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NUCLEOPHILIC SUBSTITUTION OF ALKYL HALIDES BY ZINC SALTS—3† PREPARATION OF TERTIARY ALKYL ESTERS AND ETHERS UNDER NON-SOLVOLYTIC CONDITIONS

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Abstract—Zinc salts of carboxylic acids, phenols and alcohols are found to react with tertiary alkyl halides in nonpolar solvents and in presence of a base yielding the corresponding esters and ethers in moderate to good yields.

Nucleophilic substitution at tertiary centre has attracted considerable attention in recent years. Aluminium[1] and zinc[2] alkyls have been found to react with tertiary alkyl halides to give quaternary derivatives and chlorides of zinc, copper, mercury and iron were found to catalyse substitution of tertiary alkyl chlorides by iodide[3] and azide[4] ions. Very recently, nickel acetylacetonate was found to catalyse formation of t-alkyl aryl ethers.[5] We have recently reported[6,7] that S_N1 active alkyl halides (i.e. t-alkyl, allyl and benzyl halides) readily yield substitution products with salts of zinc, copper and silver under solvolytic conditions; the zinc salts were preferred for convenience. Preferential substitution at tertiary centre without rearrangement or appreciable elimination required that the incoming nucleophile be close to the developing carbenium ion. To satisfy this condition and to explain the role of the metal ion, only moderately electrophilic metal ions being effective, we proposed an ion-quadruplet intermediate (**1**) for substitution reactions at tertiary centre in general.[7]

$$\begin{matrix} R^+X^- \\ Y^-M^+ \end{matrix}$$

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The solvolytic reaction described above is naturally limited in its applicability to hydroxylic and carboxylic compounds of low molecular weight which are liquids at ambient temperatures and extension of the reaction to solid (or high viscosity liquid) carboxylic acids and alcohols was of interest. This requires a non-participating solvent and, as already recorded,[7] a variety of polar solvents (such as acetonitrile, THF, DMF and DMSO) were unsuitable. However, in the light of the above mechanism it is possible to imagine that polar solvents could dissociate ion-quadruplets of the type **1** by solvation and, conversely, solvents of low dielectric constant and high polarizability should facilitate substitution. Reaction of α-terpinyl chloride [4-(1-chloro-1-methylethyl)-1-methylcyclohexene] with zinc acetate in a series of solvents belonging to this group was therefore examined (Table 1). In almost all cases, no reaction occurred for several hours but once started, it quickly proceeded leading, within a few minutes, to almost complete elimination and polymerization. Apparently, the zinc chloride formed in the initial reaction catalysed the elimination and it should be possible to prevent or control this reaction by addition of a suitable Lewis base. In fact, addition of pyridine (or triethylamine to a lesser extent) effectively controlled the elimination process and yielded α-terpinyl acetate in moderate yields. Among the various solvents and temperature conditions studied (Table 1), refluxing benzene containing one equivalent of pyridine was most convenient in terms of speed of reaction and yield of the product.

Reaction of zinc acetate with other alkyl halides under the above conditions was then examined (Table 2). Both t-butyl chloride and bromide furnished t-butyl acetate, with the bromide giving higher yield of the product in a shorter time. 2-Butyl bromide was non-reactive after 100 h at reflux temperature in the presence of pyridine, but yielded 36% of the acetate after 40 h in the absence of pyridine. Evidently, zinc chloride formed in the reaction acted as a Lewis acid catalyst for the substitution reaction. 1-Butyl bromide was unaffected on refluxing with zinc acetate in benzene for 100 h with or without pyridine. Benzyl halides were precipitated out of the solution with pyridine and in the absence of pyridine, the major product (70%) was diphenylmethane (by Friedel–Crafts alkylation), the remainder being benzyl acetate. Use of collidine in place of pyridine prevented salt formation as well as Friedel–Crafts alkylation but the reaction was extremely slow. The

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†References 6 and 7 to be considered Parts 1 and 2 respectively.

Table 1. Reaction of α-terpinyl chloride with $Zn(OAc)_2$ in different solvents

Solvent	Without pyridine				With pyridine			
	Temp. °C	Time h	Terpinyl acetate	Hydrocarbons and polymers	Temp. °C	Time h	Terpinyl acetate	Hydrocarbons
CS_2	25	100	No Reaction	-	-	-	-	-
Ether	25	100	No Reaction	-	-	-	-	-
CH_2Cl_2	25	4	-	100	40	80	48	52
$CHCl_3$	25	4	-	100	60	26	35	65
C_6H_6	80	4	-	100	80	12	44	56
$(CH_2OMe)_2$	85	4	8	92	85	24	43	57
Pyridine	-	-	-	-	80	72	40	60

