

## SOLVOLYTIC DISPLACEMENT OF ALKYL HALIDES BY METAL SALTS

### PREPARATIVE PROCEDURES FOR ALLYL-, BENZYL- AND TERTIARY ALKYL-OXY DERIVATIVES USING THE ZINC SALTS

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**Abstract**—Reaction of allylic, benzylic and tertiary alkyl halides with zinc oxide in protic solvents leads to the formation of the corresponding alcohols, ethers and esters in good yields. The scope and limitations of this reaction have been examined. The possible involvement of ion quadruplets in the reaction is suggested.

Nucleophilic substitution at saturated carbon is one of the most extensively investigated reactions.<sup>1</sup> The reaction conditions may vary; for example: simple solvolysis,<sup>2</sup> Lewis acid or metal-salt assisted solvolysis<sup>3</sup> and reaction of alkyl halides with metal salts in aprotic solvents.<sup>4</sup> It is known that solvolytic reactions generally lead to substitution products in the case of primary and secondary alkyl halides and sulphonates, but yield considerable amount of elimination products when the substrate is a tertiary alkyl derivative. Among tertiary alkyl halides the proportion of the elimination products in solvolytic reactions increases with the size of the substituents on the  $\alpha$ -C atom<sup>5</sup> and with the decreasing ionising capacity of the solvent (for example, in anhydrous ethanol and acetic acid).<sup>6</sup> For these reasons solvolytic displacement is seldom useful as a preparative procedure for the conversion of tertiary alkyl halides into the corresponding alcohols, ethers, esters etc. The relatively recent discovery<sup>3</sup> of a  $Hg^{+2}$  assisted solvolytic method for such conversions is also limited to primary and secondary alkyl halides and yields mixtures of products with tertiary halides. The reported method of preparation of *t*-butyl acetate from *t*-butyl halides using mercuric acetate under non-solvolytic conditions has not been tested with other tertiary alkyl systems. Also, a serious limitation of the reactions with mercuric salts is the competitive formation of organomercurials with olefinic substrates.

We have recently reported<sup>7</sup> that when solvolysis is carried out in the presence of equivalent amount of the corresponding Zn salt, tertiary alkyl halides yield predominantly the substitution products. The reaction proceeds favourably with a variety of solvents and substrates and is of immense preparative value in view of the ready accessibility of the tertiary alkyl halides by Markownikov addition of hydrogen halides to tri-substituted and 1,1-disubstituted olefins. As we have demonstrated,<sup>8</sup> the process is particularly useful for the production of several perfumery and flavouring compounds from monoterpenic hydrocarbons which are abundantly available. The reaction is also applicable to allylic and benzylic halides. The results of experiments on various aspects of this reaction are discussed here.

As recorded earlier,<sup>7,8</sup> we observed that  $\alpha$ -terpinyl chloride [4-(1-chloro-1-methylethyl)-1-methylcyclohex-

ene]<sup>9</sup>, when stirred with equimolar quantity of zinc acetate in acetic acid, yielded  $\alpha$ -terpinyl acetate almost exclusively. Other commonly available metal acetates were not as effective in bringing about the transformation (Table 1). Alkali and alkaline earth metal acetates were not reactive at room temperature and at higher temperatures led to considerable amounts of elimination products. Cuprous and silver acetates furnished  $\alpha$ -terpinyl acetate in good yields but took longer time; mercuric acetate was not attempted for reasons mentioned above. Of the three metal (Cu, Ag and Zn) salts, the Zn salt was preferred for the following reasons: (1) the reaction was clean and isolation of the product was easy; (2) in extending the reaction to other solvents, zinc oxide could substitute for the corresponding salt as it readily forms the salt, *in situ*, on contact with various protic solvents; and (3) the zinc oxide, when desired (as in some process applications),<sup>8</sup> could be conveniently regenerated. Indeed,  $\alpha$ -terpinyl chloride readily furnished the corresponding alcohol, ethers and esters when reacted with zinc oxide and a variety of hydroxylic and carboxylic acid solvents (Table 2). The yield of the oxygenated derivatives, however, was lower with longer chain primary alcohols and carboxylic acids and with secondary alcohols; tertiary alcohols, understandably, gave rise to predominantly the elimination products.

In view of the versatility and obvious usefulness of the reaction, its applicability to other classes of alkyl halides was examined (Table 3). The reaction did not occur with primary and secondary alkyl halides to any noticeable extent (under the conditions studied) unless they were allylic or benzylic. Even in the latter case, the reaction was faster with secondary, and more so, with tertiary halides. Both  $\alpha$ ,  $\alpha'$ - and  $\gamma$ ,  $\gamma'$ -dimethylallyl chlorides yielded the primary acetate and optically active *trans*-carvyl chloride gave a racemic mixture of *cis*- and *trans*-carvyl acetates. Bromides were more reactive than chlorides and higher reaction temperatures generally led to higher proportion of elimination products.

