SYNTHESIS AND REACTIVITY OF 1,1-DIHYDRO-2-OXIMINO-3-ARYL-3H-NAPHTHO[2,1-b]PYRANS

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Abstract - A series of 1,1-dihydro-2-oximino-3-arylnaphtho[2,1-b]pyrans were synthesised in good yields by reduction of the corresponding 2-nitronaphthopyrans using Raney Nickel and hydrazine hydrate or sodium borohydride in ethanol. Further, the Beckmann rearrangement product on the oxime using phosphorous pentachloride in ether was identified as 1-cyanomethyl-2-naphthol. Whereas using sulfuric acid as the catalyst the product was characterised as 4-arylnaphth[1,2-f][1,4]oxazepine.

Naphthopyrans occur frequently in nature and are of interest because of the occurrence of the benzopyran system in the active constituents of several plants.[1] The 3-substituted naphtho[2,1-b]pyrans have been reported earlier by Livingstone[2,3] and Casiraghi.[4] Introduction of a nitro group by direct substitution is difficult in the naphthopyran ring. There have been no references in literature known of with substituents in the 2-position of the naphthopyran ring. In this connection, the Japanese report[5] on the synthesis of 2-phenyl-3-nitro-3H-benzopyran derivatives was interesting. The condensation of substituted β-nitrostyrenes (**1**) with 2-naphthol-1-aldehyde (2) in triethylamine resulted in compounds which were characterised on the basis of spectral data as 2-nitro-3-aryl-3H-naphtho[2,1-b]-pyrans (**3a-d**) (Table 1).

The reduction of the nitro group to an amino group was not successful either by metal acid combination (zinc/HCl) or by ferrous sulphate in distilled water. Then the use of Raney nickel and hydrazine hydrate was attempted. However, the product obtained was not the expected amino compound but an oximino product. The pmr spectrum of **4a** revealed a one proton singlet at δ 11.51 due to the hydroxyl proton, which disappeared on deuterium exchange. On the basis of analytical, ir, pmr, and mass spectral data, the structure of **4a** was confirmed as 1,1-dihydro-2-oximino-3-phenyl-3H-naphtho[2,1-b]pyran. (Table I, Scheme I). It is

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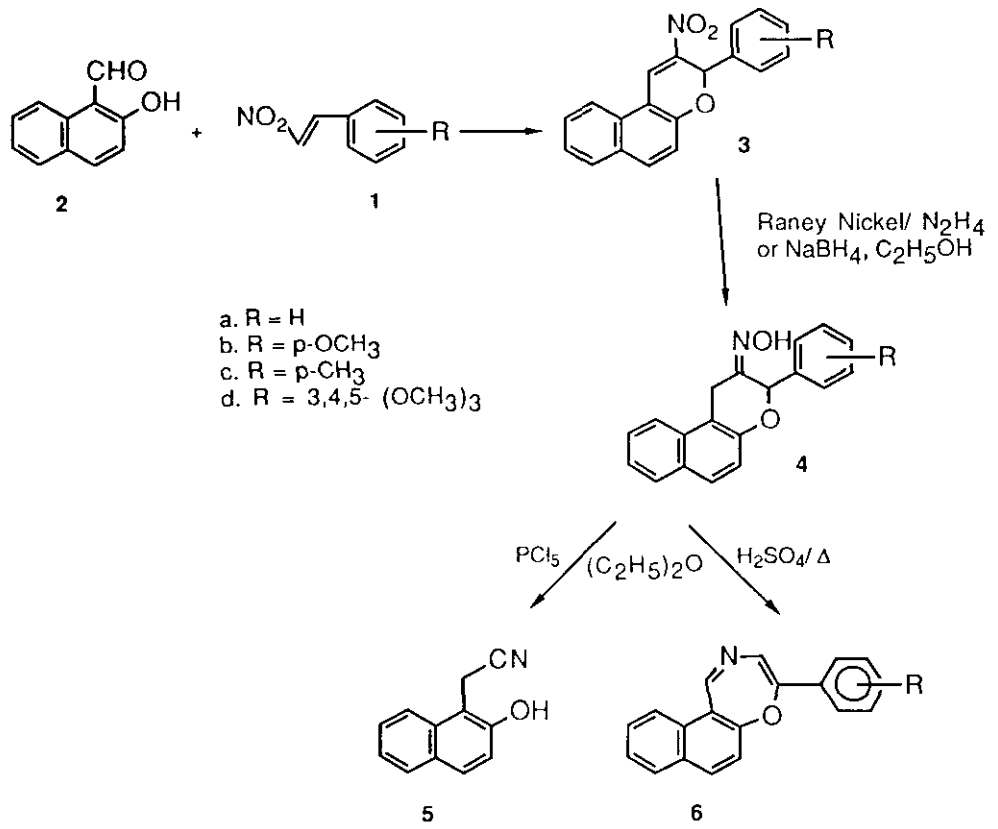
interesting to note that Hanson et al.[6] have shown that 6-nitrocholesteryl acetate was reduced by chromous chloride in tetrahydrofuran to the corresponding oxime. Varma et al.[7] have synthesised 1,1-dihydro-2-nitro-3-phenyl-3H-naphtho[2,1-b]pyran derivatives in good yields by selective reduction of **3a** using sodium borohydride in methanolic tetrahydrofuran. But we observed that the reduction of **3a** with sodium borohydride in ethanol gave the same oximino compound **4a** as indicated by superimposable ir, pmr, and mass spectral data.



