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Note

Synthesis of homoanisic acid

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Synthesis of homoanisic acid by Erlenmeyer condensation via the formation of azalactone is discussed.

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p-Methoxyphenylacetic acid which is also called as homoanisic acid is used for the synthesis of numerous perfumes, drugs, dyes and paints[1,2]. It is used as an intermediate for the preparation of anisindione, an anticoagulant and dextromethorphan, an antitussive drug[2,3]. Hence it is in a very high demand.

Results and Discussion

Synthesis of homoanisic acid was carried out in four steps (**Scheme I**) using easily available and cheaper raw materials. First step involved synthesis of 2-phenyl-4-(4'-methoxybenzal)-oxazol-5-one, also called as azalactone, by condensation of anisaldehyde with hippuric acid in the presence of sodium acetate and either acetic anhydride or acetic acid. Yield of azalactone was calculated for reactions involving the use of acetic anhydride and also for reactions using various concentrations of acetic acid (**Table I**). The yields of pure azalactone, obtained by washing crude product with ethanol alone and by washing it with ethanol as well as with water, were compared (**Table I**). The maximum yield of azalactone (70 %) was obtained when 0.01 molar acetic acid was used and when crude azalactone was washed only with ethanol. The same reaction with acetic anhydride resulted in 62 % yield of pure azalactone (**Table I**). Since glacial acetic acid is cheaper than acetic anhydride and the yield of azalactone obtained was also more with acetic acid, use of acetic acid was recommended.

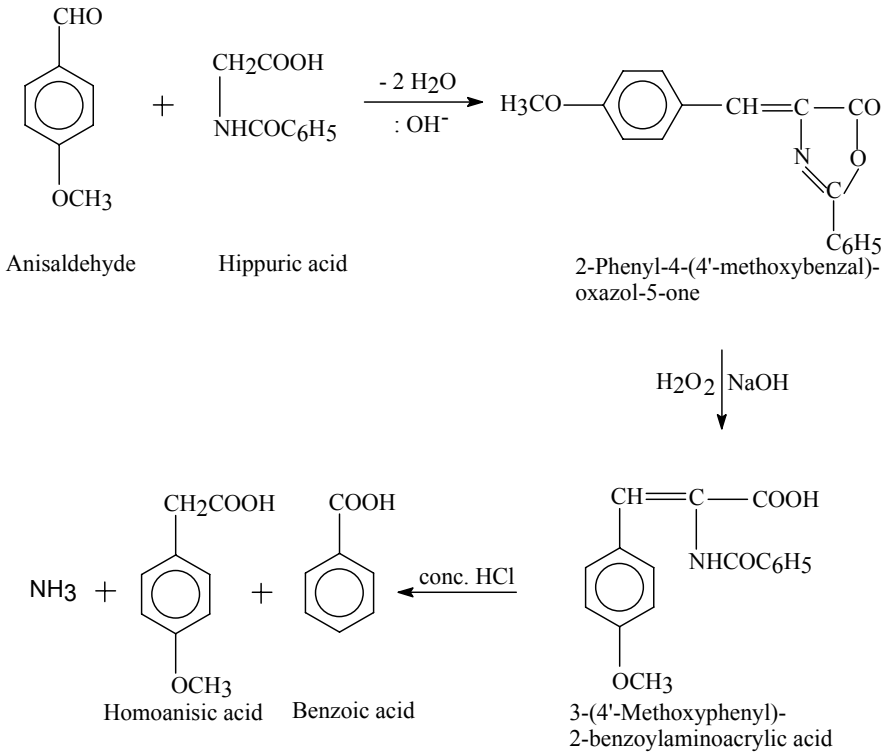
In step 2, azalactone was hydrolyzed using 10 % sodium hydroxide and then oxidized with a mixture of 30 % H_2O_2 and 40 % NaOH to get 3-(4'-methoxyphenyl)-2-benzoylaminoacrylic acid[4]. Acidification of this compound yielded a mixture of homoanisic acid and benzoic acid[5]. Various parameters like time of reflux, reaction temperature, quantity of 10 % NaOH, 30 % H_2O_2 and 40 % NaOH were standardized to get the maximum yield of homoanisic acid (**Table II**). For hydrolysis of azalactone, 10 % NaOH was used, whereas 40 % NaOH was used for maintaining sufficiently basic condition during decarboxylation of the hydrolyzed product and for oxidation by H_2O_2. Excess of 10 % as well as 40 % NaOH may lead to the formation of 3-(4'-methoxyphenyl)-2-amino-acrylic acid as an impurity along with benzoic acid. In presence of excess H_2O_2, 4-methoxybenzoic acid was found to be formed. For 10 mmoles of azalactone, only 0.5 mL of 30 % H_2O_2 was found to give the maximum yield of homoanisic acid along with little of benzoic acid. Similarly, the yield of mixture of these two acids was more (60 %) at 60 ^oC as compared to that at 80 ^oC (54 %). The percent yields of mixture of acids under different reaction conditions are mentioned in **Table II**.

Step 3 involved separation of homoanisic acid from benzoic acid. This was done in two ways. In the first method, the mixture of acids was dissolved in hot water and less soluble homoanisic acid was filtered off from the solution of benzoic acid. Homoanisic acid was obtained in pure form by this procedure only if the reaction mixture is not overheated. In the second method, separation of two acids was attempted by their esterification with methanol. Two esters were separated by fractional distillation. Methyl homoanisate was obtained in 51 % yield.