The role of the Zn salt does not appear to be catalytic in nature as at least molar equivalent of the salt is required for the completion of the reaction. With 0.05 molar equivalents of zinc acetate, the reaction stops after the production of about 5% of the acetate and under forcing conditions elimination occurs, probably

Table 1. Reaction of  $\alpha$ -terpinyl chloride with different metal acetates in acetic acid

Metal Acetate	Temp ( $^{\circ}$ C)	Time (hr)	Products	Yield(%) of the acetate
NaOAc	25	24	No reaction	-
NaOAc	60	8	$\alpha$ - Terpinyl acetate + hydrocarbons	40
Mg(OAc) <sub>2</sub>	25	24	No reaction	-
Ca(OAc) <sub>2</sub>	25	24	No reaction	-
Ba(OAc) <sub>2</sub>	25	24	No reaction	-
AgOAc	25	4	$\alpha$ - Terpinyl acetate	78
CuOAc	25	8	$\alpha$ - Terpinyl acetate	85
Zn(OAc) <sub>2</sub>	25	2	$\alpha$ - Terpinyl acetate	90

due to the action of zinc chloride that is formed. Also, while Lewis acids are known to catalyse solvolytic reactions,<sup>10</sup> they are not specific to tertiary alkyl or activated alkyl halides nor are they known to yield higher proportion of substitution products with tertiary alkyl halides. In fact, when  $\alpha$ -terpinyl chloride was stirred with acetic acid in presence of Lewis acids such as zinc chloride, ferric chloride or boron trifluoride, the products were essentially the olefins; aluminium chloride was non-reactive.

From the results discussed above the following generalisations may be made: (1) alkyl halides, tertiary, allylic or benzylic, undergo solvolysis in protic solvents

in presence of zinc oxide to yield predominantly the substitution products; (2) the reaction is fairly general with respect to solvents, being applicable to water, low molecular weight primary alcohols and carboxylic acids; (3) primary and secondary halides do not react and in the case of benzylic halides, the rate of the reaction increases with increasing substitution on the  $\alpha$ -C atom; (4) no rearrangement products are formed in case of tertiary alkyl halides but allylic halides undergo extensive isomerisation; (5) bromides react faster and at lower temperatures compared to chlorides, higher temperatures generally leading to competitive elimination; and (6) the reaction, which requires molar equivalents of the zinc

Table 2. Reaction of  $\alpha$ -terpinyl chloride with zinc oxide in different protic solvents

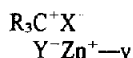
Solvent	Temp( $^{\circ}$ C)	Time(hr)	Product	b.p. ( $^{\circ}$ C/Torr)	Yield (%)
Aq. acetone (80%)	Reflux	6	$\alpha$ - Terpineol	90-95/5	85
Formic acid	15	2	$\alpha$ - Terpinyl formate	62-65/2	95
Acetic acid	25	2	$\alpha$ - Terpinyl acetate	74-76/2	90
Propionic acid	40	2	$\alpha$ - Terpinyl propionate	71-74/0.5	70
Butyric acid	45	2	$\alpha$ - Terpinyl butyrate	82-84/0.2	65
Methanol	Reflux	6	$\alpha$ - Terpinyl methyl ether	102/20	95
Ethanol	Reflux	6	$\alpha$ - Terpinyl ethyl ether	93/3	85
n-Propanol	Reflux	6	$\alpha$ - Terpinyl-n-propyl ether	94-98/4	60
Isopropanol	Reflux	6	$\alpha$ - Terpinyl isopropyl ether	92-94/5	30
t-Butanol	Reflux	6	Hydrocarbons + $\alpha$ - Terpineol	-	75+25

Table 3. Reaction of alkyl halides with zinc oxide in acetic acid

Alkyl halide	Temp (°C)	Time (hr)	Product	B.P. (°C/Torr)	Yield (%)
n-Butyl bromide	25	48	--	-	-
s-Butyl chloride	25	48	--	-	-
t-Butyl chloride	15	0.5	t-Butyl acetate	-	96
$\alpha$ -Terpinyl bromide	15	0.5	$\alpha$ -Terpinyl acetate	74-76/2	85
1-Chloro-p-menthane	40	2	1-Acetoxy-p-menthane	72-74/2	65
Allyl bromide	100	5	Allyl acetate	104/760	100
$\gamma,\gamma$ -Dimethyl allyl chloride	15	0.5	$\gamma,\gamma$ -Dimethyl allyl acetate	64/30	98
$\alpha\alpha$ -Dimethyl allyl chloride	15	0.25	$\gamma,\gamma$ -Dimethyl allyl acetate	64/30	98
(+) <u>trans</u> Carvyl chloride	25	2	Carvyl acetate(cis:trans;1:3)	68/0.3	96
Bensyl chloride	75	6	Bensyl acetate	215/760	86
Bensyl bromide	75	1	Bensyl acetate	215/760	85
$\alpha$ -Phenyl ethyl chloride	25	1.25	$\alpha$ -Phenyl ethyl acetate	210/760	95
$\alpha$ -Phenyl ethyl bromide	15	1	$\alpha$ -Phenyl ethyl acetate	210/760	97
2-Chloro-3-methyl-2-phenyl butane	10	0.1	2-Acetoxy-3-methyl-2-phenyl butane	73/0.1	88

salt for completion, appears to be different from other Lewis acid catalysed reactions in its specificity and product composition.