Scheme 1

Table 1

Compd	R	mp °C (solvent for recryn.[a])	Yield %	Molecular formula	Analytical data % carbon calcd	% hydrogen calcd	% nitrogen calcd
3a[7]	H	235(M)	75	$C_{19}H_{13}NO_3$	75.24	4.29	4.62
					75.06	4.16	4.71
3b	p-OCH_3	252(M)	72	$C_{20}H_{15}NO_4$	72.07	4.50	4.20
					72.18	4.48	4.15
3c	p-CH_3	172(B)	70	$C_{20}H_{15}NO_3$	75.70	4.73	4.41
					75.56	4.70	4.35
3d	3,4,5-$(OCH_3)_3$	168(B)	65	$C_{22}H_{19}NO_6$	67.17	4.83	3.56
					67.08	4.72	3.42
4a	H	205(B)	71	$C_{19}H_{15}NO_2$	78.89	5.19	4.84
					78.75	5.06	4.72
4b	p-OCH_3	212(EA)	70	$C_{20}H_{17}NO_3$	75.23	5.32	4.38
					75.16	5.18	4.19
4c	p-CH_3	210(B)	68	$C_{20}H_{17}NO_2$	79.20	5.66	4.62
					79.06	5.53	4.61
4d	3,4,5-$(OCH_3)_3$	180(EA)	65	$C_{22}H_{21}NO_5$	69.65	5.54	3.64
					69.56	5.46	3.55
5		182	45	$C_{12}H_9NO$	78.68	4.91	7.65
					78.55	4.83	7.52
6a	H	140(80:20)[b]	34	$C_{19}H_{13}NO$	84.13	4.79	5.16
					84.01	4.68	5.02
6b	p-OCH_3	160(60:40)[b]	38	$C_{20}H_{15}NO_2$	79.73	4.98	4.65
					79.65	4.86	4.57
6c	p-CH_3	172(80:20)[b]	40	$C_{20}H_{15}NO$	84.21	5.26	4.91
					84.02	5.13	4.87
6d	3,4,5-$(OCH_3)_3$	220(60:40)[b]	35	$C_{22}H_{19}NO_4$	73.13	5.28	3.87
					73.08	5.11	3.82

a: M: Methanol; B: Benzene; EA: Ethyl acetate

b: Column eluant ratio, Benzene: Ethyl acetate

It was also interesting to study the Beckmann rearrangement of the oxime obtained by the reduction of the nitro compound. Grob et al.[8] have shown that although ketoximes are not normally conducive to the eliminative cleavage, the presence of electrofugal substituents promotes the Beckmann fragmentation to nitriles under these (phosphorous pentachloride) conditions. **4a** was treated with phosphorous pentachloride in ether, and the product that was obtained was identified[9] as 1-cyanomethyl-2-naphthol (5) by ir, pmr and mass spectral data. Beckmann rearrangement with sulphuric acid is very well known. The reaction of **4c** with sulphuric acid afforded a product characterised by analytical, ir, pmr and mass spectral data as 4-p-tolylnaphth[1,2-f][1,4]oxazepin (**6c**) (Table I, Scheme I). The pmr spectrum of **6c** revealed a singlet at δ 6.60 and 6.90. This structure was supported by the fragmentation pattern of the compound in mass spectra. Similarly three other 4-substituted naphthoxazepines have been prepared.

