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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-arylox-2-(substituted benzyldiene)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.

Recently some of the aza analogs of 1 have been synthesized by several groups and attract much attention since they retain potent antitumor activity.

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.

We now report the cyclodehydration of 1-arylox-2 substituted benzyldiene hydrazines 4

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(a-c) using polyphosphate ester\textsuperscript{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\textsuperscript{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\textsuperscript{4} was refluxed for 3-4 hr. After workup 1-(3',4',5'-trimethoxyphenyl)-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, \textsuperscript{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\textsuperscript{-1} and at 1650 cm\textsuperscript{-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\textsuperscript{-1} assigned to C=N stretching and 1610-1615 cm\textsuperscript{-1} due to N=N stretching frequencies. \textsuperscript{1}H NMR spectra of 5(a-c) showed singlets at δ 7.25, 7.4 and 9.3 assigned to C\textsubscript{8}-H and C\textsubscript{5}-H and C\textsubscript{4}-H respectively. C\textsubscript{8}-H was relatively up field when compared to C\textsubscript{5}-H because of the shielding effect of the pendant 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\textsubscript{4}-H in phthalazine 5(a-c) with δ 9.3. The down field absorptions of C\textsubscript{4}-H in 5(a-c) was in agreement with the earlier observation\textsuperscript{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\textsuperscript{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-aryl-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\(_3\)): \(\delta\) 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\(_6\)N\(_2\) 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\(_6\)): \(\delta\) 3.8-3.9 , (bs, 9H ,OCH\(_3\)), 5.9 (s, 2H, OCH\(_2\)O), 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\(_{10}\)O\(_6\)N\(_2\) 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(shoulder C=N), 1650 (amide C=O), 1590 (aromatic C=C) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 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\(_{18}\)H\(_{16}\)O\(_3\)N\(_2\) 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] 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 % NH₄OH 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; ¹H NMR (CDCl₃): δ 3.9 (s, 9H, 3xOCH₃), 4.1 (s, 6H, C₆ & C₇-OCH₃), 7.05 (s, 2H, C₂-H & C₆-H), 7.25 (s, 1H, C₅-H), 7.4 (s, 1H, C₆-H), 9.3 (s, 1H, C₇-H). Mass spectrum m/e (relative intensity) for C₁₉H₂₀O₂N₂: 356 (M⁺,100), 329 (M'-HCN 26.1), 328(M'-N₂, 15.4), 297(6.1),189(26.9), 161(13.8). Anal. Caled 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; ¹H NMR (CDCl₃): δ 3.9 (s, 9H, 3xOCH₃), 6.2 (s, 2H, OCH₂O), 6.9 (s, 2H, C₂-H & C₆-H), 7.2 (s, 1H, C₅-H), 7.3 (s, 1H, C₆-H), 9.3 (s, 1H, C₇-H); Mass spectrum m/e (relative intensity) for C₁₉H₂₀O₃N₂: 340(M⁺,100), 313(M'-HCN, 25.0), 312 (M'-N₂, 22.0), 295 (20.0), 265(25.0). Anal. Caled 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; ¹H NMR (CDCl₃): δ 4.0 (s, 6H, 2xOCH₃), 7.2-7.4 (m, 7H, Ar-H), 9.4 (s, 1H, C₄-H); Mass spectrum m/e (relative intensity) for C₁₆H₁₄O₂N₂: 266 (M⁺, 100), 239(M'-HCN, 31.3), 238(M'-N₂, 12.6), 189(M'-C₆H₅, 32.2), 61(17.8). Anal. Caled C 72.18, H 5.26, N 10.53; found C 72.20, H 5.25, N 10.55.

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