Tetrahedron Vol 47, No 10/11, pp 1997-2004, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

IODINE OXIDATIVE COUPLING OF DIENE AND TRIENE-DIOLATES OF UNSATURATED CARBOXYLIC ACIDS.

M.J Aurell, S.Gil, M.Parra, A.Tortajada, and R Mestres*

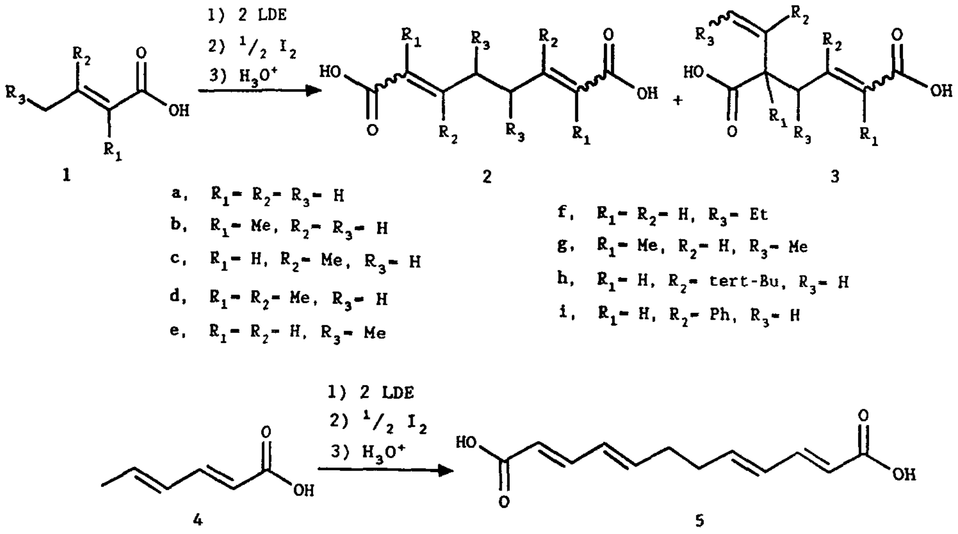
Departament de Química Orgànica Universitat de València, Burjassot, València, Spain

(*Received in UK* 4 *October* 1990)

ABSTRACT.- Oxidative Coupling of the dianions of unsaturated carboxylic acids 1, and 4 with iodine, which provides a convenient and facile preparation of γ,γ and ε,ε-dicarboxylic acids 2 and 5, apparently occurs through SET substitution of intermediate iodo-carboxylates.

We have reported that some octa-2,6-dienedioic and dodeca-2,4,8,10-tetraenedioic acids **2a** to **2c** and **5** can be easily prepared by oxidative coupling of the lithium dienediolates of unsaturated carboxylic acids **1a** to **1c** and **4** with silver or copper salts, and more conveniently with iodine [1,2] A wider range of substituents illustrates now the synthetic applicability of this coupling reaction (Scheme I), and some experiments suggest that coupling occurs through an intermediate lithium iodo-carboxylate, which is subject to SET substitution by the lithium dienediolate

Scheme I



1 2 3

a, R_1= R_2= R_3= H
b, R_1= Me, R_2= R_3= H
c, R_1= H, R_2= Me, R_3= H
d, R_1= R_2= Me, R_3= H
e, R_1= R_2= H, R_3= Me
f, R_1= R_2= H, R_3= Et
g, R_1= Me, R_2= H, R_3= Me
h, R_1= H, R_2= tert-Bu, R_3= H
i, R_1= H, R_2= Ph, R_3= H

4 5

The success of the synthetic method hinges on the high γ,γ-regioselectivity of the coupling reaction, as well as on the different solubility of the dimers in water. This feature allows easy separation of the insoluble γ,γ-coupling dimers **2** and **5** from the water soluble α,γ-isomeric dimers **3**, which can be extracted from the water filtrates In no case have the α,α-coupling dimers been observed