EXPERIMENTAL

Melting points were determined in capillary tubes on a melting point apparatus and are uncorrected. The uv spectra were recorded on Beckmann DB spectrophotometer, the ir spectra were recorded on Shimadzu IR 435 spectrophotometer and the pmr spectra on a JEOL FX-90 FT-NMR spectrometer and were referenced to TMS as the internal standard. The mass spectra were recorded on RMU-6 Hitachi instrument at 70 ev.

General procedure for the synthesis of 2-nitro-3-aryl-3H-naphtho[2,1-b]pyrans (3a-d).

To a mixture of the appropriate β-nitrostyrene[10] (0.005 mol) and 2-naphthol-1-aldehyde (1.72 g; 0.01 mol) was added triethylamine (0.2 g; 0.002 mol) and the reaction mixture was warmed on a steam bath for 30 min. On cooling, the desired compound that separated was filtered and washed with a little amount of methanol to remove any traces of the starting material. The compounds were recrystallised from suitable solvents (Table I).

3b Ir: (υ, cm^{-1}); 1620 (>C=N), 1550, 1490 ($\geq C\text{-}NO_2$). Pmr: (δ, ppm); 2.51(s, 3H, OCH_3), 6.90(s, 1H), 7.02-8.01(m, 10H, aromatic), 9.01(s, 1H, C_1-H). Ms: M^+

333(8%), m/z 288(30%), 287(100%), 272(10%), 242(15%), 215(15%), 189(5%), 144(5%).

3c Ir: (υ, cm^{-1}); 1620 (>C=N), 1540, 1490 ($\gtrless C\text{-}NO_2$). Pmr: (δ, ppm); 2.52(s, 3H, CH_3), 6.92(s, 1H), 7.01-8.02(m, 10H, aromatic), 8.98(s, 1H, C_1-H). Ms: M^+ 317(13%), m/z 272(22%), 271(100%), 256(8%), 255(10%), 228(12%), 226(10%), 207(15%).

General procedure for the synthesis of 1,1-dihydro-2-oximino-3-aryl-3H-naptho[2,1-b]pyrans (4a-d). Reduction with Raney nickel/hydrazine hydrate 2-Nitro-3-aryl-3H-naphtho[2,1-b]pyran (3a) (3.03 g; 0.01 mol) was taken in methanol (100 ml) and freshly prepared Raney nickel (0.3 g) was added followed by the addition of hydrazine hydrate (3 ml, 80% w/v) dropwise so that a steady evolution of hydrogen was maintained. After the addition was complete the reaction mixture was refluxed on a steam bath for 6 h to ensure completion of the reduction and to destroy the excess of hydrazine hydrate. It was filtered hot and the methanolic filtrate was concentrated and poured into a minimum amount of crushed ice. The solid that separated was filtered and washed with water. It was dried and recrystallised from a suitable solvent (Table 1).

4a Uv: λ_{max} (MeOH) 315 (log ε 4.44), 330 (log ε 4.55). Ir : (υ , cm^{-1}); 1620 (>C=N), 3250-3150 (OH). Pmr: (δ, ppm); (DMSO-d_6) 3.37(s, 2H, CH_2), 5.91(s, 1H), 7.28(m, 11H, aromatic) 11.51(s, 1H, OH). Ms: M^+ 289(87%), m/z 271(100%), 244(11%), 231(5%), 181(4%), 157(7%).

4b Ir: (υ, cm^{-1}); 1620 (>C=N), 3250-3150 (OH). Pmr: (δ, ppm); (DMSO-d_6) 2.51(s, 3H, CH_3), 3.36(s, 2H, CH_2), 5.91(s, 1H), 7.20-8.01(m, 10H, aromatic), 11.50(s, 1H, OH). Ms: M^+ 319(78%), m/z 302(100%), 287(16%), 286(18%), 270(12%), 183(48%), 175(30%), 157(45%), 135(42%), 121(40%).

4c Ir: (υ, cm^{-1}); 1620 (>C=N), 3250-3150 (OH). Pmr: (δ, ppm); (DMSO-d_6) 2.50(s, 3H, CH_3), 3.37(s, 2H, CH_2), 5.92(s, 1H), 7.21-8.02(m, 10H, aromatic), 11.51(s, 1H, OH). Ms: M^+ 303(75%), m/z 286(100%), 271(15%), 270(13%), 183(35%), 157(40%), 128(25%), 119(28%), 105(33%).