In the last step, methyl homoanisate was hydrolyzed by refluxing it with 10 % NaOH to get homoanisic acid in 61 % yield.

Experimental Section

Melting points of the synthesized compounds are uncorrected. IR spectra in KBr were recorded on a JASCO FTIR 410 spectrometer; ^1H NMR spectrum in $CDCl_3$ on a VARIAN-360L at 60 MHz ^1H NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm); and mass spectrum on a quadrupole mass spectrometer by the Electron Impact (EI) method.



Scheme I

Table I — Percent practical yield of azalactone with acetic anhydride and acetic acid

% Yield of azalactone	Acetic anhydride		Acetic acid*		Molarity of acetic acid		
	Washing with EtOH- H_2O	Washing with EtOH	Washing with EtOH- H_2O	Washing with EtOH	0.06	0.05	0.01
	50	62	52	70	67♦	67♦	70♦

* 0.01 molar acetic acid
♦ % yields of azalactone by washing with ethanol only

Synthesis of 2-phenyl-4-(4'-methoxybenzal)-oxazol-5-one (azalactone). A mixture of anisaldehyde (2.6 g, 20 mmoles), hippuric acid (3.84 g, 20 mmoles), sodium acetate (1.6 g, 20 mmoles) and acetic anhydride (6 mL, 60 mmoles) or acetic acid (6 mL, 0.01 *M*) was heated on a steam-bath for 2 hr. The mixture was cooled and diluted with ethanol (30 mL). It was allowed to stand overnight, filtered and then the solid was washed either with a mixture of ethanol and water or only with ethanol. The product thus obtained was dried to get azalactone; IR (KBr): 1730 (C = O str, lactone), 1690 (C=N str), 1589, 1554, 1484 (C=C str, Ar), 1109 cm^{-1} (C-O-C str, ether).

Synthesis of a mixture of homoanisic acid and benzoic acid. Azalactone (3.7 g, 10 mmoles) was refluxed for 6 hr with NaOH (10 mL, 10 %). After cooling, the reaction mixture was further treated with NaOH (1.0 mL, 40 %), H_2O_2 (0.5 mL, 30 %) and water (1.5 mL) in an ice-salt bath. It was acidified with HCl and was extracted with (2×15 mL) benzene. Benzene was recovered from the dried combined extracts to get the residue of a mixture of homoanisic acid and benzoic acid.

Separation of homoanisic acid from benzoic acid.

(a) **Separation using difference in solubility of homoanisic acid and benzoic acid**. The mixture of acids was dissolved in sufficient quantity of warm water. The mixture was filtered while warm. The residue on the filter paper was of homoanisic acid while benzoic acid was recovered from the filtrate.

Table II — Effect of various modifications on the percent practical yield of the mixture of homoanisic acid and benzoic acid

% Yield of mixture of acids	Time of reflux (hr)			Quantity of 10 % NaOH (mL)			Quantity of 30 % H_2O_2 (mL)			Quantity of 40 % NaOH (mL)		Reaction temperature °C	
	6	5	4	40	20	10	0.5	1.5	2.2	1.75	1	60	80
	60	68	58	57	60	78	81	60	56	60	80	60	54

All the quantities are for 3.7 g (10 mmoles) of azalactone.

(b) **Separation of acids by esterification**. The mixture of acids (2.8 g) was refluxed with absolute methanol (20 mL) and conc. H_2SO_4 (3 mL) for 5 hr. After the esterification, methanol was distilled off. The mixture of esters was diluted with water (10 mL) and then extracted with benzene. The benzene layer was washed with 10 % sodium carbonate solution and then with water. It was dried and distilled to separate methyl homoanisate [b.p. 142-43 °C; IR (KBr): 3020 (C-H str), 1670 (C=O str), 1589, 1576, 1508, 1474 (C=C str, Ar), 1120 cm^{-1} (C-O-C str, ether)]; from methyl benzoate [b.p. 78 °C, IR: 2980 (C-H str), 1678 (C=O str), 1584, 1549, 1508, 1482 cm^{-1} (C=C str, Ar)].

Hydrolysis of methyl homoanisate[4]. Methyl homoanisate (1.92 g, 10 mmoles) was refluxed with NaOH (5 mL, 10 %) for 30 min. The clear solution was poured, while stirring, in a mixture of ice and conc. HCl. Homoanisic acid immediately crystallized out. It was filtered after 30 min and dried properly. Pure homoanisic acid melted at 86 °C; IR (KBr): 2937 (C-H str, alkyl group), 1694 (C=O str, carboxy group), 1613, 1584, 1515, 1458 (C=C str, Ar), 1244 (O=C-O^- str, carboxylate anion), 1109 cm^{-1} (C-O-C str, ether); ^{1}HNMR ($CDCl_3$): δ 10.9 (s, 1H, COOH), 7.4 (d, *J* = 8.4 Hz, 2H, ArH), 7.0 (d, *J* = 8.4 Hz, 2H, ArH), 4.0 (s, 3H, OCH_3), 3.8 (s, 2H, CH_2); Mass:m/z (%) 121 (100), 122(8.3), 166 (M^+) (10.0), 91 (7.8), 77 (10.8), 78 (3.9), 66 (3.9), 45 (8.8), 39 (4.5), 29 (3.9); Anal. Calcd for $C_9H_{10}O_3$: C, 64.67; H, 6.46; O, 28.74. Found: C, 64.52; H, 6.12; O, 28.86 %.

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