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REDUCTION OF ALKYL 2,4-ALKADIENOATES WITH SODIUM DITHIONITE UNDER PHASE TRANSFER CONDITIONS

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Abstract. The reduction of alkyl 2,4-alkadienoates, bearing alkyl substituents on the diene system, with sodium dithionite, under phase transfer conditions, gives satisfactory yields of E:Z isomeric mixtures of the corresponding 3-alkenoates, except in the case of the C-2 substituted substrate which afforded the E-3-alkenoate as the only reduction product.

INTRODUCTION

In the context of our ongoing interest in the study of the application of sodium dithionite as reducing agent in organic synthesis, under phase transfer catalysis (PTC),[1,2] we have reported on our preliminary results of the reduction of methyl sorbate as a model for preparation of β, γ-unsaturated esters from α, β, γ, δ-diunsaturated substrates.[3] Under PTC conditions, this reaction afforded a high yield (72%) of a 53:47 E:Z isomeric mixture of methyl hex-3-enoate. This result compared favorably with those obtained using other related synthetic procedures, such as the Birch reduction of α, β, γ, δ-diunsaturated acids.[4]

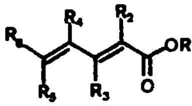
In the present communication, we describe the study of the reduction of alkadienoates Ia-Ie to assess the influence of methyl substitution in all the different positions of the conjugated diene system on the yield and stereochemistry of the reduced products.

RESULTS AND DISCUSSION

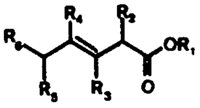
As shown in Table 1, reduction of alkadienoates Ia-Ie to the corresponding β, γ-unsaturated derivatives was generally achieved in satisfactory yields, using a 1.5-3.6 molar excess of sodium dithionite in a water:benzene two phase system, containing sodium bicarbonate and a commercial phase transfer catalyst. From our previous experience[5] we selected Activion 1008 and Adogen 464[6] as catalysts, the latter exhibiting a better performance in all cases studied.

The stepwise addition of the reductant led to an improvement of the yields obtained, presumably, by avoidance of the fast decomposition of the sodium dihionite, under the reaction conditions. Generally, the transformation was completed after two hours and, as in the case of methyl sorbate, afforded E:Z isomeric mixtures of the corresponding 3-alkenoates, with predominance of the E-isomer.

Table 1. Sodium dithionite reduction of alkyl 2,4-alkadienoates under phase transfer conditions.



I



II

	R_1	R_2	R_3	R_4	R_5	R_6
a	C_2H_5	CH_3	H	H	H	CH_3
b	CH_3	H	CH_3	H	H	$(CH_3)_2C{=}CHCH_2CH_2CH(CH_3)CH_2$
c	CH_3	H	H	CH_3	H	CH_3
d	CH_3	H	H	H	CH_3	$(CH_3)_2C{=}CHCH_2CH_2$
e	C_2H_5	CH_3	H	H	CH_3	$(CH_3)_2C{=}CHCH_2CH_2$

Entry	Substrate	Reagents ratio[vi]	Reduction method[vii]	Time(h)	Product	E : Z ratio	Yield[viii] %	Recovered substrate
1	Ia[i]	1:0.3: 5: 2.25	A	2	IIa	100:-	61 (61)	-
2	"	1:0.3: 8: 3.6	A	2	"	100:-	60 (60)	-
3	"	1:0.3: 5: 2.25	B	0.5	"	100:-	29 (37)	21
4	"	1:0.3: 8: 3.6	B	0.5	"	100:-	28 (31)	9
5	Ib[ii]	1:0.3: 5: 1.5	A	2	IIb	35:65	67 (88)	24
6	"	1:0.3: 5: 2.25	C	1	"	36:64	73 (90)	19
7	"	1:0.3: 8: 3.6	A	2	"	36:64	68 (80)	15
8	Ic[i]	1:0.3: 8: 3.6	A	2	IIc	72:28	59 (59)	-
9	Id[iii]	1:0.3: 8: 3.6	A	2	IId	59:41	43 (46)	6
10	Id[iv]	1:0.3: 8: 3.6	A	2	"	59:41	32 (40)	21
11	Id[iii]	1:0.3: 5: 2.25	B	4	"	61:39	22 (31)	29
12	Ie[v]	1:0.3: 8: 3.6	A	2	IIe	50:50	30 (48)	38
13	"	1:0.3: 5: 2.25	C	1	"	50:50	14 (31)	55
14	"	1:0.3:22:10	-	24	"	50:50	37 (37)	-

