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Further Evidence for the Mechanism of Formation of Coumarin by Perkin Reaction from salicylaldehyde and a Novel Synthesis of 1,1-diphenyl-2(2'-hydroxyphenyl) ethene from O-*α,α*-diphenylacetylsalicylaldehyde with Et_3N

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Abstract

The mechanism of formation of coumarin (1) by Perkin reaction from salicylaldehyde was shown to involve exclusively a base-catalyzed intramolecular aldol-type condensation of O-acetyl salicylaldehyde (2) as an obligatory intermediate followed by dehydration. Direct evidence in support of this contention was provided by the formation of coumarin and 3-phenyl coumarin(5) as the sole products in the reactions of O-acetyl salicylaldehyde(2)with Et_3N or NaOAc and O-α-phenyl acetyl salicylaldehyde (4) with Et_3N, respectively. A novel synthesis of 1,1-diphenyl-2(2'-hydroxyphenyl)ethene(8a) was achieved by the reaction of O-α,α-diphenylacetylsalicylaldehyde (6) with Et_3N. A plausible mechanism of formation of 8a in the above reaction is proposed. The formation of 8a is assumed to involve an intermediate β-lactone (9) formed through two consecutive intramolecular condensation. Base-catalyzed decarboxylation of 9 finally gives 8a.

Introduction

Perkin reaction[1-3] provides a useful method for the synthesis of α,β-unsaturated aromatic acids and involves the condensation of a carboxylic anhydride with an aromatic aldehyde in presence of a weak base like sodium or potassium acetate or triethylamine . The mechanism of Perkin reaction has been the subject of numerous investigations carried out over a period of more than 50 years , which led to the postulation of a generally accepted mechanism for this reaction involving an intermolecular aldol-type condensation followed by dehydration.

Although the first example of Perkin reaction involves the synthesis of coumarin(1), by the reaction of sodium salt of salicylaldehyde with Ac_2O reported by Perkin himself [2] in 1868 , and later also achieved by the reaction of salicylaldehyde with Ac_2O in presence of fused sodium or potassium acetate or Et_3N , the actual mechanism of formation of coumarin by these reactions has not been clearly explained and is difficult to be explained by this generally accepted intermolecular mechanism.of Perkin reaction. This is because the α,β-unsaturated aromatic acid which is expected to be formed by the normal intermolecular aldol-type condensation of salicylaldehyde with Ac_2O would have the *trans*-configuration and is unlikely to lactonize under the reaction condition. Later Crawford and Shaw[4] has postulated that the formation of coumarin in the above reaction may take place both intermolecularly and intramolecularly and in the former case lactonization takes place prior to elimination of H_2O or HOAc . They have provided some convincing evidence particularly in support of the intramolecular mechanism. The formation of the minor product O-acetyl coumaric acid(10-12%) (3) in the above reaction may, however, be satisfactorily explained by the generally accepted intermolecular mechanism of Perkin reaction. In this paper we report further convincing evidence in support of the intramolecular mechanism of the formation of coumarin.

We also report in this paper the results of the reaction of O-α,α-diphenylacetylsalicylaldehyde (6) with Et_3N, which we have come across in course of our studies on the mechanism of formation of coumarin.

