THE PREPARATION OF COUMARIC ACIDS *VIA* STYRYLISOXAZOLES

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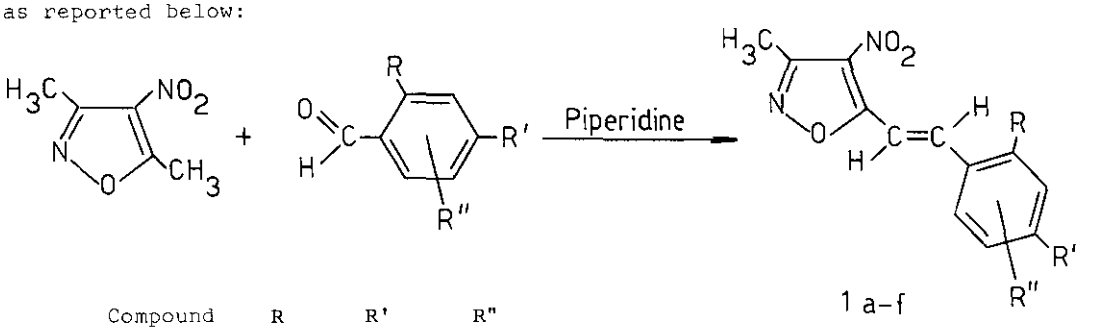
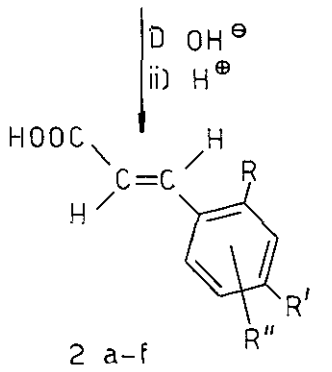
Abstract — The preparation of coumaric acids (2a-f) by hydrolysis of the requisite 3-methyl-4-nitro-5-styrylisoxazoles (1a-f) is reported.

It is well established[1] that o- and p-coumaric acids may be prepared from phenolic aldehydes by using the Knoevenagel-Doebner reaction or the Perkin reaction. Alternatively, the alkaline hydrolysis of coumarins is also used for the preparation of o-coumaric acids. Following previous studies on the preparation of cinnamic acids[2] and arylpropiolic acids[3] *via* styrylisoxazoles, we have extended this procedure to the synthesis of o- and p-coumaric acids. The 3-methyl-4-nitro-5-styrylisoxazoles (1a-f) used, were prepared by condensing the requisite o- or p-hydroxybenzaldehydes with 3,5-dimethyl-4-nitroisoxazole in presence of piperidine[4], as reported below:



1 a-f

Compound	R	R'	R"
a	OH	H	H
b	OH	H	5-Br
c	OH	H	5-OCH_3
d	OH	OCH_3	H
e	H	OH	3-OCH_3
f	H	OH	3,5-OCH_3



2 a-f

Coumaric acids were obtained by alkaline hydrolysis followed by acidification of compounds **1a-f**. These results are expected on the ground of the chemical behaviour of 3-methyl-4-nitroisoxazol-5-yl group which may be considered as a masked carboxyl group[5]. When compound **1a** was hydrolyzed with $Na^{18}OH$ followed by acidification with HCl gas, the corresponding o-coumaric acid with two labelled oxygens in the carboxyl group was obtained. In fact the mass spectrum of this compound showed a signal at m/e 168 (M^+). This finding is in agreement for an isoxazole ring opening through the nucleophilic attack of the hydroxyl group to the C-5 of the isoxazole ring, with the same mechanism already reported in ref.(5) for the hydrolysis of 3-methyl-4-nitro-5-styrylisoxazole.

The mps of the coumaric acids (**2a-f**), prepared with this method, are listed in the Table and compared with those reported in the literature. Nmr spectra for compounds **2a-f** were consistent with the proposed structures; in particular they showed signals attributable to the olefinic protons with coupling constants of 16 Hz, as requested for *trans* structures.

Table: Yields and physical data of compounds **2a-f**.

Compound	Yield %	Mp °C		^{1}H nmr (DMSO-d_6), δ	
		Found	Lit.	-CH=CH-COOH	-CH=CH-COOH
2a	78.1	214-215 dec.	208[1];209[6];214[7]	7.85	6.48
2b	85.0	233-234 dec.	224 dec.[8]	7.75	6.48
2c	75.2	184-185 dec.	191-193[9]	7.82	6.48
2d	75.2	195-198 dec.	195-198 dec.[10]	7.79	6.34
2e	49.7	171-172	173[1]	7.49	6.26
2f	72.9	190-192 dec.	192[1]	7.50	6.39

Analytical results for C and H, performed for compounds **2b** and **2c** which showed mps different from those reported in ref.(8,9), were in agreement with the expected values. Thus the differences in the mps may be attributed to the decomposition which occurs during the melting point determinations.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Nmr spectra were recorded on a Perkin-Elmer R 32 spectrometer and reported in δ units with tetramethylsilane as internal standard. Ir spectra were recorded on a Perkin-Elmer 283 spectrophotometer in potassium bromide pellets. The uv spectra were determined on a Cary 14 spectrophotometer. Mass spectral data were taken with a LKB 2091 mass spectrometer. Compounds **1a-f** were obtained according to the procedure reported in ref. (4) for the preparation of 3-methyl-4-nitro-5-styrylisoxazole. The hydroxyaldehydes were supplied by Aldrich Europe and used with no further purification. The $H_2{}^{18}O$ (99.8 atom %) was supplied by Prochem B.O.C. limited, London.