Table 2. Reaction of alkyl halides with $Zn(OAc)_2$ in aprotic solvents

Alkyl halide	Solvent	Base	Temp. °C	Time h	Product	b.p. °C/Torr	yield %
t-BuCl	C_6H_6	Pyridine	80	18	t-BuOAc	96/690	33
t-BuBr	C_6H_6	Pyridine	80	2	t-BuOAc	96/690	50
2-BuBr	C_6H_6	Pyridine	80	100	No reaction	-	-
2-BuBr	C_6H_6	-	80	40	2-BuOAc	110/690	36
n-BuBr	C_6H_6	-	80	100	No reaction	-	-
$PhCh_2Br$	C_6H_6	-	80	2	$PhCH_2Ph$ + $PhCH_2OAc$	114/1 77/5	70 22
$PhCH_2Br$	$CHCl_3$	-	60	24	No reaction	-	-
$PhCH_2Br$	C_6H_6	Collidine	80	100	$PhCH_2OAc$	77/5	70
$CH_2{=}CHCH_2Br$	C_6H_6	Pyridine	80	6	$CH_2{=}CHCH_2OAc$	102/690	20
(+) trans-Carvyl chloride	$CHCl_3$	Pyridine	25	16	(+) cis/trans carvyl acetate	69/0.3	70

Table 3. Reaction of proton-active substances (ROH) with ZnO and α-terpinyl chloride

R	Reaction Time (h)	Percentage conversion[b]	Product[c]	b.p. °C 0.4 Torr	Yield (%)	^{1}H N.M.R.
PhCO	20	30	PhCOOT	152	79	1.60(6H,s),1.67(3H,s),2.05(7H,br), 5.40(1H,br),7.50(3H,m),8.05(2H,m).
PhCH=CHCO	24	34	PhCH=CHCOOT	178	78	1.55(6H,s),1.67(3H,s),1.95(7H,br), 5.40(1H,br),6.35(1H,d,J=16 Hz), 7.50(6H,m).
$PhCH_2CO$	24	37	$PhCH_2COOT$	148	93	1.40(6H,s),1.70(3H,s),1.80(7H,m), 3.45(2H,s),5.33(1H,br),7.30(5H,s).
$PhOCH_2CO$	8	34	$PhOCH_2COOT$	156	85	1.40(6H,s),1.60(3H,s),1.85(7H,m), 4.50(2H,s),5.35(1H,br),6.90(3H,m), 7.25(2H,m).
Ph	7	36	PhOT	130	48	1.20(6H,s),1.67(3H,s),2.05(7H,m), 5.45(1H,br),7.10(5H,m).
$PhCH_2$	42	45	$PhCH_2OT$	143	37	1.20(6H,s),1.65(3H,s),1.95(7H,br), 4.40(2H,s),5.40(1H,br),7.30(5H,s).

a for reaction conditions see Experimental.

b based on recovered ROH

c T = α-terpinyl.

Table 4. Reaction of proton-active substances (ROH) with ZnO and t-butyl bromide

R	Reaction time (h)	Percentage conversion[b]	Product	b.p. °C/ Torr.	Yield[b]	^1H N.M.R.
PhCO	12	54	$PhCOOCMe_3$	86/1.5	91	1.60(9H,s),7.50(3H,m),8.10(2H,m).
PhCH=CHCO	10	53	$PhCH=CHCOOCMe_3$	112/0.4	95	1.53(9H,s),6.40(1H,d,J=16 Hz), 7.50(6H,m).
$PhCH_2CO$	12	64	$PhCH_2COOCMe_3$	132/9	93	1.45(9H,s),3.45(2H,s),7.30(5H,s).
$PhOCH_2CO$	9	67	$PhOCH_2COOCMe_3$	120/2	95	1.45(9H,s),4.45(2H,s),6.90(3H,m), 7.25(2H,m).
Ph	5	50	$PhOCMe_3$	70/2.5	83	1.33(9H,s), 7.00(5H,m).
$PhCH_2$	30	52	$PhCH_2OCMe_3$	98/5	72	1.30(9H,s),4.40(2H,s),7.30(5H,br).

a for reaction conditions, see Experimental.

b based on recovered ROH.

