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PREPARATION OF RACEMIC AND ENANTIOMERICALLY PURE CYCLIC KETENE ACETALS

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Abstract: Cyclic ketene acetals have been prepared from a-haloaldehyde dimethylacetals by transacetalization and subsequent elimination in PTC without solvent conditions. No racemization has been observed when an enantiomerically pure diol has been used. Stability and storage conditions have been studied.

Cyclic ketene acetals have been claimed as usefull copolymers to introduce ester groups in polymeric aliphatic chains[1,2]. Our interest is the use of the title compounds, that behave as ketene equivalent, as dipolarophiles in the same way as vinyl ketene acetals do[3]. The use of compounds bearing a chiral center may induce chirality in the new adducts.

Cyclic ketene acetals have been prepared by elimination of HX (X=Br,Cl) from 2-halomethyl-1,3-dioxolanes or dioxepanes. However, the procedure for transacetalizations of halomethylaldehyde acetals was not so explicit and the eliminations required strong reaction conditions (generally potassium tert-butoxide/100^{o}C)[4,5,6].

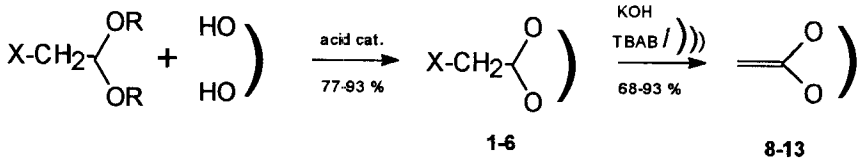
In 1991, solid-liquid PTC was applied, with good results, to promote elimination reactions[7]. This procedure required the use of two moles of potassium tertbutoxide in THF, at 0^{o}C. Isolation of reaction products generally

required a double distillation and one of them (2-methylene-1,3-dioxolane) has not been isolated in a pure state, probably due to their high tendency to polymerize.

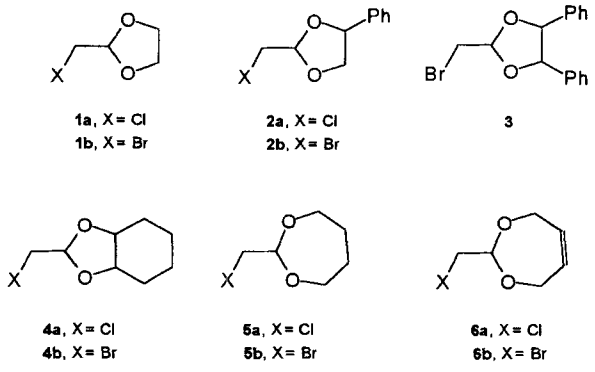
Solid-liquid PTC in the absence of solvent showed to be a useful procedure to perform several reactions. For instance, elimination of 2-bromooctane[8] or the preparation of alkynes[9] or 1-chloroalkynes[10] have been succesfully performed.

Results and Discussion

We have prepared the title compounds by transacetalization of haloacetaldehyde dimethylacetal and subsequent elimination using ultrasound coupled with solid-liquid PTC in the absence of solvent[11] (Scheme 1). The nature of the leaving group, base, phase transfer agent, the reaction conditions and the influence of ultrasound have been analysed.



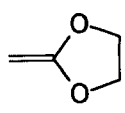
Scheme 1



Transacetalization was performed by literature procedures, heating at 120°C for one hour and using Dowex 50(H^+) or sulfuric acid as acid catalysts. Reactions and yields are reproducible up to 500 mmoles.

Table 1. Preparation of 2-methylene 1,3-dioxolanes or dioxepanes (PTC).

starting product	base	acetal : base mole ratio	time (h)	temp. (°C)	yield
1b	KOH	1:2	2	80	polymerization
2a	KOH	1:2.5	15	60	30
2b	KOH	1:2	1.5	90	68
2b	$KOBu^t$	1:1.5	2	60	51
4b	$KOBu^t$	1:1.5	4	75	36
5a	KOH	1:2.5	14	110	0
5b	KOH	1:2.5	1	80	63
5b	$KOBu^t$	1:1.5	15	80	50
6b	KOH	1:2	2	90	41
6b	$KOBu^t$	1:1.5	15	70	30



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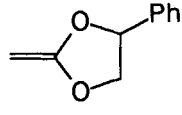

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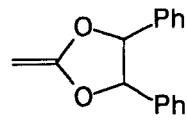

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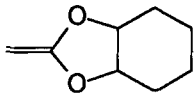

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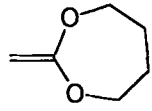

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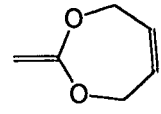

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Eliminations are performed by mixing at 0°C the cyclic haloacetal, the phase transfer agent (TBAB or Aliquat 336) (2%), and the base. The reaction mixture was heated at the adequate temperature for the required time.