Reduction with sodium borohydride To a stirred solution of **3a** (3.03 g; 0.01 mol) in ethanol (100 ml), sodium borohydride (1.96 g ; 0.04 mol) was added in portions cooling to 5-10 °C. The reaction mixture was stirred at this temperature for 1 h. Ethanol was distilled off and the excess of sodium borohydride in the residue was decomposed with dil. acetic acid. The reaction mixture was extracted with ethyl acetate, and the organic layer was washed with water and dried (Na_2SO_4). On evaporating the solvent, the solid that separated was filtered and recrystallised from benzene. **4a** was obtained (1.85 g, yield 65%), mp 205 °C. Mixed mp with the product obtained from Raney nickel reduction sample was not depressed.

Reaction with phosphorous pentachloride. 4a (1.44 g; 0.005 mol) was dissolved in dry ether (25 ml) and the solution was cooled in an ice bath. Phosphorous pentachloride (2.56 g; 0.01 mol) was added in portions to the cooled solution, which was then allowed to warm to room temperature. The mixture was left to stand for several hours. The solvent was evaporated and the residue was poured over crushed ice. The solid that separated was filtered and recrystallised from chloroform: methanol (9:1), mp 182 °C, (Lit.,[9] 177 °C) (0.42 g; yield 45%). Similar compounds prepared from other substituted napthopyrans also yielded the same 1-cyanomethyl-2-naphthol.

5 Ir: (υ,cm^{-1}); 1630 (>C=N), 3300 (OH). Pmr: (δ, ppm); 4.11(s, 2H, $-CH_2$), 7.20-7.82(m, 6H, aromatic), 9.81(s, 1H, OH). Ms: M^+ 183(100%), m/z 165(100%), 156 (46%), 128(80%), 102(24%), 76(24%).

General procedure for the synthesis of 4-arylnaphth[1,2-f][1,4]oxazepines. **4a** (0.01 mol) was added in small portions to well stirred conc. sulphuric acid (15 ml) taken in a flask protected by a calcium chloride guard tube . The temperature was held below 25 °C by external cooling. After the addition the solution was heated at 100-110 °C for 1 h and then brought down to room temperature. At this temperature, the pH was carefully adjusted to 6 with aq. ammonia. The mixture was extracted with ethyl acetate . The extract was dried (Na_2SO_4) and the solvent was distilled off. The residue was adsorbed on neutral alumina and chromatographed on a column using benzene: ethyl acetate as the eluants in the ratios given in the Table to give the compound (Table 1).

6a Ir: (υ,cm^{-1}); 1620 (>C=N). Pmr: (δ, ppm); 6.61(s, 1H), 6.91(s, 1H), 7.21-8.11(m,

11H, aromatic). Ms: M^+ 271(100%), m/z 243(6%), 242(7%).

6b Ir: (υ, cm^{-1}); 1620 (>C=N). Pmr: (δ, ppm); 2.51(s, 3H, CH_3), 6.59(s, 1H), 6.90(s, 1H), 7.19-8.10(m, 10H, aromatic). Ms: M^+ 301(100%), m/z 286(10%).

6c Uv : λ_{max} (MeOH) 430 ($\log \varepsilon$ 4.91) Ir: (υ, cm^{-1}); 1620 (>C=N), Pmr: (δ, ppm); 2.51(s, 3H, CH_3), 6.62(s, 1H), 6.90(s, 1H), 7.21(d, 2H), 8.01(d, J = 1.71 Hz, C_2-H, C_6-H, 2H, phenyl ring), 8.51(s, 2H), 7.30-7.51(m, 4H, aromatic). Ms: M^+ 285 (100%), m/z 284(18%), 270(12%), 257(6%), 256(8%), 242 (6%), 241(10%).

ACKNOWLEDGEMENT

The authors are grateful to Prof. C. V. Ratnam, Chemistry Department, Osmania University, Hyderabad - 500007, India, Dr. M. Vairamani, Scientist, Indian Institute of Chemical Technology, Hyderabad-500007, India, for interesting discussions in mass spectra. RR is thankful to the University Grants Commission, New Delhi for financial assistance.

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Received, 22nd April, 1989