Proc. Indian Acad. Sci., Vol. 82 B, No. 6, 1975, pp. 224–229

Synthesis of α-aryloxy cinnamic acids

G. BAGAVANT, M. K. GURJAR AND B. H. PATWARDHAN
Department of Chemistry, Nagpur University Campus, Nagpur 440010

MS received 28 May 1975

ABSTRACT

The Perkin-Oglialoro reaction was used for the synthesis of α-aryloxy-cinnamic acids, but the yields were very low. The potassium tertiary butoxide catalysed condensation of aryloxyacetic ester and aldehydes leads to the formation of α-aryloxycinnamic acids and its corresponding ester, in good yields through an "oxocyclic intermediate pathway". The sodium ethoxide catalysed condensation however yields only the esters through an "aldol pathway", which on saponification give α-aryloxycinnamic acids. These alternative synthetic approaches to Perkin-Oglialoro reaction products, afford excellent methods for the synthesis of α-aryloxycinnamic acids.

1. INTRODUCTION

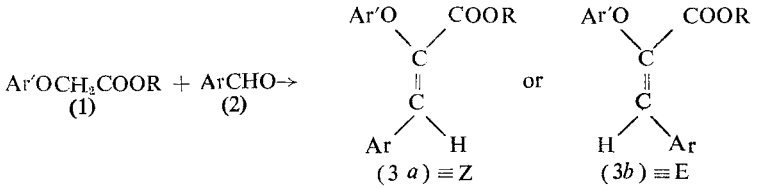
THE Perkin-Oglialoro[1] reaction has been used by Oglialoro[2] and Flammang, Wermuth and Schreiter[3] to prepare α-(phenoxy) and α-(*p*-chlorophenoxy) cinnamic acids by the condensation of aldehydes with phenoxyacetic and *p*-chlorophenoxyacetic acids, in the presence of triethylamine and acetic anhydride.

α-Aryloxycinnamic acids are likely to be of physiological interest as several aryl and aryloxyacetic acids possess hormonal property[4] and α-phenylcinnamic acids show antibacterial and antifungal activity.[5]

α-Aryloxycinnamic acids have been synthesised by Perkin-Oglialoro reaction of phenoxy-, *p*-chlorophenoxy-, 2 : 4 dichlorophenoxy- and β-naphthoxy acetic acids (table 2) but the yields are found to be very low. Modifications with change of catalyst and temperature do not show any improvement.

In an earlier paper,[6] as an alternative synthetic approach to the Perkin-Oglialoro method of preparation of cis α-phenylcinnamic acids, it was shown that the alkoxide catalysed condensation of phenylacetic ester and aldehydes led to the formation of cis α-phenylcinnamic acids and the corresponding ester. It was shown that the products are obtained by the initially formed oxyanion, reacting internally with a nucleophilic centre and loss of

anion, in an " oxocyclic intermediate pathway " to the acid and in addition, in an " aldol pathway " leading to the ester. As an extension of this reaction, phenoxy[7]-, *p*-chlorophenoxy-, 2 : 4 dichlorophenoxy- and β-naphthoxy[8]-acetic esters were condensed with aryl aldehydes in the presence of potassium tertiary butoxide when excellent yields of the acid and ester were obtained (table 1). The ester on saponification yields the same acid.



Acid ; R = H
Ester ; R = CH_3 or C_2H_5

It was observed that when this reaction was carried out under identical experimental condition in sodium ethoxide as catalyst, the main product was only the ester (in about 70%) and a small quantity of aryloxyacetic acid ($< 5\%$) was obtained in the acid fraction (table 3). The ester on hydrolysis yields α-aryloxycinnamic acid quantitatively.

The acid products obtained in these reactions were identical with ones obtained in the Perkin reaction, indicating that the same isomer (Z or E) was formed. The hydrogen had a δ value 7·05 ppm identical to the value reported for the *Z* compound by Flammang *et al.* and the series with Ar' = Ph showed in the ultraviolet spectra that the LE band is of lower intensity than that of ET band, characteristic of transcinnamic acid system. Earlier workers have reported that the acid from the Perkin reaction is the 'cis' isomer. The identity of these products distinctly indicates that in an " oxocyclic intermidiate pathway " also, the 'cis' isomer is formed which corresponds to *Z*.

