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HOMOLYTIC REDUCTIVE ALKYLATION OF METHYLVINYL KETONE WITH ETHERS BY Ti(III) DECOMPOSITION OF *t*-BUTYL HYDROPEROXIDE

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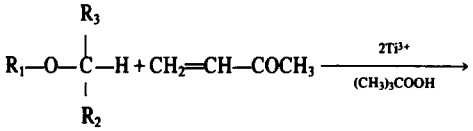
Abstract—Reductive alkylation of methylvinylketone has been accomplished by hydrogen abstraction from cyclic ethers with the redox couple: *t*-butyl hydroperoxide-titanous chloride. A redox free radical mechanism is proposed and the selectivity of the hydrogen abstraction by *t*-butoxy radicals and reduction of α-ketoalkyl radical by titanous ions is discussed.

The addition of α-oxyradicals, generated by hydrogen abstraction from ethers, to olefins in chain processes (Scheme 1) is a well known method for C–C bond formation.[1]

These reactions afford useful synthetic results only with high ratios of ether to olefin and with non-polymerizable olefins in order to facilitate the chain-transfer step of the hydrogen abstraction from the ether by the adduct radical and to prevent olefin telomerization. The results are very poor with polymerizable vinyl monomers owing to the high values of their homopolymerization rate constants,[2] when $k_2 > k_1$, telomerization or polymerization prevails over the chain transfer.

We have recently reported[3] the possibility of carrying out carbon free radical additions to easily polymerizable vinyl monomers conjugated with electron withdrawing groups (i.e. vinyl ketones) in the presence of reducing metal ions (Ti(III), Cr(II), etc), based on the high rates of reduction of electrophilic carbon-centered radical adducts by metal salts, which compete with the polymerization rate.

We now describe a new method of reductive homolytic alkylation of methyl vinyl ketone with ethers by the redox free-radical reaction of eqn (1).

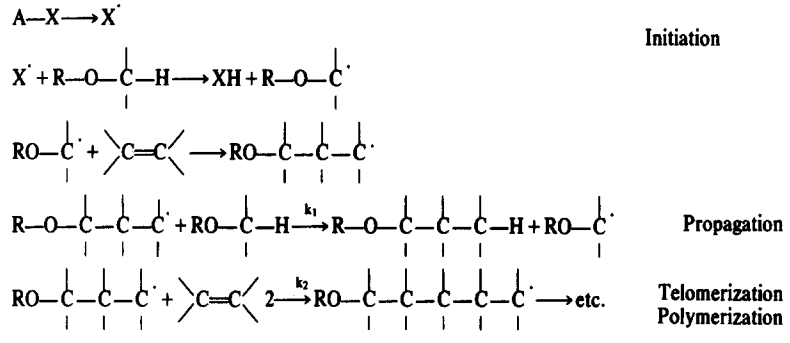


(1)

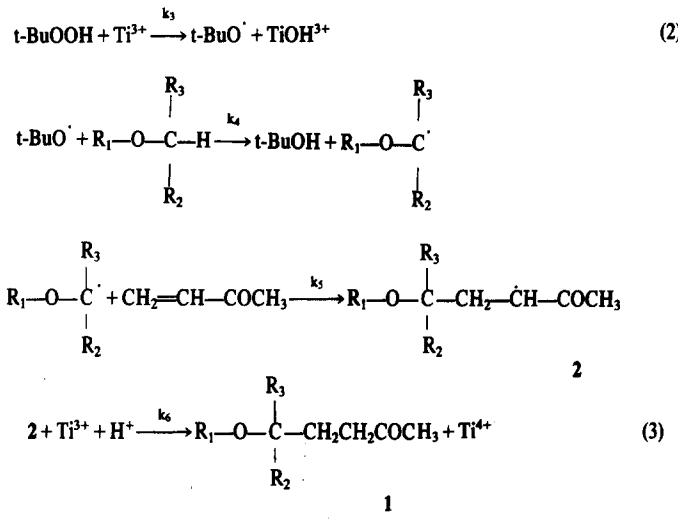
1

The mechanism of Scheme 2 can be envisaged for this reaction:

Several features of this mechanism emphasise the importance of the choice of the cyclic ethers for the reductive alkylation. The redox couple *t*-BuOOH/Ti^{3+} is a well known source of *t*-butoxy radicals; recent studies[4] have shown that the rates of hydrogen abstraction from C–H bonds by *t*-butoxy radicals are higher than those previously considered; with cyclic ethers, values of 10^6–10^7 M^{-1} sec at −60° have been reported, about an order of magnitude higher than with acyclic ethers. These high rate constants help to reduce the parasitic side reactions



Scheme 1.