The high γ-regioselectivity is generally found even for those acids which afford poor reaction yields, and is in contrast with that shown by most ionic reactions (alkylation and aldol addition) of the same dienediolates, which occur at the α carbon atom under kinetic conditions The effect of substituents on regioselectivity suggests that coupling is partly directed by steric effects Thus, γ,γ-coupling is favoured by α-substitution, and tiglic, trimethylacrylic, and α-methylpentenoic acids **1b**, **1d** and **1g** afford better yields of the corresponding dimeric acids **2b**, **2d** and **2g** than crotonic, dimethylacrylic, and pentenoic acids **1a**, **1c** and **1e**, respectively On the contrary, methyl or ethyl substitution at the γ carbon atom, as in pentenoic, and hexenoic acids **1e** and **1f**, is accompanyied by a strong decrease in yields, the starting acids being partly recovered Upon substitution by a methyl at the ß carbon, poor results are obtained, whereas bulkier groups favour γ,γ-coupling, as in acids **1h** and **1i**

TABLE

Oxidation of Lithium Polyenolates of Unsaturated Carboxylic Acids with Iodine[a]

Starting Acid	γ,γ-dimer	(%)[a]	Configurations	α,γ-dimer[b]	Global Yield (%)
1a	2a	62	trans,trans	26	90
1b	2b	82	trans,trans	10	97
1c	2c	40	cis and trans[c]	16	64
1d	2d	77	cis,cis	11	88
1e	2e	33[d]	trans,trans		33
1f	2f	10[de]	trans,trans		30
1g	2g	41	trans,trans	25	66
1h	2h	80	cis,cis	10	90
1i	2i	63	cis,cis	34	97
5	5	60[f]	all trans	11	71

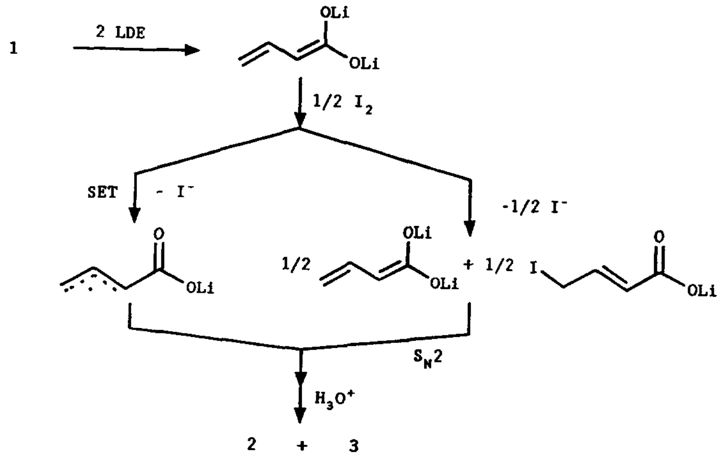
a - Pure solid compound recovered by filtration, b - Recovered as an oil from water filtrates, along with an additional small amount (2-5%) of γ,γ-dimer Yields estimated from ^{1}H NMR integration curves of mixtures, c - Mixture of stereoisomers - d - The crude material was extracted with ethyl acetate, e - Much starting material was recovered along with dimer, f - Pure compound when washed with methanol

Stereoselectivities found now are in keeping with those observed for ionic reactions of the dienediolates Thus, acids which have no ß substituent, namely crotonic, and tiglic acids **1a** and **1b**, as well as sorbic acid **4** are well known for giving trans γ-adducts on aldol addition to ketones,[3-5] and the same trans configurations have been now obtained as well from pentenoic, hexenoic, and methylpentenoic acids **1e**, **1f**, and **1g** In the presence of a ß substituent the common trend for γ-addition to ketones is changed to cis selectivity [3,6] It is thus not surprising that exclusive cis selectivity is observed for oxidative coupling of trimethylacrylic, tert-butylbutenoic, and ß-phenylcinnamic acids **1d**, **1h** and **1i**, though senecioic acid **1c** is exceptional in affording cis-trans mixtures Diastereoisomeric mixtures result from pentenoic, hexenoic and methylpentenoic acids **1e** to **1g**, as ^{1}H NMR and ^{13}C NMR spectra reveal