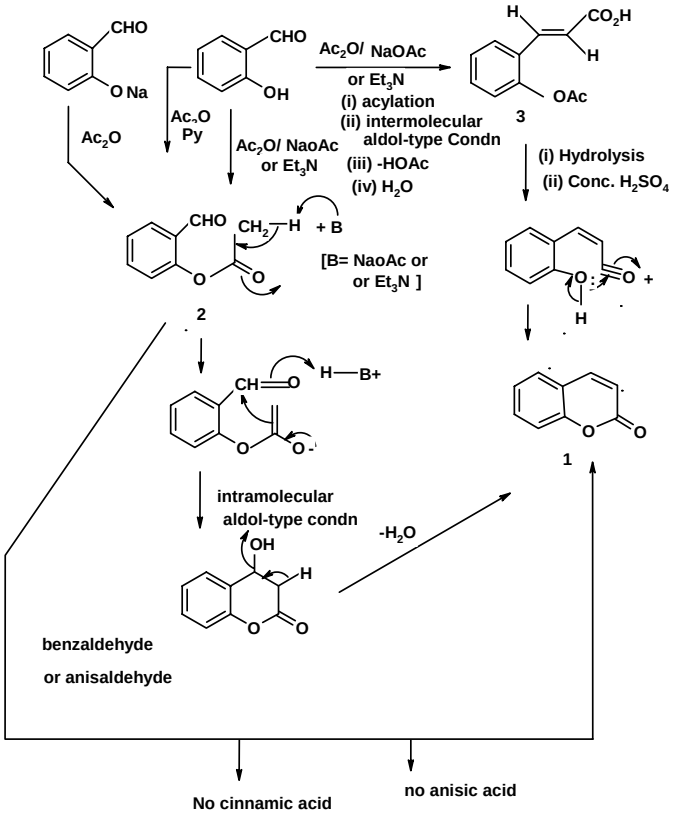
Results and Discussion

The untenability of an intermolecular mechanism for the formation of coumarin in the Perkin reaction of salicylaldehyde led us to assume that the above reaction must, therefore, involve a suitable intramolecular mechanism. A plausible reaction of this type appeared to be an intramolecular aldol-type condensation of the initially formed *O*-acetyl salicylaldehyde (2) as an intermediate followed by dehydration . The validity of the above conjecture was established by carrying out the reaction with (2) itself in absence of Ac_2O. Thus , *O*-acetylsalicylaldehyde(2) , when gently boiled with Et_3N for 14hrs or heated with fused NaOAc at 175-80° for 8 hrs afforded coumarin (1) as the sole condensation product in *ca* 50 % and ca 40% yields, respectively, and no coumaric or *O*-acetyl coumaric acid (3) could be detected in the reaction products in both the reactions. In the reaction carried out by Perkin himself , sodium salt of salicylaldehyde was assumed to react with Ac_2O to form O-acetyl salicylaldehyde (2) and NaOAc . Intramolecular aldol-type reaction of (2) in presence of NaOAc , followed by dehydration finally gave coumarin(1). The above contention was confirmed by the isolation of (2) by gently heating sodium salt of salicylaldehyde with Ac_2O for a short period . That O-acetyl coumaric acid (3) is not an intermediate for the formation of coumarin in Perkin reaction was indicated by the fact that it remained unchanged on treatment with NaOAc or Et_3N under Perkin reaction condition , and on hydrolysis with 10 % aq. methanolic NaOH followed by acidification gave coumaric acid and no coumarin . Coumaric acid , however , on gentle heating with conc. H_2SO_4 readily cyclised to coumarin presumably through the intermediate acyl ion. The possibility of generation and participation of ketene in the aforesaid reactions, particularly with Et_3N was ruled out by appropriate experimental studies. Thus when the reaction of 2 was carried out in presence of benzaldehyde or anisaldehyde, coumarin was again the sole product and no cinnamic or anisic acid could be detected. The above results and the mechanism of formation of coumarin are shown in Scheme 1.

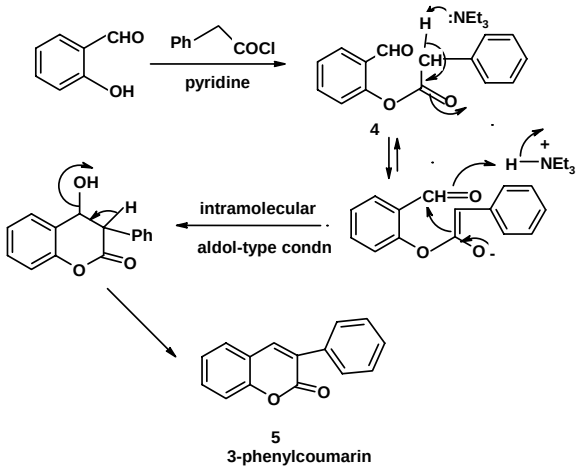
The formation of coumarin by the Perkin reaction thus involves an intramolecular aldol-type condensation of O-acetyl salicylaldehyde (2) as an obligatory intermediate and constitutes an example of intramolecular Perkin reaction.

