

## A Convenient Route for Butyrolactone Synthesis

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**Summary:** 1,1-Diaryl-ethylene oxides(Ia-c) react with ethyl cyanoacetate or malononitrile and ethyl aceto-acetate in the presence of sodium ethoxide to give  $\gamma,\gamma$ -diaryl- $\alpha$ -cyano(IIa-c) and  $\gamma,\gamma$ -diaryl- $\alpha$ -aceto(IIIa-c)- $\gamma$ -butyrolactones, respectively. Alkaline hydrolysis of II afforded the corresponding  $\alpha$ -carboxy- $\gamma$ -butyrolactones(IVa-c). Decarboxylation of IV yielded  $\gamma,\gamma$ -diaryl- $\gamma$ -butyrolactones(Va-c). Also, (Ia-c) react with sodioacetylacetone to give 3-acetyl-5,5-diaryl-5-hydroxy-2-pentanones(VIa-c). The structure elucidation of the products is based on chemical transformations, spectral and chemical data.

It was reported [1] that  $\gamma,\gamma$ -diaryl- $\gamma$ -butyrolactones have chemotherapeutic activity on pathogenic viruses. This reported activity coupled with our interest in the chemistry of butyrolactones led us to report a convenient method for the synthesis of  $\gamma,\gamma$ -diaryl- $\gamma$ -butyrolactones(Va-c).

This method involves ring opening of the diaryl-ethylene oxides(Ia-c) using sodio-derivatives of ethyl cyanoacetate, malononitrile, ethyl acetoacetate and malonic ester. This method seems to be more suitable compared with the reported [2] synthesis of  $\gamma,\gamma$ -diaryl- $\gamma$ -butyrolactones via Stobbe condensation method. In the latter method the butyrolactones were obtained in low yield, since they were formed together with the corresponding itaconic acids [2]. A rather defect of the Stobbe condensation method is the possibility of isomerisation [2,3].

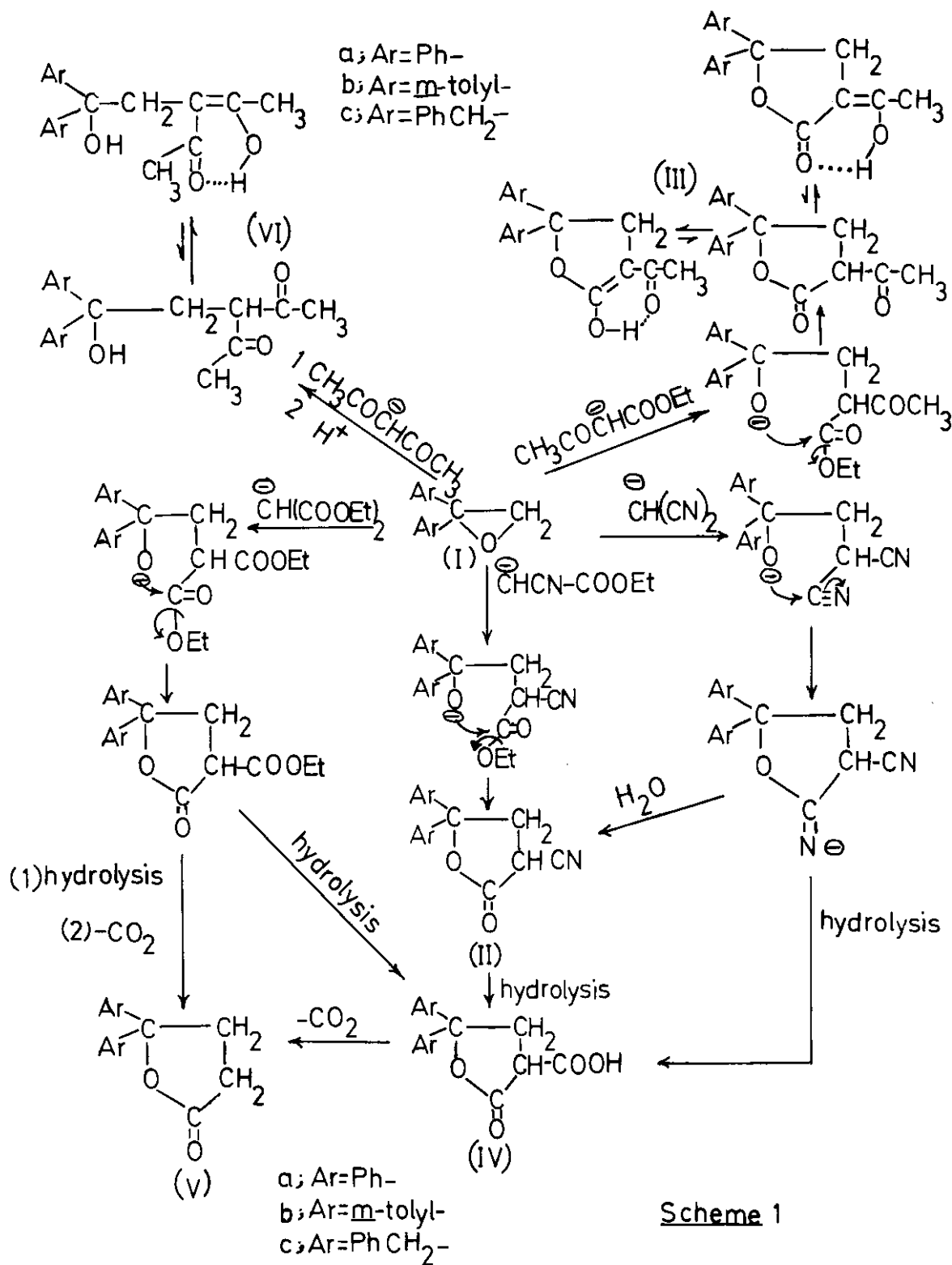
When ethyl chloroacetate is allowed to react with aryl magnesium-halides(Ar=Ph-, PhCH<sub>2</sub>-, *m*-tolyl),