Flammang *et al.*[3] have shown that the structure of the Perkin product is in conformity with the Zimmermann overlap orbital theory[9]; the mixed anhydride (4) would lead to the ethylenic acid isomer *Z*, through the trans elimination of acetic acid molecule from its rotational isomer (4 *a*). In the corresponding case of the oxyanion (5), in the " oxocyclic intermediate pathway ", it is observed that the identical conformer (5 *a*) would lead by lactonic pathway to the same acid *Z* and the " aldol pathway " to the ester which has been shown to have the same conformation as the acid.

The difference in behaviour between sodium ethoxide and potassium tert. butoxide have been explained[8] by applying Sicher's[10] interpretation that the base, in an elimination reaction, is not only involved in abstracting the proton (E_2H) but in addition, by nucleophilically assisting the Cα–X

Table 1. Condensation of aryloxyacetic ester and aldehydes in potassium tertiary butoxide.

Sl. No.	Ar′	Ar	Acid fraction m.p.	$\nu_{C=O}$ cm^{-1}	Yield %	Neutral fraction m.p.	R	$\nu_{C=O}$ cm^{-1}	Yield %
1.	Ph	Ph	180°	1680	34	..	CH_3	..	61
2.	,,	p-$CH_3OC_6H_4$	200°	1678	26	90°	CH_3	1723	66
3.	,,	3:4 $(OCH_3)_2$ C_6H_3	158°	..	33	..	CH_3	..	45
4.	,,	3:4 (O.CH_2.O) C_6H_3	197°	1680	41	114°	CH_3	1727	50
5.	,,	p-Cl C_6H_4	178°	1693	44	84°	CH_3	1720	52
6.	,,	p-$CH_3C_6H_4$	195°	..	48	80°	CH_3	..	45
7.	p-Cl C_6H_4	Ph	174°*	1700	43	70°	C_2H_5	1725	52
8.	,,	p-$CH_3OC_6H_4$	179°	..	40	87°	C_2H_5	..	49
9.	,,	p-Cl C_6H_4	184°	1680	39	88°	C_2H_5	1720	33
10.	,,	3:4 $(OCH_3)_2$ C_6H_3	190°*	1687	36	..	C_2H_5	..	44
11.	β-$C_{10}H_7$	Ph	199°	1680	49	89°	C_2H_5	1720	50
12.	,,	p-$CH_3OC_6H_4$	211°	1670	33	90°	C_2H_5	1727	50
13.	,,	p-$CH_3C_6H_4$	238°	..	38	119°	C_2H_3	..	47
14.	,,	3:4 (O.CH_2.O) C_6H_3	227°	1678	50	97°	C_2H_5	1725	50
15.	,,	p-$C_6C_6H_4$	215°	1695	46	130°	C_2H_6	..	50
16.	2:4 (Cl_2) C_6H_3	Ph	154°	1698	52	..	CH_3	..	18
17.	,,	p-$CH_3OC_6H_4$	175°	1693	38	..	CH_3	..	31

* The mixed m.p. undepressed with authentic sample.

Table 2. The Perkin reaction of aryloxyacetic acid and aromatic aldehydes

Sl. No.	Ar′	Ar	Acid fraction m.p.	Obs. Eq. wt.	Calc. Eq. wt.	Yield %
1.	β-$C_{10}H_7$	Ph	199°	289	290	12
2.	,,	p-$CH_3OC_6H_4$	211°	318	320	10
3.	,,	3:4 (O.CH_2.O) C_6H_3	227°	335	334	9
4.	,,	3:4 $(OCH_3)_2$ C_6H_3	221°	347	350	10
5.	p-ClC_6H_4	Ph	174°	273	274	40
6.	,,	3:4 $(OCH_3)_2$ C_6H_3	190°	332	334	27
7.	2:4 (Cl_2) C_6H_3	Ph	..	..	..	Nil
8.	,,	p-$CH_3OC_6H_4$	..	..	..	Nil