i) 2E,4E isomer 97% pure; ii) 2E,4E:2Z,4E isomer ratio 59:41; iii) 2E,4E:2E,4Z isomer ratio 59:41; iv) 2E,4E:2E,4Z isomer ratio 96:4; v)2E,4E:2E,4Z isomer ratio 62:38; vi) Substrate:Adogen(Activion in entries 13-14):bicarbonate:dithionite; vii) method A: 50% addition at t=0, 25% at t=30 min, 25% at t=60 min; method B: 50% addition at t=0, 50% at t=15 min; method C: 66% addition at t=0, 34% at t=30 min; viii) Numbers in parentheses represent the yield based on converted substrate.

Remarkably, the reduction of ethyl (2E,4E)-2-methylhexa-2,4-dienoate (Ia), under two different reaction conditions, led to the exclusive formation of ethyl (E)-2-methylhex-3-enoate (IIa) (cf. entries 1 and 2). However, at short reaction times a low recovery was obtained (cf. entries 3 and 4), suggesting the plausible transient formation of an intermediate adduct which at a later stage would be transformed into the reduction product.

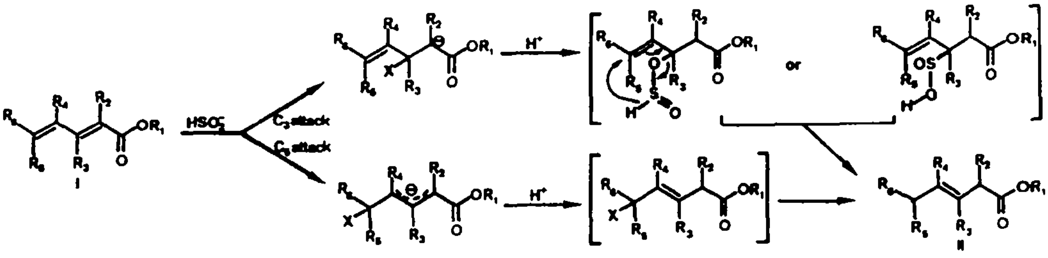
Surprisingly, the reduction of a 59:41 mixture of methyl (2E,4E:2Z,4E)-3,7,11-trimethyl-2,4,10-dodecatrienoate (Ib) furnished excellent yields of isomeric mixtures of the corresponding 3-alkenoate (IIb), in which the Z isomer was predominant under all the studied reaction conditions (cf. entries 5-7).

On the other hand, opposite results were obtained in the reduction of almost isomeric pure (97%) methyl (2E,4E)-4-methylhexa-2,4-dienoate (Ic) which afforded a 72:28 E:Z mixture of the corresponding ester IIc (cf. entry 8).

Analogously, the reduction of mixtures of two different isomeric ratios (59:41 and 96:4 2E,4E:2E,4Z) of methyl 5,9-dimethyldeca-2,4,8-trienoate (Id) gave the same 59:41 E:Z mixture of 3-alkenoate (IId) (cf. entries 9-11). In this case, the reaction was slower and the yields obtained were lower, when compared to those of the above mentioned substrates, pointing to the importance of the occurrence of a C-5 methyl substituent at the end of the diene system for the outcome of the reduction. However, in spite of these shortcomings, the overall two step sequence from the precursor aldehyde to the 3-alkenoate (IId) is more convenient than a recently reported four step procedure involving deconjugation of the corresponding 2-alkenoate in the last step.[7]

Likewise, the same difficulties were observed in the reduction of a 62:38 2E,4E:2E,4Z mixture of ethyl 2,5,9-trimethyldeca-2,4,8-trienoate (Ie), which under extreme conditions, by stepwise addition of up to a 10 molar excess of sodium dithionite, afforded after 24 h a complete transformation, but only a modest 37% yield (cf. entries 12-14).