reactivity of allyl bromide was similar; however, (+)-*trans*-carvyl chloride readily reacted with zinc acetate (in benzene, $CHCl_3$, or CH_2Cl_2) and pyridine yielding a racemic mixture of *cis* and *trans*-carvyl acetates (1:2). These results parallel the known reactivity of these alkyl halides under solvolytic conditions, indicating that a similar mechanism may be operative even under non-solvolytic conditions. The above results indicated that the present conditions of substitution are conveniently applicable mainly for the preparation of tertiary alkyl esters from the corresponding tertiary alkyl halides and not for other substituted alkyl halides. Nevertheless, the reaction is applicable to the preparation of tertiary alkyl esters of several carboxylic acids and ethers of phenols and alcohols which are otherwise not easily accessible. Thus, the important flavour and perfumery chemicals α-terpinyl benzoate, cinnamate, phenylacetate and phenoxyacetate could be conveniently prepared from the readily available α-terpinyl chloride (Table 3). The zinc salt of the acid was prepared *in situ* by the reaction of zinc oxide (or carbonate) with the carboxylic acid in refluxing benzene. For large scale preparations the recovered acids could be recycled and the hydrocarbon byproduct (mainly a mixture of limonene and terpinolene in the ratio 3:2) may be reused after partly converting to α-terpinyl chloride using hydrogen chloride.[7] Substitution of the carboxylic acid by an alcohol or phenol yielded the corresponding ethers.

Use of t-butyl bromide in 50% excess of the theoretical amount improved the yield of t-butyl esters which can be very conveniently prepared by this method (Table 4). This method of preparation of t-butyl esters compares favourably with the other methods of preparation[8] of these compounds which are widely used as alkali-stable protective groups in organic synthesis.

The applicability of the above reaction to other proton-active substances such as thiols, thiolalkanoic acids and substituted phosphorous acids is now under investigation. Preliminary results are encouraging.

EXPERIMENTAL

B.ps are uncorrected. ^1H NMR spectra were recorded in CCl_4 on a Varian EM 390 (90 MHz) instrument using TMS as internal standard.

Reaction of α-terpinyl chloride with $Zn(OAc)_2$ in different solvents

$Zn(OAc)_2$ (10 mmol) in the appropriate solvent (Table 1, 20 ml) was stirred under reflux with α-terpinyl chloride (10 mmol) and pyridine (10 mmol). The reaction was continued until TLC (silica gel, hexane) showed that the terpinyl chloride was absent. The reaction mixture was washed with dil HCl, followed by sat aq. $NaHCO_3$, dried and evaporated. α-Terpinyl acetate was isolated by column chromatography on silica gel (solvent, hexane: EtOAc: 98:2) and the yield of the product determined (Table 1).

Reaction of alkyl halides with $Zn(OAc)_2$

The alkyl halide (10 mmol) and $Zn(OAc)_2$ (10 mmol) were stirred in benzene or chloroform under the conditions given in Table 2 and worked up as described above. The results are summarised in Table 2.

Preparation of Zinc Salts

Zinc oxide (10 mmol) was stirred under reflux with the carboxylic acid, alcohol or phenol (20 mmol) in benzene (50 ml) for 2 h in a flask equipped with a Dean–Stark tube to remove water as it is formed. For small scale preparations, it is convenient to replace the Dean–Stark tube with a small Soxhlet filled with anhyd.Na_2SO_4, so that the condensed solvent is dried before it is returned to the reaction flask. Molecular sieves (3A or 4A type) were also used in alternative procedures.

Preparation of the Esters and Ethers

To the above mixture containing the zinc salt and benzene was added the alkyl halide (20 mmol of α-terpinyl chloride or 30 mmol of t-butyl bromide) and pyridine (molar equivalent to the quantity of the halide). The mixture was stirred under reflux while the progress of the reaction was followed by ^1H NMR. At the end of the reaction, the unreacted acid or phenol was recovered by extraction with satd. aq. $NaHCO_3$ or aq. NaOH and acidification. The remainder of the reaction mixture was washed with dil HCl (to remove pyridine) followed by sat aq. $NaHCO_3$, dried (Na_2SO_4) and evaporated. The pure ester is obtained by distillation under reduced pressure. When alcohols were used for etherification, the alcohol and the ether are conveniently separated by chromatography on silica gel. The properties and the yield of the isolated products are given in Table 3.

REFERENCES

[1] J. P. Kennedy, N. V. Desa and S. Sivaram, *J. Am. Chem. Soc.* **95**, 6386 (1973).
[2] M. T. Reetz, B. Wenderoth, R. Peter, R. Steinbach and G. Westermann, *J. Chem. Soc.* Chem. Commun. 1202 (1980).
[3] J. A. Miller and M. J. Nunn, *Ibid.* Perkin I 416 (1976).
[4] J. A. Miller, *Tetrahedron Letters* 2959 (1975).
[5] F. Camps, J. Coll and J. M. Moreto, *Synthesis* 186 (1982).
[6] S. Anandaraman, K. N. Gurudutt, C. P. Natarajan and B. Ravindranath, *Tetrahedron Letters* **22**, 2198 (1980).
[7] K. N. Gurudutt, B. Ravindranath and P. Srinivas, *Tetrahedron* **38**, 1843 (1982).
[8] S. Ohta, A. Shimabayashi, M. Aono and M. Okamoto, *Synthesis* 833 (1982).