The above mechanism was further corroborated by the following reactions. Thus, O-α-phenylacetyl salicylaldehyde(4) when heated under reflux in presence of Et_3N for 1.5 hrs afforded 3-phenylcoumarin(5) in more than 90 % yield. The mechanism of formation of 5 is again an example of intramlecular Perkin reaction and involves a similar mechanism as in the case of the conversion of O-acetylsalicylaldehyde(2) to coumarin as shown in Scheme 2.

This has prompted us to study the action of Et_3N on O-α,α-diphenylacetylsalicylaldehyde(6) which would be expected to form 4-hydroxy-3,3-diphenyl-3,4-dihydrocoumarin(7). But contrary to this expectation, the product was a stilbene derivative.

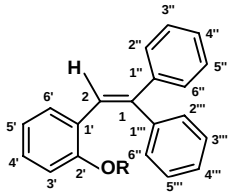


Scheme 1. Mechanism of formation of coumarin in the Perkin reaction



Scheme 2. Mechanism of formation of 3 -phenylcoumarin

The structure of the compound was established as 1,1-diphenyl-2-(2'-hydroxyphenyl) ethane (8a) from detailed spectral and chemical evidence.



8a: R=H
8b: R=Ac

The stilbene derivative 8a, mp 134 ^{o}C, analyzed for $C_{20}H_{16}O$ which was confirmed by its mass spectrometrically derived molecular weight 272. The UV absorptions of 8a, λ_{max} 207.5, 240(sh), 290(sh) and 316nm (logε 4.05, 4.0, 3.52 and 3.60) resemble those of stilbene derivatives. It exhibited alkali-induced bathochromic shift of its UV maxima [$\lambda_{max\ (\ EtOH\text{-}1M\ NaOH)}$ 218.5, 234(sh), 287.5 and 355.5(logε 4.30, 4.22, 4.03 and 4.0) indicated the presence of a phenolic hydroxyl group. This was also indicated by its IR spectrum showing an intense band at ν_{max} 3477cm^{-1}. The presence of a single hydroxyl group in the compound was confirmed by the formation of a monoacetyl derivative 8b, $C_{22}H_{18}O_2$(M^+ 314), mp123 ^{o}C with Ac_2O and pyridine. The compound exhibited bands at ν_{max} 1208 and 1756 cm^{-1} for a phenolic acetate function. The 500Mz ^{1}H NMR of 8a and 8b and 125Mz ^{13}C signals of 8a and 6 shown in Table1 confirmed the proposed structures of the compounds.

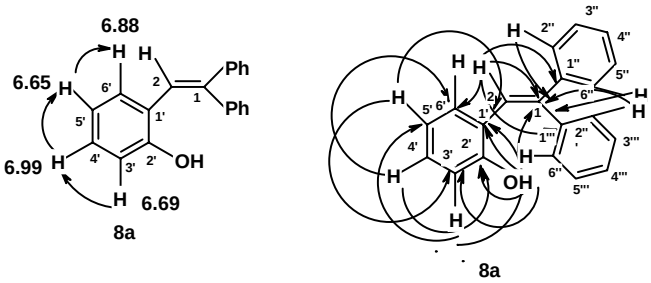
Table 1. ^{l}HNMR spectral data of **8a** and **8b** and ^{13}C NMR spectra data of **8a** and **6**