Fox and Renaud [7] have studied the oxidative coupling of the equivalent dianions of saturated and phenyl substituted carboxylic acids to substituted succinic acids, and found equivalent results for electrochemical and iodine oxidation, except for isolation of iodo-acids in some of the latter oxidations On the question whether the iodo-carboxylates were side products or reaction intermediates, these authors found that tertiary iodo-acids were not converted to the succinic acids under reaction conditions, but that sodium iodoacetate afforded cross coupling products on reaction with some dianions. These observations led to conclude that radical coupling mechanism and S_N2 type substitution on intermediate iodo-carboxylates were operative for oxidations with iodine, although internal trapping experiments failed as decisive argument for the first mechanism

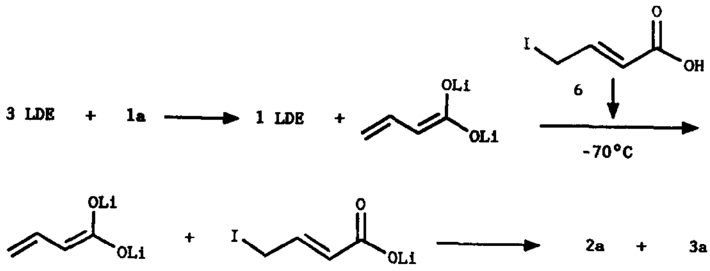
We first assumed that a similar reaction scheme would give account of our results (Scheme II), although in no case any iodo-butenoic acid was observed among our products. In order to find out the possibility of intermediacy by the iodoacid, 4-iodo-2-butenoic acid **6** was prepared from the corresponding

Scheme II



bromoacid[8] and added to a mixture of the lithium dienediolate of crotonic acid and one equivalent of base, (Scheme III) under the same conditions (slow addition at -70°C and stirring for 1 or 2 h at room temperature) as for oxidative coupling by iodine. Under these conditions the γ,γ-dimer **2a** was obtained in a 52% yield. The resulting water solution contained about 47% of the corresponding α,γ-dimer **3a**, and a very small additional amount of **2a**, as was observed by the ^{1}H NMR spectrum. These relative amounts of isomeric dimers are very similar to those obtained in some runs for oxidative coupling of crotonic acid dienediolate with a slight excess of iodine.

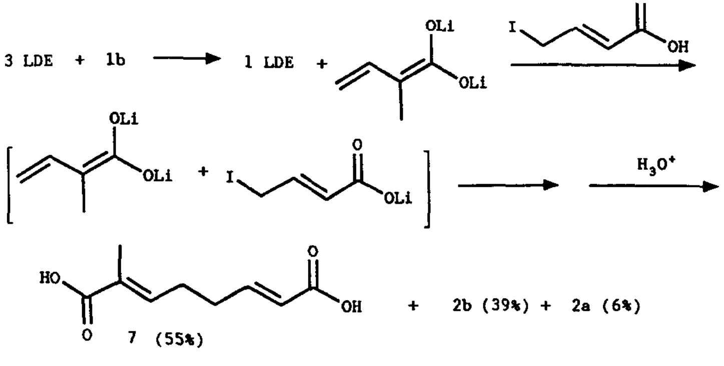
Scheme III



The intermediacy of the iodo-carboxylate seemed thus well established to us, although we could not observe any iododerivative among coupling products, even when excess of iodine was used Thus, in a run in which tiglic acid **1b** dienediolate was oxidized with a large excess of iodine, the γ,γ-dimer **2b** was obtained in lower yield (53%) than usual, but no iodoacid was observed. Most probably, the iodo acid transforms into a water soluble amino acid by substitution of iodine by the amine present in the solution. Thus, we have found that when 4-iodobutenoic acid **6** and diethylamine are dissolved in THF, the iodoacid is mostly recovered on immediate work up (evaporation of solvent, extraction of neutrals, and acidification), but not found when that solution is allowed to stand under our common reaction conditions (1 h at room temperature).[9]