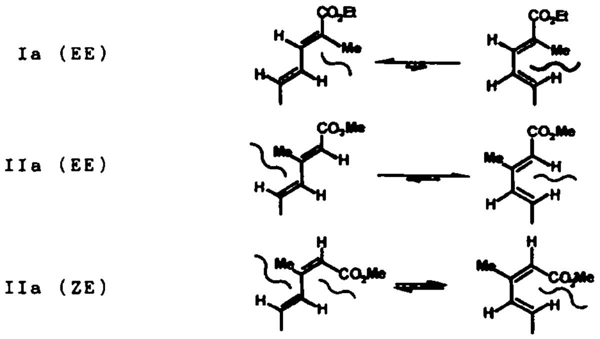
Plausibly, as we have previously pointed out,[2] in the reductions with sodium dithionite under phase transfer catalysis, the sulfoxylate anion is the reactive species in the organic layer. As shown in Scheme 1, two equivalent mechanisms might be envisaged by attack of this moiety either at C-3 or at C-5, followed by protonation and hydride transfer. Alternatively, initial hydride transfer from the reducing agent at C-5 would led to an intermediate allyl anion whose protonation would afford the final product. Apparently, initial attack at C-5 seems to be the favored pathway, as inferred from the reluctance of the reduction to take place when an alkyl substituent is present at this position, although we have no conclusive proof for this preference.



C_3 attack: X = OS(O)H or S(O)OH
C_5 attack: X = H, OS(O)H or S(O)OH

Scheme 1

On the other hand, as mentioned above in the reduction of Ia, the presence of a C-2 substituent in the diene moiety enhanced the stereoselectivity of the reaction when compared with the results obtained with other substrates, even with the parent unsubstituted methyl sorbate. As depicted in Scheme 2, this remarkable stereoselectivity could be accounted for assuming that it is originated either from the enhanced conformational preference of the s-trans form of the starting diene, due to the presence of the methyl substituent, or from the preferred stereochemistry in an intermediate allyl anion species. By the same token, the surprising predominance of the Z isomer of IIb in the reduction of the 3-substituted substrate (Ib), could be similarly rationalized.



Scheme 2

EXPERIMENTAL PART

Analytical methods. The NMR spectra were recorded in a Bruker WP80SY spectrometer operating at 1.88 T (5 mm spinning tubes: $CDCl_3$ with TMS as internal standard; chemical shifts given in ppm downfield (δ), and coupling constants in Hz. Gas chromatographic (GC) analyses were carried on Carlo Erba instruments, models 4130 or 4300 using a fused silica capillary column (25 m x 0.32 mm I.D.; SE-54 with H_2 as carrier gas) or glass column (2 m x 1/8" I.D.; 3% OV-101 on chromosorb W, with N_2 as carrier gas).

Starting 2,4-alkadienoates. The substrate dienoates (all known compounds) were conveniently obtained through Horner-Emmons olefination of the appropriate aldehydes with the corresponding alkoxycarbonylphosphonates:

-Ia(E,E) b.p. 53-55/0.3 torr. ^{1}H NMR: 1.30 (t, J = 7.0, $OCCH_3$), 1.88 (d, J = 6.0, $CH_3C=$), 1.92 (s, $CH_3C=$), 4.20 (q, J = 7.0, OCH_2), 6.18 (dq, J = 15.2 and J' = 6.0, $HC_5=$), 6.30 (dd, J = 15.2 and J' = 10.3, $HC_4=$) and 7.10 (d, J = 10.3, $HC_3=$) ppm.[8] ^{13}C NMR: 12.5 (CH_3), 14.3 ($OC\underline{C}H_3$), 18.7 (C-6), 60.4 (OCH_2), 125.0 (C-2), 127.5 (C-4), 137.4 (C-3), 138.4 (C-5), 168.5 (COO) ppm.