followed by dehydro-halogenation, 1,1-diaryl ethylene oxides(I) are formed.

Ia-c react with ethyl cyanoacetate or malononitrile in the presence of sodium ethoxide to give  $\gamma,\gamma$ -diaryl- $\alpha$ -cyano- $\gamma$ -butyrolactones(IIa-c). The structure of the latter products is based upon: (i) elemental analysis, (ii) their IR spectra exhibit bands at 1750-1770( $\text{C}=\text{O}$  of saturated  $\gamma$ -lactone), 2250-2265  $\text{cm}^{-1}$  ( $\text{C}=\text{N}$ ) and (iii) identical m.p. & m.m.p. of the products obtained from reactions of Ia-c with ethyl cyanoacetate and malononitrile (cf. Scheme 1, Table 1).

Hydrolysis of IIa-c with aqueous potassium hydroxide afforded the corresponding  $\alpha$ -carboxylactones(IVa-c). The structural assignment of IV is inferred from: (i) their analytical data, (ii) IR spectra exhibit bands at 1750-1770 (saturated  $\gamma$ -lactonic  $\text{C}=\text{O}$ ), 1690-1710(carboxylic  $\text{C}=\text{O}$ ) and 2900-3300  $\text{cm}^{-1}$  (broad, carboxylic OH) and (iii) the product in each case showed no depression in m.p. on admixture with that obtained from the reaction of Ia-c with diethyl malonate (cf. Scheme 1 & experimental).

On refluxing (IVa-c) with copper bronze-quinoline mixture, decarboxylation occurred with the formation of



Scheme 1

the corresponding butyrolactones (Va-c), in good yield. The structure of Va-c is substantiated from: (i) analytical data, (ii) IR spectra show bands at 1745-1755  $\text{cm}^{-1}$  (saturated  $\gamma$ -lactonic  $\text{>C=O}$ ) and (iii) identical m.p & m.m.p with the decarboxylated products obtained in each case from reaction of I with malonic ester (cf. Scheme 1, experimental).

Ethyl acetoacetate reacts with (Ia-c) in the presence of sodium ethoxide to give  $\gamma,\gamma$ -diaryl- $\alpha$ -aceto-butylolactones (IIIa-c). The structure of (III) is illustrated from: (i) elemental analyses and (ii) their IR spectra showed bands at 1745-1760 (saturated  $\gamma$ -lactonic  $\text{>C=O}$ ), 1620-1640 (exocyclic  $\text{>C=O}$ ) and 3200-3500  $\text{cm}^{-1}$  (attributed to enolisation of III which is stabilised by chelation via intramolecular hydrogen bonding) (cf. Scheme 1, experimental).