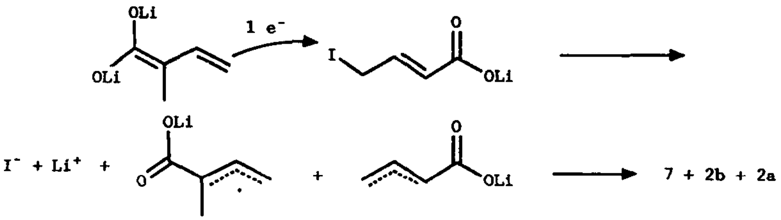
There was still the question whether the mechanism of the substitution step was an SN2-type reaction or a SET process. A cross coupling experiment between the same iodo-carboxylate and the

Scheme IV



dianion of tiglic acid **1b** was then carried out (Scheme IV) Methyloctadienedioic acid 7 would be expected as the exclusive γ,γ-coupling dimer for a S$_N$2-type reaction, whereas mixtures of γ,γ-dimers **2a**, **2b**, and 7 could result from radical intermediates, as in Scheme V. In fact, when solid material was isolated, a mixture of the three possible γ,γ-coupling compounds was obtained, as could be established by HPLC and by a ^{1}H NMR spectrum of the esterified mixture

Scheme V



From the present results we conclude that oxidative coupling of the dianions of unsaturated carboxylic acids is a very convenient method for preparation of octadienedioic acids, especially from substituted butenoic acids When a ß substituent is present in the butenoic acid, double bond cis configurations can be anticipated; otherwise, trans isomers result. The coupling reaction apparently ocurrs through intermediacy of iodo-carboxylates, which react with the dienediolates by a SET process

Experimental Section.

Melting points were determined with a Kofler hot plate apparatus, and are uncorrected I r spectral data were obtained for liquid film or potasium bromide discs, with a Perkin-Elmer 281 spectrophotometer 200 MHz n.m r spectra were recorded for $CDCl_3$ solutions, with a Bruker AC-200 spectrometer A Konik chromatograph with a S5-W column and hexane/ethyl acetate (9 1) run under isokratic conditions was used for HPLC analysis Kieselgel 60 was used for column chromatography

Elemental analyses were determined by Servicio de Semimicroanálisis del Centro de Investigación y Desarrollo de Barcelona.

Tetrahydrofuran (THF) was distilled from sodium diphenylketyl immediatelly before use Diethylamine was dried over CaH_2 and distilled before use Generation and reactions of the dienediolates were carried out in argon, under standard conditions for exclusion of moisture.

The generation of the dilithium dienediolate of the acids with 2 equiv. of lithium diethylamide, as well as addition conditions and general work-up procedures have been described[2,6] Lithium diethylamide has been usually prepared from lithium naphtalenide, except for oxidation of sorbic acid dianion, when work up becomes simpler by use of butyl lithium The reaction temperatures -70°C were achieved with a solid CO_2-Me_2CO bath

Esterifications were performed by treatment of acids with diazomethane or by reflux in MeOH with H_2SO_4 as catalyst

(Z,Z)-2,3,6,7,-tetramethylocta-2,6-dienedioic acid (2d). Reaction for 1 h at 20°C and working up gave a white solid (781 mg, 77%), mp 264-266°C (dec) (MeOH), IR 3460-2300, 1660, 1610 cm-^{1} Anal Cald for $C_{12}H_{18}O_4$ C, 63 70, H, 8 02 Found C, 63 73, H, 8 04

(Methyl ester) ^{1}H NMR 3 71 (s, 3 H), 2.21 (s, 2 H), 2 00 and 1.99 (s), 1.88 and 1 87 (s), ^{13}C NMR 170 05, 145 49, 123 19, 51 29, 33 72, 21 04, 15 21

Configuration was established by a differential NOE experiment

(R,R + R,S)(E,E)-4,5-dimethylocta-2,6-dienedioic acid (2e). Reaction for 1 h at 20°C and working up gave an oil By extraccion with ethyl acetate, a yellow syrup was obtained (296 mg, 33%) White prisms (from hexane-ether), mp 144°C (dec) IR 2500-2300, 1685, 1640 cm^{-1} Anal Cald for $C_{10}H_{14}O_4$· C, 60 59, H, 7.12 Found C, 60 38; H, 7 29