Table 3. Condensation of aryloxyacetic ester with aldehydes in sodium ethoxide

Sl. No.	Ar′	Ar	Neutral fraction			Yield %
			m.p.	R	$\nu_{c=o}$ cm^{-1}	
1.	Ph	p-Cl C_6H_4	84°	CH_3	1720	66
2.	Ph	Ph	..	CH_3	..	55
3.	p-Cl C_6H_4	Ph	70°	C_2H_5	1720	70
4.	,,	p-$CH_3OC_6H_4$	87°	C_2H_5	..	72
5.	β-$C_{10}H_7$	Ph	89°	C_2H_5	1720	75
6.	,,	p-$CH_3OC_6H_4$	90°	C_2H_5	1727	69
7.	,,	3:4 (O.CH_2.O) C_6H_3	97°	C_2H_5	1725	72
8.	2:4 (Cl_2) C_6H_3	Ph	..	CH_3	..	75

bond fission (E_2C). In the above cases the initially formed oxyanion which would cyclise to β-lactone (6), on the attack of the strong base would cleave to the α, β unsaturated acid (3 *a*) due to the operation of both E_2H and E_2C mechanisms, whereas with a weak base where the nucleophilic assistance is small and is insufficient to cleave Cα-O bond as in an E_2C pathway, the lactone reverts back to the oxyanion.

2. Experimental

Perkin reaction of β-naphthoxyacetic acid and anisaldehyde in the presence of triethylamine and acetic anhydride

β-Naphthoxyacetic acid (20 g) and anisaldehyde (13·6 g) were refluxed in the presence of 20 ml of acetic anhydride and 20 ml of triethylamine for about 35 minutes. The reaction mixture was cooled, diluted and acidified with concentrated hydrochloric acid. The solid residue was filtered and repeatedly extracted with 2% sodium hydroxide solution. The combined alkaline phase on acidification gave α-(*β-naphthoxy*) 4′-*methoxycinnamic acid* (3 g, 9%), crystallised from aqueous ethanol, [m.p. 211°, Eq. wt. obs., 318, calc. for $C_{20}H_{16}O_4$, Eq. wt. 320 (Found: C, 74·89; H, 5·06; reqd.: C, 75·01; H, 5·00%), $\nu_{c=o}$ 1670 cm^{-1} (α, β-unsaturated acid).

Condensation of methyl phenoxy acetate and p-*chloro-benzaldehyde in potassium tert. butoxide*

A mixture of methyl phenoxy acetate (4·1 g) and *p*-chloro-benzaldehyde (3·5 g) was added to potassium tert. butoxide (1 g of potassium in 25 ml of tert. butanol) and stirred for 45 minutes under inert anhydrous condition, at room temperature. The reaction mixture was acidified with 6N hydro-

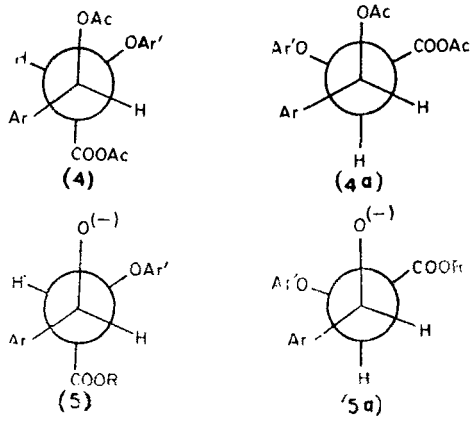
chloric acid and tert. butanol removed under reduced pressure and the residue was extracted with ether. Ethereal phase was repeatedly washed with ice-cold sodium carbonate solution. The combined alkaline phase on acidification gave α-(*phenoxy*) 4′-*chlorocinnamic acid* (3 g, 44%), crystallised from aqueous ethanol, mp. 178°, Eq. wt. obs. 273, calc. for $C_{15}H_{11}O_3Cl$, Eq. wt. 274 (Found: C, 65·46; H, 3·93; reqd.: C, 65·57; H, 4·00%), $\nu_{C=O}$ 1693 cm^{-1} (α, β-unsaturated acid).