The nature and proportion of the base and the reaction conditions have been varied. Selected results are gathered in Table 1.

Table 2. Effect of ultrasonic irradiation and the presence of catalyst. [a]

Starting product	US	catalyst	time (h)	temp. (°C)	yield
1b	-	+	2	80	0 [b]
1b	+	+	1	75	68
2b	-	-	1.5	90	37
2b	-	+	1.5	90	68
2b	+	+	1	75	81
2b	+	-	1	75	65
5b	-	-	1	75	20
5b	-	+	2	90	41
5b	+	+	1	75	70
5b	+	-	1	75	22

a) base: KOH; substrate:base 1:2, mole ratio ; catalyst: TBAB.
b) polymerization.

Results obtained show that potassium hydroxide is more efficient that potassium tert-butoxide. This fact must be explained considering that the use of potassium tert-butoxide produces a vigorous reaction involving extrusion of hydrogen bromide that causes decomposition of the reaction products.

The best results are obtained using potassium hydroxide in a 2 mole ratio, temperatures around 80-90°C and reaction times over two hours. However, results are not completely satisfactory. 2-Methylene-1,3-dioxolane has not been isolated and reaction yields are moderate.

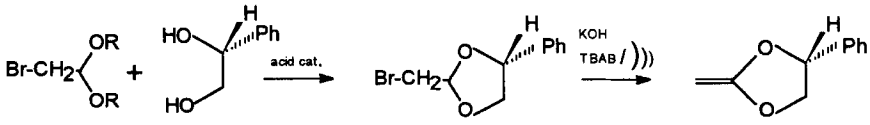
The use of ultrasonic irradiation have a positive effect and yields increase when reactions are performed in an ultrasonic bath (50 kHz, 200W) at 75°C for one hour (Table 2). The activation by ultrasonic irradiation is due to the implosion of the ultrasonic cavities and the fragmentation and reduction of the

particle size, with the subsequent increase in the reaction surface[12] together with a better dispersion of the solids in the liquid phase.

Best results are obtained using a combination of both methods, ultrasonic irradiation and phase transfer catalysis in the absence of solvent (Table 2).

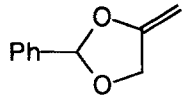
On the other hand, isolation of the reaction products is achieved by direct distillation from the reaction crude. In this way, 2-methylene-1,3-dioxolane is isolated in a pure state (no polymerization has been observed in the ^{1}H-NMR spectrum).

Starting from (R)-phenyl-1,2-ethanediol and using the standard reaction conditions no racemization was observed and the enantiomerically pure (R)-2-methylene-4-phenyl-1,3-dioxolane was isolated (Scheme 2). Differentation between both enantiomers was performed using (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.



Scheme 2

Other kind of acetals have been also prepared using this method. 4-Bromomethyl-2-phenyl-1,3-dioxolane (**7**) yields 4-methylene-2-phenyl-1,3-dioxolane (**14**) in 93% yield. The bromoderivative was prepared from bromomethyloxirane and benzaldehyde using literature procedure for chlorocompounds[13].



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Cyclic ketene acetals are unstable compounds and polymerize easily. The presence of humidity, trazes of acid or an increase in the temperature promote a rapid polymerization of the title compounds. We have studied the stability and

the best storage conditions of these compounds. Addition of catalytic amounts of bases (triethylamine or potassium carbonate) or radical inhibitors (2,4,6-tri-tertbutylphenol or phenothiazine) provides stabilization for two weeks at room temperature. However, under nitrogen or at -20°C cyclic ketene acetals are stable for at least six months.

Experimental

All reagents are commercial quality. IR spectra were recorded with a Philips PU 9500 spectrophotometer. NMR spectra ($CDCl_3$) were recorded on a Bruker AW-80 (80MHz) and on a Varian Unity (300MHz) using TMS as internal standard.