	δ_H		δC			
	8a	8b		8a	6	
H-2	6.95(s)	6.83 (s)	C-1	139.4	C-1	128.5
			C-2	128.4	C-2	151.9
H-3’	6.69 (br,d,	7.18(br.d,	C-1’	124.3	C-3	123.0
	J=8.05Hz)	J=8.4Hz	C-2’	152.9	C-4	135.1
			C-3’	115.5	C-5	126.4
H-4’	6.99(appt.t,	6.90(appt.t,	C-4’	122.5	C-6	128.0
	J_1=7.84Hz	J_1=8.74Hz	C-5’	120.2	CHO	188.2
	& J_2=7.34Hz)	& J_2=7.84Hz)	C-6’	130.4	C-1’	170.6
			C-1’’	142.8[a]	C-2’	56.8
H-5’	6.65(appt.t,	6.88(app.t,	C-2’,’	128.3[b]	C-1’’	128.5
	J_1=7.48Hz	J_1=7.76Hz	C-6’’		C-2’’	128.6[a]
	& J_2=7.46Hz)	& J_2=7.50Hz)	C-3’’,	128.1[c]	C-6’’	
			C-5’’		C-3’’	128.8[b]
H-6’	6.88(br. d,	6.99(br. d,	C-4’’	130.2	C-5’’	
	J=7.50Hz)	J=7.78Hz)	C-1’’’	144.4[a]	C-4’’	128.8
			C-2’’’	127.9[b]	C-1’’’	137.4
10H of	7.15-	7.12-	C-6’’’		C-2’’’	128.5[a]
of the two	7.30(m)	7.32 (m)	C-3’’’,	127.7[c]	C-6’’’	
Ph-rings			C-5’’’		C-3’’’	128.7[b]
			C-4’’’	130.2	C-5’’’	
Ar-OH	5.10(s)	-				
OAc	-	2.27(s)			C-4’’’	129.8

^{13}C NMR spectra were run in $CDCl_3$ and the chemical shifts were measured with $\delta_{(TMS)}$= $\delta_{(CDCl3)}$ +79.9ppm. [a,b,c] Values are interchangeable in each column.

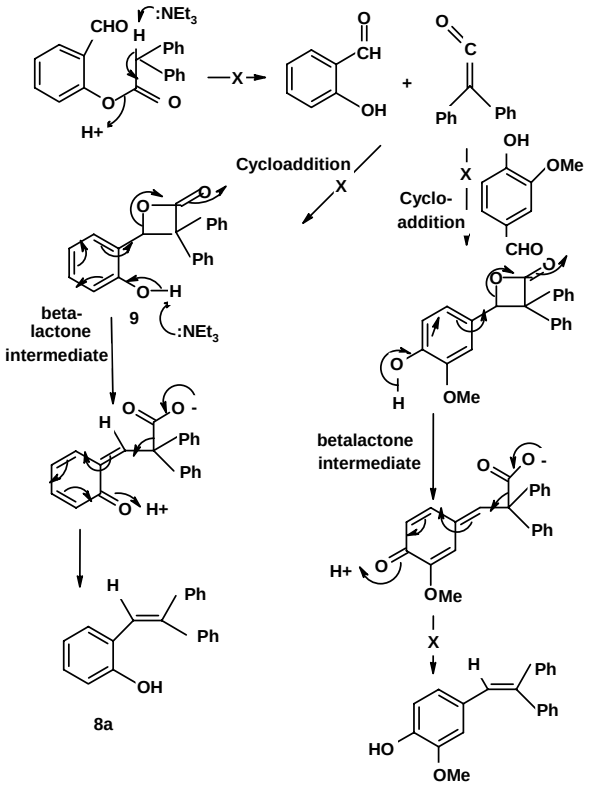
The degree of protonation of each carbon atom of 8a and 6 were confirmed by DEPT experiments and that of 8a by the HMQC and HMBC spectral analysis with $J_{C\text{-}H}$ parameters set to 160Hz and 7Hz, respectively.

The structure of 8a was further confirmed by ^{1}H-^{1}H (COSY) and long range ^{1}H-^{13}C (HMBC) correlations. The more important correlations exhibited in the COSY and HMBC spectra of 8a are shown in its structural diagram.