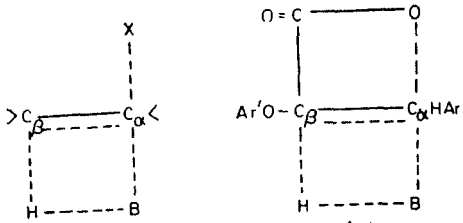
The neutral fraction on solvent removal gave *methyl* α-(*phenoxy*) 4′-*chloro cinnamate* (4 g, 52%), crystallised from petroleum—ether-solvent ether, m.p. 84° (Found: C, 66·50; H, 4·58; reqd.: C, 66·54; H, 4·50%), $\nu_{C=O}$1720 cm^{-1} (α, β-unsaturated ester).

α′-(*-chlorophenoxy*) *cinnamic acid* (*authentic sample*).—It was prepared[3] by refluxing the mixture of *p*-chlorophenoxyacetic acid (7·4 g), benzaldehyde (4·2 g) in the presence of 5 ml of triethylamine and 10 ml of acetic anhydride for 10 hours. After adding 10 ml of water and refluxing further for 30 minutes, the reaction mixture was poured over ice and extracted with ether. The ether layer was repeatedly washed with 10% potassium bicarbonate solution. The combined alkaline layer on acidification gave α-(p-*chloro-phenoxy cinnamic acid* (4·5 g, 40%), crystallised from aqueous ethanol. The uv and the melting point (174°) was identical with the acid [table 1 (7)] and did not depress the mixed melting point, confirming the identity of the structure.

Condensation of ethyl p-*chlorophenoxy acetate and benzaldehyde in sodium ethoxide*

A mixture of ethyl *p*-chlorophenoxy acetate (5·3 g) and benzaldehyde (2·7 g) was added to sodium ethoxide (0·7 g of sodium in 25 ml of ethanol) and stirred for 45 minutes at room temperature under inert anhydrous condition. The working up was done as given above. The alkaline phase on acidification gave p-*chlorophenoxy-acetic acid* (0·5 g), m.p. 155°.





(6)

The neutral fraction on solvent removal gave *ethyl* α-(p-*chlorophenoxy*) *cinnamate* (5·1 g, 70%), crystallised from petrolum ether-solvent ether, m.p. 70°, $\nu_{C=O}$ 1720 cm^{-1} (table 3).

Saponification of methyl α-(*phenoxy*) 4′-*chloro cinnamate*

Methyl α-(phenoxy) 4′-chlorocinnamate (2 g) was refluxed with 8% sodium hydroxide solution (30 ml) in the presence of ethanol (30 ml) for 6 hours and acidified to congo red.

It gave α-(*phenoxy*) 4′-*chloro cinnamic acid* (1·9 g), crystallised from aqueous ethanol, m.p. 178°. The mixed m.p. with the acid obtained above was undepressed.

ACKNOWLEDGEMENT

We thank Dr. S. M. Verma of Banaras Hindu University, Dr. M. S. Wadia of Poona University and Prof. T. R. Kasturi, Indian Institute of Science, Bangalore, for infrared and microanalysis. We are grateful to C.S.I.R. for a SRF (BHP) and the Department of Atomic Energy for a JRF (MKG).

REFERENCES

1. Johnson, J. R., *Organic Reactions*, John Wiley and Sons, London **1** 210 (1942).
2. Oglialoro, *Gazz. Chim. Ital.* **20** 505 (1890).
3. Flammang, M., Wermuth, C. G. and Schreiter, J., *Bull. Soc. Chim. Fr.* **12** 4619 (1972).
4. Finar, I. L., *Organic Chemistry*, ELBS and Longmans, Green & Co. Ltd., London **2** 419 (1964).
5. Pearl and Bayer, *J. Org. Chem.* **16** 216 (1951).
6. Patwardhan, B. H. and Bagavant, G., *Ind. J. Chem.* **10** 59 (1972).
7. Patwardhan, B. H., *Ind. J. Chem.* **12** 891 (1974).
8. Gurjar, M. K. and Bagavant, G. (Communicated).
9. Zimmermann, H. E., Singer, L. and Thyagarajan, B. S., *J. Am. Chem. Soc.* **81** 108 (1959).
10. Sicher, J., *Angew. Chem. Intern. Ed. Engl.* **11** 211 (1972).