Preparation of 2-halomethyl-1,3-dioxolanes or dioxepanes (**1-6**). In a round bottom flask equiped with a distillation system (Vigreux column) the catalyst and equimolecular amounts of the appropriate halomethylaldehyde dimethylacetal and diol were placed. Reaction mixture was heated at 120°C for one hour and products were isolated by direct ball-to-ball distillation when sulfuric acid was used. The crude was filtered off and the residue was washed with dichloromethane when Dowex 50 (H^+) was used, removal of solvent and ball-to-ball distillation afforded the pure products.

2-Chloromethyl-1,3-dioxolane (**1a**): 93%; b.p.(°C/mmHg): 175/720 (lit.155-159/740)[4] ; IR(neat) $\nu_{max}(cm^{-1})$: 2892, 1046, 944. ^{1}H-NMR, δ(ppm): 3.51(d, 2H, J=7Hz), 3.95 (d, 4H, J=7.2Hz), 5.14 (t, 1H, J=7Hz). 2-Bromomethyl-1,3-dioxolane (**1b**): 94%; b.p.(°C/mmHg): 69-72/10 (lit. 172-175/745)[4]; IR(neat) $\nu_{max}(cm^{-1})$: 2891, 1114, 1038, 973. ^{1}H-NMR, δ(ppm): 3.30 (d, 2H, J=7Hz), 4.00 (d, 4H, J=7Hz), 5.10 (t, 1H, J=7Hz). 2-Chloromethyl-4-phenyl-1,3-dioxolane (**2a**): 79%; b.p.(°C/mmHg): 96-100/0.01 (lit. 96-97/0.01)[5]; IR(neat) $\nu_{max}(cm^{-1})$: 2960, 1186, 1143. ^{1}H-NMR, δ(ppm): 3.50-4.50 (m, 4H), 4.90-5.60 (m, 2H), 7.30 (s, 5H). 2-Bromomethyl-4-phenyl-1,3-dioxolane (**2b**): 87%; b.p.(°C/mmHg): 100/0.01; IR(neat) $\nu_{max}(cm^{-1})$: 2884, 1186, 1143. ^{1}H-NMR, δ(ppm): 3.20-4.50 (m, 4H), 4.90-5.50 (m, 2H), 7.30 (m, 5H). 2-Bromomethyl-4,5-diphenyl-1,3-dioxolane (**3**): 89%; purified by recristallization from hexane m.p.: 84-85 (lit. 85.2-85.4)[15] ; IR (KBr) ν_{max} (cm^{-1}): 2984, 1420, 1200. ^{1}H-NMR, δ(ppm): 3.77 (d, 2H), 5.43 8s, 2H), 5.45 (t, 1H), 7.10 (m, 10H). 8-Chloromethyl-7,9-dioxabicycle[4.3.0]nonane (**4a**): 71%; b.p.(°C/mmHg): 55-58/0.05; IR(neat) $\nu_{max}(cm^{-1})$: 2934, 2862, 1126,

1027. ^{1}H-NMR, δ(ppm): 1.00-2.30 (m, 8H), 3.40 (m, 2H), 4.00-4.20 (m, 2H), 5.00-5.45 (m, 1H). 8-Bromomethyl-7,9-dioxabicycle[4.3.0]nonane (**4b**): 73%; b.p.(°C/mmHg): 64/0.05; IR(neat) ν_{max}(cm^{-1}): 2935, 2862, 1126, 1027. ^{1}H-NMR, δ(ppm): 1.00-2.30 (m, 8H), 3.45 (m, 2H), 4.00-4.25 (m, 2H), 5.00-5.45 (m, 1H). 2-Chloromethyl-1,3-dioxepane (**5a**): 75%; b.p.(°C/mmHg): 81-84/10 (lit. 74-75/6)[16]; IR(neat) ν_{max}(cm^{-1}): 2935, 2862, 1126, 1027. ^{1}H-NMR, δ(ppm): 1.60-1.80 (m, 4H) 3.40 (d, 2H, J=7Hz), 3.50-4.10 (m, 4H), 4.80 (t, 1H, J=7Hz). 2-Bromomethyl-1,3-dioxepane (**5b**): 76%; b.p.(°C/mmHg): 91-94/10; IR(neat) ν_{max}(cm^{-1}): 2876, 1137. ^{1}H-NMR, δ(ppm): 1.60-1.80 (m, 4H) 3.20 (d, 2H, J=7Hz), 3.40-4.10 (m, 4H), 4.80(t, 1H, J=7Hz). 2-Chloromethyl-1,3-dioxep-5-ene (**6a**): 77%; b.p.(°C/mmHg): 82/25; IR(neat) ν_{max}(cm^{-1}): 1448, 1443, 1134. ^{1}H-NMR, δ(ppm): 3.50 (d, 2H, J=7Hz), 4.00-4.70 (m, 4H), 4.90 (t, 1H, J=7Hz), 5.75 (s, 2H). 2-Bromomethyl-1,3-dioxep-5-ene (**6b**): 78%; b.p.(°C/mmHg): 90/25; IR(neat) ν_{max} (cm^{-1}): 3031, 1447, 1423, 1130. ^{1}H-NMR, δ(ppm): 3.32 (d, 2H, J=7Hz), 4.00-4.70 (m, 4H), 4.90 (t, 1H,J=7Hz), 5.67 (s, 2H).