-Ib(E,E) ^{1}H NMR: 0.90 (d, J = 6.0, CH_3), 1.60 (s, $CH_3C=$), 1.68 (s, $CH_3C=$), 2.28 (d, J = 1.6, $CH_3C=$) 3.71 (s, OCH_3), 5.08 (t, J = 7.8, $HC_{10}=$), 5.85 (s, $HC_2=$) and 5.95-6.35 ($HC_4=$, $HC_5=$) ppm. (Z,E) ^{1}H NMR: 1.98 (d, J = 1.7, $CH_3C=$), 5.60 (s, $HC_2=$), 7.64 (d, J = 16.0, $HC_4=$) ppm (cf. lit. 9).

-Ic(E,E) b.p. 68-70°/5 torr. ^{1}H NMR: 1.75 (s, $CH_3C=$), 1.80 (d, J = 7.0, $CH_3C=$), 3.78 (s, OCH_3), 5.80 (d, J = 16.2, $HC_2=$), 6.00 (q, J = 7.0, $HC_5=$) and 7.30 (d, J = 16.2, $HC_3=$) ppm. ^{13}C NMR: 11.4 (C-6), 14.1 (CH_3), 50.9 (OCH_3), 114.7 (C-2), 133.5 (C-4), 135.9 (C-5), 149.3 (C-3), 167.6 (COO) ppm.[10]

-Id(E,E) ^{1}H NMR: 1.60 (s, $CH_3C=$), 1.68 (s, $CH_3C=$), 1.88 (s, $CH_3C_5=$), 3.74 (s, OCH_3), 5.10 (b, $HC_8=$), 5.82 (d, J = 15.4, $HC_2=$), 5.98 (d, J = 11.4, $HC_4=$) and 7.68 (dd, J = 15.4 and J' = 11.4, $HC_3=$)ppm.[10] ^{13}C NMR: 15.9 (CH_3C-5), 16.1 (c-CH_3C-9), 24.1 (t-CH_3C-9), 24.9 (C-7), 38.8 (C-6), 49.8 (OCH_3), 117.1 (C-2), 121.9 (C-4, C-8), 130.7 (C-9), 137.7 (C-3), 148.3 (C-5), 166.5 (COO) ppm.[11]

-Ie(E,E) ^{1}H NMR: 1.30 (t, J = 6.7, $OCCH_3$), 1.60 (s, $CH_3C=$), 1.70 (s, $CH_3C=$), 1.94 (s, 2x $CH_3C=$), 4.10 (q, J = 6.7, OCH_3), 5.10 (b, $HC_8=$), 6.15 (d, J = 11.2, $HC_4=$) and 7.52 (d, J = 11.2, $HC_3=$) ppm.[12]

General procedure for 2,4-alkadienoate reduction. A mixture of the 2,4-alkadienoate, phase transfer catalyst and sodium bicarbonate in benzene and water was vigorously stirred under nitrogen. Sodium dithionite was added portionwise (procedure A: 50% at t=0, 25% at t=30 min, 25% at t = 60 min; procedure B: 50% at t=0 and 50% at t=15 min; procedure C: 66% at t=0 and 34% at t=30 min) to the heated mixture (oil bath at 100°, providing a gentle reflux). After cooling, the aqueous layer was separated and extracted twice with diethyl ether. The combined organic extracts were washed with water, dried ($MgSO_4$) and the solvent removed in vacuo to give a residue. This residue was first analyzed by gas chromatography and later separated by silica gel column chromatography (CC; ratio SiO_2: crude/ 20:1) and the fractions containing the reduced compound joined and characterized by NMR and analyzed by capillary gas chromatography.

-Ethyl 2-methylhex-3-enoate, IIa. From Ia (97%, 2*E*,4*E* by GC; 0.77 g, 5.00 mmole), 25 ml of each solvent, Adogen (0.70 g, 1.50 mmole), and sodium dithionite (2.45 g, 11.15 mmole, addition mode A) (Table 1, entry 1), after 2 h reflux a 61% yield of IIa was obtained (identical result was accomplished using a 3.6 ratio of sodium dithionite). ^1H NMR: 1.00 (t, J = 7.0, CH_3C), 1.23 (d, J = 7.0, CH_3C), 1.27 (t, J = 7.0, $OCCH_3$), 2.0 (b, $CH_2C=$), 2.95 (b, =CCHCO), 4.12 (q, J = 7.0, OCH_3), 5.40-5.70 (2x HC=) (cf. lit. 13). ^{13}C NMR: 12.0 (C-6), 12.7 ($OC\underline{C}H_3$), 15.9 (CH_3), 23.9 (C-5), 41.3 (C-2), 58.8 (OCH_3), 126.5 (C-4), 132.1 (C-3), 173.5 (COO) ppm.

