. **^{1}H NMR** spectra were obtained on Varian A60 spectrometer with tetramethylsilane as an internal reference. **IR** spectra were recorded on a Perkin Elmer Model 399-6B spectrometer. Mass spectra were recorded on Hitachi RMU 67 spectrometer at 70 eV.

General procedure for the preparation of 1-aroyl –2 (substituted benzylidene) – hydrazine 4(a-c) .

To a solution of veratraldehyde (**2a**) (16.6 g, 0.12 mol) and 3,4,5-trimethoxy benzoic acid hydrazide (**3a**) (27 g, 0.1 mol) [prepared from 3,4,5-trimethoxy benzoic acid according to the procedure described by Kudryashova et.al[5].] In dry ethanol (200 mL), sodium hydroxide pellets (3 g) was added and the mixture refluxed for 6 hr. Rotary evaporator to 100 mL concentrated the reaction mixture; the solid separated was filtered and washed repeatedly with hot water. The crude product was recrystallised from ethanol to give 4a as pale yellow crystalline solid. Yield 30.5 g 82 %, m.p 177-78° C. **IR** (nujol): 3240-3140 (N-H), 1660 (shoulder C=N), 1650 (amide C=O), 1590 (aromatic C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.75-3.9 bs, 15H, $5OCH_3$), 6.6-7.1 (m, 3H, Ar-H), 7.25 (bs, 2H, Ar-H), 8.35 (s, 1H, HC=N),8.7 (bs, 1H, NHCO), Mass spectrum m/e (relative intensity) for $C_{19}H_{22}O_6N_2$ 374 (M^+,100), 195(18.9), 167(13.5),164(3.4), 163(15.8),137(11.3). Anal. calcd.C 60.96, H 5.88, N 7.49; found C 60.83, H 5.91, N 7.5%.

4b: yield 72 %, m.p 201-4°C.**IR** (nujol): 3230-3140 (N-H), 1660(shoulder C=N), 1650 (amide C=O) 1600 (aromatic C= C) cm^{-1}; **^{1}H NMR** ($CDCl_3$+ DMSO–D_6): δ 3.8-3.9 , (bs, 9H ,OCH_3), 5.9 (s, 2H, OCH_2O), 6.8 –7.0 (bm, 5H, Ar-H), 8.3 (s, 1H, HC=N), 8.6 (bs, 1H, NHCO); Mass spectrum m/e (relative intensity) for $C_{18}H_{18}O_6N_2$ 358 (M^+,15.5), 211(39.5), 196 (18.3), 195(100).Anal Calcd. C 60.34, H 5.03, N 7.82; found C 60.32, H 5.03, N 7.58.

4c: yield 83 %, m.p 171-72°C. **IR** (nujol): 3200-3100 (N-H), 1660(shoulderC=N), 1650 (amide C=O), 1590 (aromatic C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.5 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 7.0-8.0 (bm, 8H, Ar-H), 8.4 (s, 1H, HC=N), 8.6 (bs, 1H, NHCO); Mass spectrum m/e (relative intensity) for $C_{16}H_{16}O_3N_2$ 284 (M^+, 100), 164 (5.3), 163 (11.8), 137(8.9), 105(42.5), 77(8.3). Anal. calcd. C 67.61, H 5.36, N 9.86; found C 67.57, H 5.61, N 9.89.

General procedure for preparation of 1-aryl phthalazines 5(a-c).

A mixture of 4a (6 g, 0.016 mol) and freshly prepared polyphosphate ester (**PPE**) (60 mL) [prepared from refluxing a mixture of phosphorus pentoxide (75 g), diethyl ether (75 mL) and chloroform (150 mL) until the solution was clear][4] were refluxed for 10 hr in anhydrous condition The cooled reaction mixture (5-10 °C) was poured onto ice (250 g), basified by adding 10 % NH_4OH and stirred for 15 minutes. The organic layer was separated and washed with 5% sodium hydroxide solution (3 x 30 ml) and finally with water. After evaporating the solvent, the solid was recrystallised from benzene to give pale yellow crystalline solid 5a, yield 3.5g (61%) m.p 173-74°C; IR (nujol): 1630(C=N), 1590 (aromatic C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.9 (s, 9H, 3xOCH_3), 4.1 (s, 6H, C_6 & C_7 –OCH_3), 7.05 (s, 2H, C_2-H & C_6–H),7.25 (s, 1H, C_8–H), 7.4(s, 1H, C_5–H), 9.3 (s, 1H, C_4–H); Mass spectrum m/e (relative intensity) for $C_{19}H_{20}O_5N_2$ 356 (M^+,100), 329 (M^+–HCN 26.1), 328(M^+–N_2, 15.4), 297(6.1),189(26.9), 161(13.8). Anal. Calcd C 60.05, H 5.62, N 7.87; found C 60.09, H 5.61, N 7.88.

5b: Recrystallised from ethanol, yield 62 %, m .p 204-6°C. **IR** (nujol): 1620(C=N), 1580 (aromatic C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.9(s, 9H, 3xOCH_3) 6.2(s, 2H, OCH_2O), 6.9 (s, 2H, C_2–H & C_6–H), 7.2(s, 1H, C_8–H), 7.3(s, 1H, C_5–H), 9.3(s, 1H, C_4–H); Mass spectrum m/e (relative intensity) for $C_{18}H_{16}O_5N_2$: 340(M^+, 100), 313(M^+-HCN, 25.0), 312 (M^+–N_2 , 22.0), 295 (20.0), 265(25.0). Anal.calcd C 63.36, H 4.71, N 8.24, found C 63.54, H 4.71, N 8.23.

5c: Recrystallised from ethanol, yield 78 %; m .p 167—68°C. **IR** (nujol): 1625 (C=N), 1590 (aromatic C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 4.0 (s, 6H, 2xOCH_3), 7.2-7.4(m, 7H, Ar-H), 9.4 (s, 1H, C_4–H), Mass spectrum m/e (relative intensity) for $C_{16}H_{14}O_2N_2$ 266 (M^+, 100), 239(M^+–HCN, 31.3), 238(M^+–N_2, 12.6), 189(M^+–C_6H_5, 32.2), 61(17.8) Anal.calcd C 72.18, H 5.26, N 10.53.found C 72.20, H 5.25, N 10.55.

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