Under similar conditions, Ia-c react with sodio-acetylacetone with the formation of 3-acetyl-5,5-diaryl-5-hydroxy-2-pentanones (VIa-c). The structure of the latter products is based on: (i) analytical data, and (ii) their IR spectra exhibited bands at 1630-1650 ( $\beta$ -diketonic  $\text{>C=O}$ ), 3500 (sharp, tertiary OH) and 3190-3480  $\text{cm}^{-1}$  (broad, attributed to enolisation of (VI) which is stabilised by chelation through intramolecular hydrogen bonding).

It is concluded from this investigation, that the steric factors play an important role or have superiority than the electronic factors in the reactions of 1,1-diarylethylene oxides with various carbanions. The results obtained from this study are in agreement with that reported in the literature [4].

## Experimental

All melting points are uncorrected. Infrared spectra (liquid film or KBr discs) were recorded on a Unicam SP 1200 spectrophotometer.

1,1-Di-*m*-tolyl-2-chloroethan-1-ol was prepared by the procedure used for preparation of 1,1-diphenyl or 1,1-dibenzyl-2-chloroethan-1-ol [5]; colourless crystals from absolute methanol; m.p 94-96°, (53% yield) (Found: C, 73.6; H, 6.5; Cl, 10.2  $\text{C}_{16}\text{H}_{17}\text{ClO}$ , requires C, 73.7; H, 6.4; Cl, 10.4%).

*Dehydrochlorination of 1,1-di-m-tolyl-2-chloroethanol: Formation of 1,1-di-m-tolyloxyethylene oxide:*

The dehydrochlorination was carried according to Klages procedure [6] to give colourless crystals from absolute methanol, 38% yield; m.p 48-50° (Found: C, 85.6; H, 7.0  $\text{C}_{16}\text{H}_{16}\text{O}$  requires C, 85.7; H, 7.1%).

*Reaction of (I) with ethyl cyanoacetate or malononitrile; Formation of  $\gamma,\gamma$ -diaryl- $\alpha$ -cyano- $\gamma$ -butylolactones (IIIa-c):*

Epoxides (Ia, c [5] and b) (0.03 mole) in absolute ethanol (20 ml) were added during 2 hr to a boiling stirred solution of sodioethylcyanoacetate or malononitrile (prepared from 3.5 g ethyl cyanoacetate or 2.8 g malononitrile and 1.1 g of sodium metal in 80 ml absolute ethanol). The reaction mixture was refluxed with stirring for 3 hr. Excess ethanol removed under reduced pressure and the residue poured into ice-cooled water. The resulting semi-solid product was cooled, acidified with dilute sulphuric acid, and extracted with ether several

Table-1: Characterisation Data of Compounds (II-VI)

Compound	m.P & b.p/mm °C	Solvent yield%	Formula	Analysis(Found/Calc)%		
				C	H	N
(IIa)	95-97	Pet.ether (80-100) (75%)	$C_{17}H_{13}O_2N$	78.0 77.8	5.5 5.6	4.8 5.0
(b)	104-5	Pet.ether (60-80°) (70%)	$C_{19}H_{17}O_2N$	78.1 78.3	6.1 5.8	4.6 4.8
(c)	96-98	Pet.ether (60-80°) (77%)	$C_{19}H_{17}O_2N$	78.4 78.3	5.9 5.8	4.7 4.8
(IIIa)	120-21	Pet.ether (60-80°) (70%)	$C_{18}H_{16}O_3$	77.4 77.1	5.5 5.7	
(b)	109-10	Pet.ether (80-100°) (75%)	$C_{20}H_{20}O_3$	78.0 77.9	6.6 6.4	
(c)	116-18	Pet.ether (80-100°) (80%)	$C_{20}H_{20}O_3$	77.6 77.9	6.5 6.4	
(IVa)	169-71	Benzene/ ethanol (60%)	$C_{17}H_{14}O_4$	72.5 72.3	5.6 5.8	
(b)	195-96	Benzene/ ethanol (64%)	$C_{19}H_{18}O_4$	73.2 73.5	6.0 5.8	
(c)	145-47	Benzene/ ethanol(60%)	$C_{19}H_{18}O_4$	73.3 73.5	6.1 5.8	
(Va)	85-86	Pet.ether (40-60°)(60%)	$C_{16}H_{14}O_2$	80.8 80.7	5.9 5.8	
(b)	90-92	Absolute methanol (67%)	$C_{18}H_{18}O_2$	80.9 81.1	6.8 6.7	
(c)	109-11	Pet.ether (60-80°) (75%)	$C_{18}H_{18}O_2$	81.0 81.1	6.6 6.7	
(VIa)	b.p.165-67/5	(58%)	$C_{19}H_{20}O_3$	77.4 77.1	6.5 6.7	
(b)	b.p.185-88/4	(55%)	$C_{21}H_{24}O_3$	78.0 77.7	7.1 7.4	
(c)	b.p.180-83/4	(60%)	$C_{21}H_{24}O_3$	77.9 77.7	7.2 7.4	