-Methyl 3,7,11-trimethyldodeca-3,10-dienoate, IIb. The best yield was obtained from a mixture of Ib (0.75 g, 3 mmole), 15 ml of each solvent, Adogen (0.42 g, 0.9 mmole), sodium bicarbonate (1.26 g, 15 mmole) and sodium dithionite (1.47 g, 6.75 mmole, addition mode C), after 1 h reflux (Table 1, entry 6). CC with the solvent system hexane:diethyl ether (9:1) afforded a 92% weight recovery (ratio Ib:IIb 21:79 on GC analysis) for a 90% yield based on substrate conversion. ^1H NMR: (E) 0.84 (d, J = 6.1, CH_3), 1.60 (s, $CH_3C=$), 1.68 (b, 2x $CH_3C=$), 2.97 (s, $=CCH_2CO$), 3.68 (s, OCH_3), 5.09 (t, J = 8.0, $HC_{10}=$) and 5.34 (t, J = 7.2, $HC_4=$) ppm; (Z) 1.77 (d, J = 1.5, $CH_3C=$), 3.05 (s, CH_2CO) ppm (cf. lit. 14).

-Methyl 4-methylhex-3-enoate, IIc. This compound was prepared under standard conditions with a 59% yield from Ic (Table 1, entry 8). ^1H NMR: (E) 1.00 (t, J = 7.2, CH_3), 1.62 (s, $CH_3C=$), 2.05 (q, J = 7.2. $CH_3C=$), 3.05 (d, J = 7.0, $=CCH_2CO$), 3.70 (s, OCH_3) and 5.30 (t, J = 7.0, HC=) ppm; (Z) 1.75 (s, $CH_3C=$), 3.05 (d, J = 7.0, $=CCH_2CO$) ppm.[15] ^{13}C NMR: (E) 12.6 (C-6), 16.0 (CH_3), 32.3 (C-5), 33.7 (C-2), 52.0 (OCH_3), 114.9 (C-3), 141.1 (C-4) and 173.7 (COO) ppm; (Z) 12.6 (C-6), 22.8 (C-5), 25.1 (CH_3), 33.4 (C-2), 52.0 (OCH_3), 115.7 (C-3), 141.7 (C-4) and 173.7 (COO) ppm.

-Methyl 5,9-dimethyldeca-3,8-dienoate, IId. The reduction of Id under standard conditions yielded 43% of the title compound (Table 1, entry 9). ^1H NMR: (E) 0.98 (d, J = 6.6, CH_3), 1.60 (s, $CH_3C=$), 1.68 (s, $CH_3C=$), 3.08 (d, J = 4.2, $=CCH_2CO$), 3.71 (s, OCH_3), 5.15 (t, J = 7.0 $HC_8=$) and 5.4-5.6 (HC=) ppm; (Z) 3.12 (d, J = 4.1, $=CCH_2CO$) ppm.[7]

-Ethyl 2,5,9-trimethyldeca-3-8-dienoate, IIe. The reduction of Ie was furthered for 24 hr and a stepwise addition of 10 molar excess of dithionite to afford 37% yield of IIe. ^1H NMR: 0.90 (d, J = 6.5, CH_3C_5), 1.18 (d, J = 6.5, CH_3C_2), 1.21 (t, J = 6.5, $OCCH_3$) 1.56 (s, $CH_3C=$), 1.62 (s, $CH_3C=$) 2.93 (q, J = 7.0, =CCHCO), 4.08 (q, J = 6.5, OCH_2), 5.10 (t, J = 6.5, $HC_8=$) 5.42 (d, J = 4.0, $HC_4=$) and 5.45 (d, J = 6.0, $HC_3=$) ppm.[16]

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