(Methyl ester) ^{1}H NMR 6 83 (m, 1 H), 5 8 (d, J = 15 6 Hz, 1 H), 3 72 (s, 3 H), 2 36 (dc, J = 6 6 y 5 4 Hz, 1 H), 1 03 (d, J = 6 5 Hz), 1 01 (d, J = 6.3 Hz), ^{13}C NMR 166 67, 151 46, 151 12, 121 03, 51 30, 41 20, 40.86, 16 90, 16 04

(R,R + R,S)(E,E)-4,5-diethylocta-2,6-dienedioic acid (2f).

Reaction for 1 h at 20°C and work up gave an oil By extraction with ethyl acetate, a yellow syrup was obtained (340 mg, 33%), flash chromatography purification gave a white waxy material

(Methyl ester) IR 2960, 2930 y 2870, 1720, 1655 cm^{-1}, ^{1}H NMR 6 71 (dd, J = 15 5 y 9 8 Hz), 6,66 (dd, J = 15 6 y 9 8 Hz), 5 8 (d, J = 15 6 Hz, 1 H), 3 70 (s, 3 H), 2 1 and 2 04 (m), 1 6-1 1 (m), 0 8 (c, J = 7 4 Hz), ^{13}C NMR 166 64, 166 57, 170 76, 149 35, 122 82, 122 64, 51 46, 25 21, 24 82, 11 90, 11 73

(R,R + R,S)(E,E)-2,4,5,7-tetramethylocta-2,6-diendioic acid (2g). Reaction for 1 h at 20°C and working up gave a white solid (420 mg, 41%), mp 263-265°C (MeOH), IR 3500-2200, 1685, 1640 cm^{-1} Anal Cald for $C_{12}H_{18}O_4$ C, 63 70, H, 8.02 Found C, 63 76, H, 8 10

(Methyl ester) ^{1}H NMR 6 55 (d, J = 8.8 Hz, 1 H), 3 71 and 3 70 (s, 3 H), 2.46 (m, 1 H), 1 82 (d, J = 1 5 Hz), 1 81 (d, J = 1 3 Hz), 0 98 (d, J = 6 3 Hz), 0 92 (d, J = 6 1 Hz), ^{13}C NMR 168.47, 145.60, 127 27, 51 67, 38 65, 17 82, 12 62

(E,E)-3,6-di-t-butylocta-2,6-dienedioic acid (2h) Reaction for 1 h at 20°C and working up gave a white solid (1.012 g, 80%), mp 274-275°C (MeOH), IR 3500-2240, 1690, 1605, 1400, 1365 cm^{-1}. Anal Cald for $C_{16}H_{26}O_4$· C, 68 06, H, 9 28 Found C, 68.17, H, 9 44

(Methyl ester) ^{1}H NMR 5 78 (s, 1 H), 3 67 (s, 3 H), 2 76 (s, 2 H), 1 17 (s, 9 H), ^{13}C NMR 169 85, 167 57, 113 97, 50 94, 38 62, 29 31.

Configuration was established by a differential NOE experiment

(E,E)-3,6-diphenylocta-2,6-dienedioic acid (2i). Reaction for 2 5 h at 0°C and working up gave a white solid (909 mg, 63%), mp 114-115°C (MeOH) Anal Cald for $C_{20}H_{18}O_4$ C, 75 41; H, 6 33 Found C,75 24, H, 6 07

(Methyl ester) IR 1715, 1625, 750, 690 cm^{-1}, ^{1}H NMR 7 34 (s, 5 H), 5 97 (s, 1 H),3 66 (s, 3 H), 3 22 (s, 2 H), ^{13}C NMR 166 62, 159.10, 140 81, 128 94, 128 45, 126 98, 117 85, 51 13, 29 65

Configuration was established by a differential NOE experiment.

(E)-4-Iodobut-2-enoic acid (6).