Scheme 2.

involving the reduction of *t*-butoxy radical by Ti^{3+} (eqn 4)

$$t\text{-BuO}^{\cdot} + Ti^{3+} + H^{+} \longrightarrow t\text{-BuOH} + Ti^{4+} \qquad (4)$$

However, the high rates of hydrogen abstraction allow the reaction to be carried out by adding a solution of *t*-BuOOH to a mixture of methyl vinyl ketone, Ti(III) salt and ether. This procedure gives the best yields of 1 because a relatively high concentration of Ti(III) salt is always present during the reaction. This has a negative effect because it favours reaction 2, but two more positive effects make it very useful: a high concentration of Ti(III) salt favours the α-ketoalkyl radical reduction (eqn 3) and eliminates the olefin telomerization; and a low stationary concentration of *t*-butyl hydroperoxide is attained by its fast reduction with Ti(III) salt. The latter point minimises the other more dangerous parasitic side-reactions involving the hydrogen abstraction from hydroperoxide (eqn 5) for which the very high rate constant $2.5 \cdot 10^{8}\ M^{-1}\ sec^{-1}$ at 25° has been evaluated.[5]

$$t\text{-BuOOH} + t\text{-BuO}^{\cdot} \longrightarrow t\text{-BuOO}^{\cdot} + t\text{-BuOH}. \qquad (5)$$

The peroxy radical *t*-BuOO$^{\cdot}$ is much less effective than the *t*-BuO$^{\cdot}$ radical in hydrogen abstraction.

Polar effects and stereoelectronic effects, connected with the dihedral angles of the C–H bonds adjacent to oxygen contribute to produce the high rates of abstraction. Polar effects also influence k_3 and k_6: the α-oxyalkyl radicals have a pronounced nucleophilic character,[6] which increases the addition rate to electron-deficient olefins and decrease the reduction rate by Ti(III), whereas the α-ketoalkyl radical adducts have electrophilic character[6] and are easily reduced by Ti(III).

Some examples of the reaction are reported in Table 1. The yields given are based on the hydroperoxide used; those based on the ether are almost quantitative (except with the 1,3-dioxolane) and those on methyl vinyl ketone are high (70–80%).

The selectivity observed for the radical adduct in the α-position of the ethers is high compared with the β (>90); this qualitatively agrees with the reported relative rates of hydrogen abstraction from ether, although it does not give a quantitative evaluation for the hydrogen abstraction because the intermediate radicals have different addition rates to olefins.

Table 1. Reductive alkylation of methyl vinyl ketone with ethers by Ti(III)/*t*-butyl hydroperoxide redox-couple

Ether	1 yield %	addition position	b.p.°C/ mmHg	n_D^{20}
Tetrahydrofuran	61	2	71–72/0.5	1.4496
1,4-Dioxane	63	2	81–82/0.5	1.4523
2-Methyltetrahydrofuran	48	2(68%)	80–81/0.5	1.4491
		5-trans (16%)	—	—
		5-cis (16%)	—	—
2,5-Dimethyltetrahydrofuran	40	2	76–77/0.5	1.4501
1,3-Dioxolane	30	2(4 trace)	60–61/0.5	1.4518

Tertiary hydrogens of 2-methyl tetrahydrofuran are more reactive than secondary (4.2:1), whereas *cis* and *trans* hydrogens at position 5 appear to be equally reactive in this substrate. The hydrogen at position 2 of 1,3-dioxolane is more reactive than those at position 4, in agreement with recent kinetic reports;[4] the reaction, therefore, gives rise to the acetal of an aldehyde. In this case the method of workup of the reaction mixture is quite important because of the instability of the acetal and the possible condensation of the aldehyde arising from hydrolysis. An effective way was found to be absorption of the reaction mixture of silica gel (or florisil) and fast elution with ether. This procedure also offers the best results with the other substrates and was the preferred method. This method represents a convenient and relatively selective way to obtain C–C bond formation using simple experimental conditions.