3-Methyl-4-nitro-5-[2-(2-hydroxyphenyl)ethenyl] isoxazole (1a).

Compound **1a** (yield 88.9%) had mp 240-242°C (from ethanol). Lit.: 245-246°C[12]; 230°C[13]. Uv (methanol), λ max, nm (log ε): 215 (4.22), 252 sh (3.95), 273 (4.08), 386 (4.31); ir : 3220, 1610, 1570, 1460, 1370, 1320, 1250, 975, 830, and 765 cm^{-1}. *Anal.* Calcd. for $C_{12}H_{10}N_2O_4$: C,58.54; H, 4.09; N, 11.38. Found C, 58.39; H, 4.14; N, 11.61.

3-Methyl-4-nitro-5-[2-(2-hydroxy-5-bromophenyl)ethenyl] isoxazole (1b).

Compound **1b** (yield 93.5%) had mp 259-260°C (from ethanol). Lit.:250°C[13]. Uv (methanol), λ max, nm (log ε): 227 4.27), 263 sh (4.08), 268 (4.10), 387 (4.26); ir : 3150, 1615, 1570, 1500, 1415, 1375, 1320, 1245, 980, 830, 814, and 760 cm^{-1}. *Anal.* Calcd. for $C_{12}H_9N_2O_4Br$: C, 44.30; H, 2.77; N, 8.62. Found: C,44.60; H,2.90; N,8.56.

3-Methyl-4-nitro-5-[2-(2-hydroxy-5-methoxyphenyl)ethenyl] isoxazole (1c).

Compound **1c** (yield 80%) had mp 198-199°C (from ethanol); uv (methanol), λ max, nm (log ε): 245 sh (4.02), 273 (4.00), 345 (4.04), 415 (4.15); ir : 3230, 1610, 1575, 1510, 1430, 1380, 1360, 1335, 1260, 1215, 1035, 990, 855, 835, 815, and 765 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.40; H, 4.41; N, 10.39.

3-Methyl-4-nitro-5-[2-(2-hydroxy-4-methoxyphenyl)ethenyl] isoxazole (1d).

Compound **1d** (yield 82%) had mp 266-268°C (from ethanol); uv (methanol), λ max, nm (log ε): 220 sh (4.14), 287 (4.05), 412 (4.41); ir : 3100, 1600, 1570, 1515, 1420, 1375, 1350, 1330, 1260, 1190, 1140, 1110, 975, 830, and 825 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.23; H, 4.40; N, 9.99.

3-Methyl-4-nitro-5-[2-(3-methoxy-4-hydroxyphenyl)ethenyl] isoxazole (1e).

Compound **1e** (yield 53%) had mp 192-193°C (from ethanol); uv (methanol), λ max, nm (log ε): 230 (4.06), 265 sh (4.00), 285 (4.06),405 (4.36); ir ·3530, 3400, 3060, 1620, 1585, 1570, 1510, 1355, 1280, 1160, 1130, 960, 830, and 810 cm^{-1}. *Anal.* Calcd. for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14. Found: C, 56.40; H, 4.43; N, 10.11.

3-Methyl-4-nitro-5-[2-(3,5-dimethoxy-4-hydroxyphenyl)ethenyl] isoxazole (1f).

Compound **1f** (yield 37.6%) had mp 194-195°C (from ethanol); uv (methanol), λ max, nm (log ε): 232 (4.18), 258 sh (3.93), 392 (4.02), 410 (4.37); ir : 3460, 3410, 2940, 1625, 1605, 1570, 1510, 1465, 1430, 1380, 1350, 1330, 1215, 1110, 950, 825, 818, and 810 cm^{-1}. *Anal.* Calcd.for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.93; H, 4.37; N, 9.16.

Coumaric Acids (2a-f).

Compound **1a** (1g) was refluxed with 1N sodium hydroxide (30 ml) for 2 h. The solution, filtered and acidified with concentrated hydrochloric acid to pH 1, gave o-coumaric acid (**2a**) (0.52 g; 78.1%), which was dissolved in boiling ethanol and the solution treated with charcoal. After cooling the product was filtered and recrystallized from water/ethanol, mp 214-215°C dec. Lit. 208°C[1]; 209°C corr.[6]; 214°C[7]. Ir and nmr spectra were identical with those reported in ref.(14) and (15) for an authentic sample. The same procedure was used for the preparation of coumaric acids **2b-f**. Mps, yields and spectroscopic data are reported in the Table.

Alkaline Hydrolysis of 3-Methyl-4-nitro-5-[2-(2-hydroxyphenyl)ethenyl] isoxazole (1a) with $Na^{18}OH$.

A solution of $Na^{18}OH$ (2N; 0.5 ml), prepared by treating $H_2{}^{18}O$ with Na, was added with compound **1a**(0.016 g) and refluxed for 15 min. The solution was then acidified with hydrogen chloride gas to give a solid which was filtered, dried and purified by vacuum sublimation (110°C, 10^{-1}mm Hg; 0.0053 g; 48.5%). The mass spectrum of this compound showed a peak at m/e 168, in agreement for M^+ of the expected o-hydroxycinnamic acid (o-coumaric acid) with two labelled oxygens in the carboxyl group.

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