Preparation of methylene-1,3-dioxolanes or dioxepanes (**8-14**). In a conical flask one equivalent of bromomethylacetal (**1-7**), two equivalents of KOH and TBAB (2%) were placed. Reaction mixture was submerged in a ultrasonic cleaning bath (50 KHz, 200 W) for one hour at 75 °C. Distillation of reaction crude afforded the pure product.

2-methylene-1,3-dioxolane (**8**): 68%; b.p.(°C/mmHg) 56-59/30 (lit. 78-82/760)[14] IR(neat) ν_{max} (cm^{-1}): 2096, 1684, 1476, 1052. ^{1}H-NMR, δ(ppm): 3.20 (s, 2H), 4.10 (s, 4H). 2-methylene-4-phenyl-1,3-dioxolane (**9**): 81%; b.p.(°C/mmHg) 79-81/0.01 (lit. 73/0.1)[5] IR(neat) ν_{max} (cm^{-1}): 2957, 1750, 1676, 1493, 1199. ^{1}H-NMR, δ(ppm): 3.36 (d, 1H, J=3Hz), 3.40 (d, 1H, J = 3Hz), 4.04 (dd, 1H, J=8.1, 7.5Hz), 4.53 (dd, 1H, J=8.1, 6.9Hz), 5.38 (t, 1H, J=7.2Hz), 7.39 (s, 5H). 2-methylene-4,5-diphenyl-1,3-dioxolane (**10**): 87%; purified by extraction from the reaction crude with hexane, m.p.: 67-68(diethylether) (lit. 68)[15] IR(KBr) ν_{max} (cm^{-1}): 2860, 1680, 1250, 1110. ^{1}H-NMR, δ(ppm): 3.55 (s, 2H), 5.61 (s, 2H), 7.20 (m, 10H). 8-methylene-7,9-dioxabicycle[4.3.0]nonane (**11**): 61%; b.p.(°C/mmHg) 75/0.5. IR(neat) ν_{max} (cm^{-1}): 2940, 1685, 1448, 1025. ^{1}H-NMR, δ(ppm): 1.00-1.90 (m, 8H), 3.20 (s, 2H), 4.00-4.45 (m, 2H). 2-methylene-1,3-dioxepane (**12**): 79%;

b.p.(°C/mmHg) 96-99/20 (lit. 42/5)[16] IR(neat) ν_{max} (cm^{-1}): 2846, 1738, 1657, 1569, 1130. ^{1}H-NMR, δ(ppm): 1.50-1.80 (m, 4H), 3.40 (s, 2H), 3.80-4.00 (m, 4H). 2-methylene-1,3-dioxep-5-ene (**13**): 70%; b.p.(°C/mmHg) 80/20. IR(neat) ν_{max} (cm^{-1}): 3038, 2866, 1670, 1450, 1056. ^{1}H-NMR, δ(ppm): 3.55 (s, 2H), 4.40 (s, 4H), 5.70 (s, 2H). 4-methylene-2-phenyl-1,3-dioxolane (**14**): 93%; b.p.(°C/mmHg) 80/0.01 (lit. 55/0.05)[7] IR(neat) ν_{max} (cm^{-1}): 1685, 1089, 1069. ^{1}H-NMR, δ(ppm): 3.85 (m, 1H), 4.40 (m, 1H), 4.60 (m, 2H), 6.00 (s, 1H), 7.35 (s, 5H).

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