EXPERIMENTAL

THF, 2-methyl tetrahydrofuran, 2,5-dimethyltetrahydrofuran, 1,4-dioxane and 1,3-dioxolane from Aldrich were dried over CaH_2 and distilled. Methylvinylketone was distilled at 400 mmHg

before use. 15% $TiCl_3$ aqueous solution was purchased from Carlo Erba and standardized against Cerium sulfate 0.1 *N*. *t*-Butyl hydroperoxide (Merck) was titrated iodometrically. IR spectra were recorded on a Perkin–Elmer E-177 instrument. NMR spectra ($CDCl_3$) (TMS as internal standard) were run on a Varian A-90 instrument, glc analyses were performed on a DANI 3600 instrument with flame ionization detector using a 2 m × 4 mm column packed with 3% FFAP on Chromosorb W-DMCS. Glc/M.S. data were obtained on a GC/MS Finnigan 4021 instrument.

4(2-*Tetrahydrofuryl*)2-*butanene*. *t*-Butyl hydroperoxide (2.7 g, 22 mmol) in THF (5 ml) was added over 1/2 hr to a mixture of 15% $TiCl_3$ (19 ml, 23 mmol), THF (21 ml) and methylvinyl ketone (1.8 ml, 22 mmol) at 0° with stirring. The reaction was allowed to warm to room temperature, the mixture was absorbed on a column of silica gel (0.063–0.200 mesh) (300 g) and eluted with diethyl ether (400 ml) under slight pressure. The eluted solvent was dried on K_2CO_3 and distilled to recover the ether. The residue was distilled under reduced pressure to give 4(2-tetrahydrofuryl)2-butanone b.p. 71–72°/0.5 mmHg [lit.[7a] 90–91°/12 mmHg, $n_D^{20} = 1.4485$] IR $\nu_{max} = 1710$; M.S. *m/e*: 142 ($M^{+\cdot}$, 3.6), 141 (5), 114 (3), 99 (6), 85 (10), 84 (58), 71 (98), 58 (11), 57 (9), 56 (11), 55 (13), 43 (100), NMR ($CDCl_3$) δ: 3.5–4 (m, 3H, 2.53 (t, 2H, CH_2CO), 2.14 (s, 3H, $COCH_3$), 1.3–2.1 (m, 64). The compound appeared identical with the one prepared following the reported procedure.

4-(1,4-*Dioxanyl*)-2-*butanone*. Two solutions were prepared: (a) 15% $TiCl_3$ (100 ml) and 1,4-dioxane (50 ml). (b) Methyl vinyl ketone (4.9 ml, 60 mmol), *t*-butyl hydroperoxide (68 ml, 60 mmol) in 1,4-dioxane (50 ml). The two solutions were dropped over 1.5 hr, into a flask maintained at −5°–0°, with solution (a) added 3 times faster than solution (b). The reaction was run for 1/2 hr and the addition product isolated as above (5.9 g, yield 63%). 4((1,4-dioxanyl)-2-butanone; b.p. 81–2°/0.5 mmHg; $n_D^{20} = 1.4523$; IR $\nu_{max} = 1713$; NMR ($CDCl_3$) δ: 3.3–3.9 (m, 7H, C<u>H</u>–O), 2.57 (t, 2H, $C\underline{H}_2CO$), 2.13 (s, 3H, $COCH_3$), 1.5–1.8 (m, 2H, CH_2CH–) M.S. *m/e*: 158 ($M^{+\cdot}$, 6), 115 (31), 101 (8), 100 (15), 99 (13), 87 (8), 73 (9), 72 (10), 71 (9), 58 (12), 57 (13), 43 (100).

A parallel experiment, after continuous extraction of the reaction mixture, drying and distillation, gave the same product in 40% yield.