The above features indicate a mechanism intermediate between  $S_N1$  and  $S_N2$  for the reaction under discussion. An essentially  $S_N1$  pathway is expected to result in extensive elimination from most of the tertiary alkyl halides in Table 3 due to the considerable steric strain.<sup>2</sup> The formation of predominantly substitution products, without rearrangement, with tertiary alkyl halides and at the same time isomeric products from allylic systems suggests that the reaction may be proceeding through associated ion pairs (ion quadruplets) of the type 1. Higher reaction temperature may cause dissociation of such species leading to higher proportion of elimination products as has been observed. Intermediates similar to the one now proposed could also explain certain substitution reactions of tertiary alkyl halides in aprotic solvents<sup>11,12</sup>. More kinetic and stereochemical information is, of course, necessary to fully understand the mechanism.



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The possible extension of the substitution reaction at tertiary centre to non-solvolytic conditions was of interest. Displacement of tertiary alkyl chlorides by iodide and azide ions is known to occur<sup>12,13</sup> in carbon disulphide at room temperature in presence of catalytic amounts of zinc chloride. Our experiments with zinc acetate or sodium acetate and zinc chloride and  $\alpha$ -terpinyl chloride showed that no reaction occurs at room temperature even after several hours in a variety of solvents such as carbon disulphide, acetonitrile, tetrahydrofuran, dimethylformamide, dimethylsulphoxide and pyridine. Preliminary studies have indicated that in acetone at room temperature and in other solvents at higher temperatures, elimination competes thus reducing the synthetic utility of the reaction.

In conclusion, it may be said that substitution of alkyl halides by metal salts follows a discernible pattern. The gradation of reactivity with respect to the halogen is well known.<sup>14</sup> Tertiary alkyl halides yield substitution products with moderately electrophilic metal salts which could form ion quadruplets of the type 1. Secondary and primary halides require the more reactive alkali metal salts or strongly electrophilic catalysts to assist ionisation and substitution; the reaction conditions, naturally, depend on the nature of substitution on the  $\alpha$ -C atom and the halogen. The procedures described here are particularly convenient for the substitution of tertiary alkyl, allylic and benzylic halides.

#### EXPERIMENTAL

The alkyl halides were either obtained commercially or prepared by standard methods readily available in literature. Gas chromatography was carried out on a Hewlett-Packard Model 5730A gas chromatograph using 1/4" O.D., 5 ft. glass column filled with Chromosorb W coated with 10% OV-101 and 2%

carbowax at a programmed temperature of 80–160°. The PMR spectra were recorded on Varian EM-390 instrument in  $CCl_4$  using TMS as internal standard.

*$\alpha$ -Terpinyl chloride.* This was prepared by a modification of the lit procedure.<sup>9</sup> Anhyd HCl was bubbled through previously dried limonene (200 g) at 0° for 2 hr. The mixture was allowed to stand overnight, washed with water, followed by sat  $NaHCO_3$  aq, dried ( $Na_2SO_4$ ) and distilled using a Vigreux column. After recovering 80 g of the hydrocarbon,  $\alpha$ -terpinyl chloride (140 g) was collected at 62–64°/1–2 mm.

*Reaction of  $\alpha$ -terpinyl chloride with metal acetates in acetic acid.*  $\alpha$ -Terpinyl chloride (10 mmol) in AcOH (0.1 mol) was stirred with an anhyd metal acetate (20 mmol) at room temp (25°) or on a water bath (60°). The progress of the reaction was followed by gas chromatography. The results are summarised in Table 1.

*Reaction of  $\alpha$ -terpinyl chloride with zinc oxide and protic solvents.* Zinc oxide (5.5 mmol) was stirred with a protic solvent (water, an alcohol or a carboxylic acid, 0.1 mole) for 0.5 hr and  $\alpha$ -terpinyl chloride (10 mmol) was added. The temp of the reaction was varied from 15° to the b. pt. of the solvent depending upon its reactivity. The stirring was continued till gas chromatography of an aliquot showed the absence of  $\alpha$ -terpinyl chloride. The product was brought to room temp, filtered from the inorganic salts and the solvent evaporated. In the case of the carboxylic acid solvents, where there is no separation of the Zn salts, the product was diluted with water (50 ml) and extracted with ether (2 × 25 ml). The combined ether extracts was washed with sat  $NaHCO_3$  aq, dried ( $Na_2SO_4$ ) and evaporated. The pure compounds were obtained by distillation under reduced pressure, using a Vigreux column. The results are given in Table 2.

*Reaction of alkyl halides with zinc oxide in acetic acid.* Calcined zinc oxide (5.5 mmol) was stirred for 30 min with AcOH (0.1 mol, to which about 10%  $Ac_2O$  was added to act as water scavenger and thereby prevent the formation of the alcohol). The alkyl halide (10 mmol) added to the above mixture. At the end of the reaction the product was isolated as described. The reaction time, temp and yield, which vary depending on the nature of alkyl halide, are indicated in Table 3. The purity and identity of the products were confirmed by glc and PMR spectroscopy.

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