A mixture of sodium iodide (3.5 g, 23 mmol) and 4-bromobut-2-enoic acid (3 74 g, 22.6 mmol) in dry acetone (10 ml) was stirred under Ar at room temperature for 4 h The precipitate was filtered off and washed with CCl_4 The filtrate was concentrated to half its volume and filtered again. Evaporation of solvent gave a red solid that was dried under vacuum and crystallized from CCl_4 to give white plates (1 6 g, 34%), mp 98-102°C IR 3600-2400, 1695, 1645 cm^{-1}, ^{1}H NMR 10 5 (s, 1 H), 7 14 (dt, J = 15 4 and 8 3 Hz 1 H), 5.92 (d, J = 15 4, 1 H), 3 93 (d, J = 8 3 Hz, 2 H)

Reaction of lithium 4-iodobut-2-enoate with dienediolate of but-2-enoic acid.

A solution of but-2-enoic acid (6 mmol) in THF (10 ml) was slowly added to a stirred solution of lithium diethylamide (20 mmol) in THF (10 ml) at -70°C The resulting solution was stirred for 30 min at 0°C and cooled again at -70°C A solution of 4-iodobut-2-enoic acid (1 3 g, 6,1 mmol) in THF (30 ml) was slowly added, and the mixture stirred at room temperature for 2 h Water (60 ml) was added, and the THF evaporated under vacuum. Extraction of neutrals with ether and acidification gave **2a** (527 mg, 52%) The filtrate was extracted with ethyl acetate to give **3a** as a yellow oil (480 mg, 47%)

Reaction of lithium 4-iodobut-2-enoate with dienediolate of (E)-2 methylbut-2-enoic acid.

A solution of (E)-2-methylbut-2-enoic acid (600 mg, 6 mmol) in THF (10 ml) was slowly added to a stirred solution of lithium diethylamide (20 mmol) in THF (10 ml) at -70°C. The resulting solution was stirred for 30 min at 0°C and cooled again at -70°C A solution of 4-iodobut-2-enoic acid (1.24 g, 6 mmol) in THF (20 ml) was slowly added, and the mixture stirred at room temperature for 2 h. Water (60 ml) was added, and the THF evaporated under vacuum. Extraction of neutrals with ether and acidification gave a white solid (407 mg) that showed to be (HPLC and ^{1}H NMR) **7** (55%), **2b** (34%) and **2a** (6%)

Acknowledgements

The present work was financed by Comisión Asesora de Investigación Científica y Técnica (PB85-0214). One of us (M J.A.) acknowledges a grant by Conselleria de Cultura, Educació i Ciencia de la Generalitat Valenciana.

References and Notes

1.- Aurell, M.J., Gil, S., Tortajada, A., Mestres, R., and García-Raso, A. *Tetrahedron Lett.,* **1988,** *29,* 6181.

2.- Aurell, M J., Gil, S., Tortajada, A., and Mestres, R , *Synthesis,* **1990,** 317

3 - Casinos, I , and Mestres, R., *J.Chem Soc.Perkin Trans I,* **1978,** 1651

4 - Johnson, P R., and White, J.D., *J Org Chem* , **1984,** *49,* 4424

5 - Parra, M , Mestres, R , Aparicio, D , Durana, N , and Rubiales, G *J Chem Soc Perkin Trans.I,* **1989,** 327, and references therein.

6 - Ballester, P., García-Raso, A., and Mestres, R , *Synthesis,* **1985,** 802.

7 - Renaud, P , and Fox, M A *J.Am Chem.Soc* , **1988,** *100,* 5705, *J Org Chem* , **1988,** *53,* 3745

8 - For preparation of 4-bromo-2-butenoic acid, see Bellasoued, M , Habbachi, F., and Gaudemar, M , *Synthesis,* **1983,** 745

9 - Coupling reactions by Fox are run at -70°C for very short time, and frequently after removal of the amine resulting from deprotonation of the acid, whereas in our experiments the amine has never been removed, and reactions have been carried out by addition at -70°C, and stirring for 1 h at room temperature.