Reaction with 2-methyl tetrahydrofuran. A solution of *t*-butyl hydroperoxide (4.9 g, 50 mmol) in 2-methyl-tetrahydrofuran (5 ml), was dropped into a mixture of $TiCl_3$ (85 ml, 0.1 mol), 2-methyl tetrahydrofuran (30 ml) and methyl vinyl ketone (46 ml, 50 mmol). The reaction was run and the products isolated as reported above. The ethereal residue was directly analyzed by glc on a 2 m column packed with 3% FFAP on Chromosorb W-DMCS for isomer distribution and yield determination (cyclohexanone as internal standard): the following compounds were identified by glc-M.S. spectra: first isomer eluted (16%) *trans*-4-(2(5-methyl-tetrahydrofuryl))-2-butanone *m/e*: 158 (M^+, 5), 157 (6), 155 (3), 141 (3), 139 (3), 123 (2), 114 (30), 98 (100), 85 (95), 83 (29), 67 (13), 43 (12); second isomer eluted (16%): *cis*-4(2(5-methyltetrahydrofuryl))-2-butanone *m/e*: 158 ($M^{+\cdot}$, 3), 157 (3), 155 (2.5), 141 (3), 141 (2.5), 138 (1.9), 114 (22), 98 (100), 85 (91), 43 (12) and 4(2-(2-methyltetrahydrofuryl))-2-butanone (68%) *m/e*: 158 ($M^{+\cdot}$, 0.5), 157 (2), 141 (30), 113 (10), 99 (31), 85 (100), 71 (11), 43 (13). An analytically pure sample of the latter compound was isolated by preparative liquid–liquid chromatography on Silica Gel (0.032–0.063 mesh) with hexane: ether 9:1; the compound had b.p. 80–81°0.5 mmHg, IR $\nu_{max} = 1713$, NMR ($CDCl_3$) δ, 3.78 (t, 2H, CH_2O), 2.51 (t, 2H, CH_2CO), 2.12 (s, $COCH_3$), 1.5–2.1 (m, 6H), 1.23 (s, 3H, CH_3).

4(2-(2,5-*Dimethyltetrahydrofuryl*))-2-*butanone*. The reaction was carried out as above and gave, after distillation, a 40% yield of the addition product b.p. 77–98°/0.5 mmHg, $n_D^{20} = 1.4501$; IR $\nu_{max} = 1715$; NMR ($CDCl_3$) δ: 3.8 (m, 1H, C<u>H</u>–O), 2.50 (t, 2H, $C\underline{H}_2CO$), 2.12 (s, 3H, $COC\underline{H}_3$), 1.5–2.1 (m, 6H), 1.23 (s, 3H, $C\underline{H}_3$), 1.31 (d, 3H, CH_3).

4(2-(1,3-*Dioxolanyl*))-2-*butanone*. A solution of *t*-butylhydroperoxide (2.5 ml, 25 mmol) in 1,3-dioxolane (5 ml) was added over 10 min with stirring at −5° to a mixture prepared at −5° of 15% $TiCl_3$ (42 ml, 50 mmol), 1,3-dioxolane (40 ml) and methyl vinyl ketone (2.5 ml, 27 mmol). The solution was immediately absorbed on SiO_2 and eluted with diethylether. The eluent was dried on K_2CO_3 and distilled at reduced pressure. The residue was chromatographed on SiO_2 with hexane–diethylether (9:1) as eluent. 1.08 g (30% yield) of 4-(2-(1,3-dioxolanyl-2-butanone were obtained: b.p. 68–70°/0.8 mmHg, $n_D^{20} = 1.4531$, IR $\nu_{max} = 1712$ n_D^{20}, NMR ($CDCl_3$) δ: 4.92 (t, 1H, C<u>H</u>–O), 3.8–4.0 (m, 4H), 2.56 (t, 2H, $C\underline{H}_2CO$), 2.15 (s, 3H, $COCH_3$), 1.96 (d, t, 2H). M.S. *m/e*: 144 (M^+, 10), 143 (27), 129 (8), 114 (40), 99 (43), 86 (100), 84 (88), 73 (95), 70 (55), 58 (36), 57 (35), 55 (33), 43 (52).

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