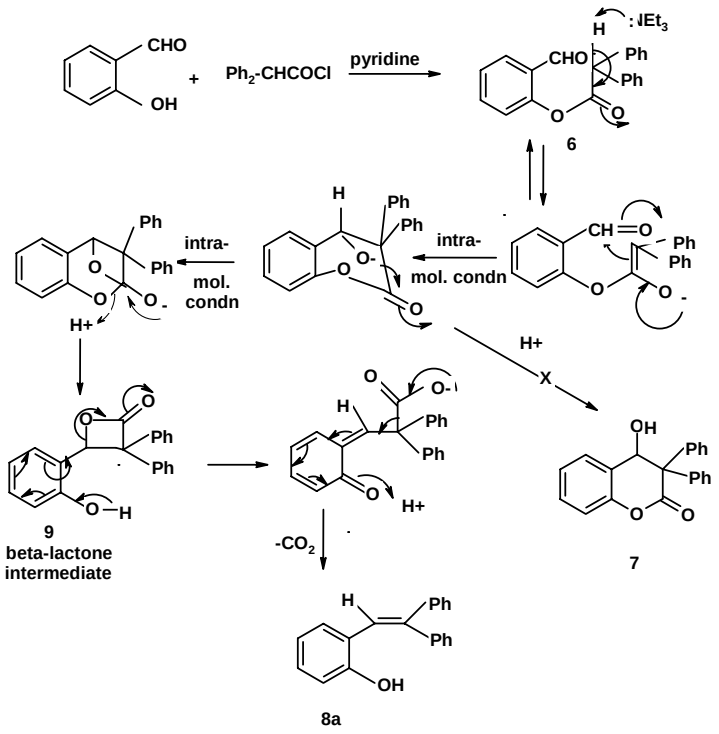


The structure of the stilbene derivative was thus firmly established as 8a. Mechanistically the formation of 8a from 6 with Et_3N is highly interesting. Two possibilities were considered. Under the reaction condition diphenylketene could be generated. This may undergo cycloaddition with the aldehyde function of salicylaldehyde to form an intermediate β-lactone (9). Base-catalyzed decarboxylation of 9 may lead to the formation of 8a as shown in Scheme 3. But this possibility was ruled out by the following facts. When the reaction was carried out with a mixture of 6 and vanillin, the reaction product after usual workup contained 8a as the sole product and no crossover products like 1,1-diphenyl-2(4'-hydroxy-3'-methoxyphenyl)ethene or O-α,α-diphenylacetylvanllin could be detected in the reaction products.

The formation of 8a may, therefore, be rationalized by a different mechanism involving two consecutive intramolecular condensations. Base-catalyzed intramolecular aldol-condensation of 6 may lead to an alkoxide ion which, instead of taking up of a proton to form the aldol(7), may intramolecularly attack the acyl ester carbonyl carbon to form the same β-lactone intermediate 9. Base-catalyzed decarboxylation of 9 may give 8a as shown in Sceme 4.



Scheme3. Possible mechanism of formation of8a involving diphenylketene



Scheme 4. Most plausible mechanism of formation of 8a involving two consecutive intramolecular condensations

The above reaction of **6** with Et_3N thus represents a novel method for the synthesis of some stilbenoids.

Experimental

Acetylsalicyladehyde(2) was prepared by acetylation of salicylaldehyde with Ac_2O and pyridine, while other acyl derivatives 4 and 6 were prepared by reaction of the corresponding acyl chlorides with salicylaldehyde in presence of pyridine. Coumarin (1) was obtained by heating 2 with NaOAc or Et_3N and 3-phenylcoumarin (5) and 8a were synthesized by heating 4 and 6 with Et_3N, respectively. 5 and 8a were obtained in 93% and 70% yields , respectively.

References

1. T. Rosen in “Comprehensive organic synthesis” edited by B. M. Trost and I. Fleming. Vol. 2, 1991.
2. J. R. Johnson, Org. React., 1, 210(1942).
3. W. H. Perkin(Jr.), J. Chem. Soc., 21, 181(1868).
4. M. Crawford and J. A. M. Shaw, J. Chem. Soc., 3435, 3438(1953).