times. The organic extract washed with water and dried over ( $\text{Na}_2\text{SO}_4$ ).

Removal of ether gave a brownish red semi-solid product. The product was triturated with pet. ether ( $80-100^\circ$ ) to give (IIa-c). Recrystallisation from a suitable solvent (cf. Table 1) afforded (IIa-c) as colourless crystals.

*Hydrolysis of (II); Formation of carboxylactones (IVa-c):*

*Method A:*

IIa-c (0.02 mole) were mixed with KOH solution (2 g in 8 ml water), heated to boiling, cooled, diluted with water and extracted with ether. Acidification of aq. layer gave a colourless solid which was filtered, washed thoroughly with water and dried. Crystallisation of the solid product from a suitable solvent (cf. Table 1) afforded  $\gamma,\gamma$ -diaryl- $\alpha$ -carboxy- $\gamma$ -butyrolactones (IVa-c) as colourless crystals.

*Method B*

*Reaction of (I) with sodiomalonic ester; Formation of (IVa-c):*

Epoxides (Ia-c) (0.22 mole) in absolute ethanol (20 ml) were added during 2 hr to a boiling stirred solution of sodiomalonic ester (prepared from 3.8 g diethyl malonate and 0.5 g sodium metal in 80 ml absolute ethanol). The reaction mixture was refluxed for 3 hr, excess ethanol removed under reduced pressure, the residue mixed with aq. KOH (2g in 8 ml water) and heated to boiling. It was diluted with water and extracted with ether. Acidification of aq. layer with dilute sulphuric acid yielded a colourless solid which was filtered, washed thoroughly with water, dried and crystallised from a suitable solvent. The product obtained in each

case showed no depression on admixture with that obtained from method A.

*Decarboxylation of (IV); Formation of (Va-c):*

A mixture of (IV) (0.5 g), copper bronze (1.5 g) and quinoline (8 ml) was heated under reflux for 4 hr. Ice-cooled dil. hydrochloric acid was added to the reaction mixture and extracted with ether. Removal of ether gave a semi-solid, which was triturated with light petrol ( $60-80^\circ$ ) to give a yellowish brown solid product. Crystallisation from a suitable solvent (cf. Table 1) afforded (Va-c) as colourless crystals. (Va-c) showed no depression on admixture with the products obtained from method B by decarboxylation under the same conditions.

*Reaction of (I) with sodioacetoacetic ester; Formation of  $\gamma,\gamma$ -diaryl- $\alpha$ -aceto- $\gamma$ -butyrolactones (IIIa-c):*

The reaction was carried out as described in the reaction of (I) with ethyl cyanoacetate, using sodioacetoacetic ester (prepared from 3.5 g; 0.026 mole ethyl acetoacetate and 0.8 g sodium metal in 80 ml absolute ethanol). After removal the excess ethanol under reduced pressure, the residue was extracted with ether. The ethereal extract was washed with dil. hydrochloric acid, water and dried over  $\text{Na}_2\text{SO}_4$ . Removal of ether gave a solid which was crystallised from a suitable solvent, to give (IIIa-c) as colourless crystals (cf. Table 1).

*Reaction of (I) with sodioacetylacetone; Formation of (VIa-c):*

Epoxides (I) reacted with a solution of sodioacetylacetone (Prepared

from 5.8 g; 0.029 mole acetylacetone and 0.8 g sodium metal in 50 ml absolute ethanol) under the same conditions described previously. Removal of ether under reduced pressure, gaved a syrupy liquids which were purified by fractional distillation under reduced pressure to give (VIa-c) as colourness liquids (cf. Table 1).

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