Mechanism of Ester Formation during Decarboxylation with t-Butyl Hypochlorite and Iodine

By **Michael R. Britten-Kelly, André Goosen,* Janet Lovelock,** and **André Scheffer,** Organic Chemistry Research Laboratory, University of Port Elizabeth, P.O. Box 1600, Port Elizabeth, South Africa

Esters are formed from carboxylic acids and alkyl iodides upon treatment with t-butyl hypochlorite and iodine in carbon tetrachloride. Evidence is presented for a heterolytic mechanism whereby the iodine in the alkyl halide is replaced by the acyloxy-group of the acyl hypoiodite in the presence of iodine monochloride.

SIGNIFICANT amounts of esters are produced in numerous decarboxylation reactions.[1,2] This paper describes a novel esterification process which was discovered when we investigated how esters were formed in decarboxylation reactions with t-butyl hypochlorite and iodine.[3,4]

In studies of the decarboxylation of carboxylic acids with t-butyl hypoiodite, generated from potassium t-butoxide and iodine, Barton and his co-workers [5] obtained alkyl iodides but did not report the presence of esters in their reaction mixtures. Ogata and Aoki [2] have proposed that acyl hypoiodites react with alkyl iodides to form esters. Investigating this hypothesis we found that mixtures consisting of a carboxylic acid, an alkyl iodide, t-butyl hypochlorite, and iodine in carbon tetrachloride produced significant amounts of esters when shaken in the dark at room temperature (Table 1). The reaction did not occur when benzyl chloride or n-butyl bromide was used in place of an alkyl iodide.

It was suggested [3] that the acyl hypoiodite rather than the free carboxylic acid was the reactant in this reaction. This conclusion was reached from the observation that the acidic proton n.m.r. signal instantaneously disappeared when a solution of the acid and t-butyl hypochlorite was treated with iodine; the signal remained unchanged upon treatment of the acid with either t-butyl hypochlorite or iodine alone. It was thus concluded that t-butyl hypoiodite, which is formed along with iodine monochloride from the rapid reaction of t-butyl hypochlorite with iodine,[6] converts the carboxylic acid into the acyl hypoiodite. The presence of iodine monochloride in the reaction mixture was found to be essential for the promotion of the reaction between acyl hypoiodite and alkyl iodide. Thus when a solution of phenylacetic acid and n-butyl iodide in carbon tetrachloride was treated in the dark with various amounts of t-butyl hypoiodite (prepared from equimolar amounts of potassium t-butoxide and iodine monochloride [7]), only traces of ester were formed (Table 2), but when an excess of iodine monochloride was added to the reaction mixture n-butyl phenylacetate was produced in 12% yield. The use of iodine monochloride, in the absence of t-butyl hypochlorite, did not promote esterification. We suggest that the function of the iodine monochloride in the esterification reaction is to activate the alkyl iodide through complex formation. Complex formation with oxygen atoms of the acyl hypoiodite is less likely, as it would reduce the nucleophilicity of this reactant.

Investigating the effect of irradiation on ester formation we demonstrated that benzyl iodide and no benzyl phenylacetate was formed when phenylacetic acid was irradiated with t-butyl hypoiodite (prepared from equivalent amounts of potassium t-butoxide and iodine monochloride). Previous studies [3] in which t-butyl hypochlorite and iodine were used in the irradiative decarboxylation of phenylacetic acid produced a significant amount of benzyl phenylacetate (13%). In accord with the above we found that irradiative decarboxylation of phenylacetic acid with molar amounts of potassium t-butoxide and iodine monochloride in the presence of n-butyl iodide did not produce n-butyl phenylacetate, but some ester was formed when an excess of iodine monochloride was used. Addition of an excess of n-butyl iodide (4 mol. equiv.) to the reaction mixture which did not contain an excess of iodine monochloride also did not produce n-butyl phenylacetate. However when iodine monochloride was added to the reaction mixture small amounts of ester products were obtained.

From an investigation of the effects of the relative amounts of reactants upon the yield of n-butyl phenylacetate (Table 2) in the dark reaction we established that the highest yield of ester was obtained when phenylacetic acid was treated with t-butyl hypochlorite (2 mol. equiv.), iodine (2 mol. equiv.), and alkyl iodide ($\geqslant$4 mol. equiv.). The low yield of ester from reactions in which an excess of t-butyl hypochlorite and iodine is present is due to the competing reaction in which iodine monochloride reacts with alkyl iodide to produce the inert alkyl chloride.[3] From one example studied we found that bromine behaves similarly to iodine with t-butyl hypochlorite in the esterification reaction.

We suggest that the reaction between the alkyl iodide and the acyl hypoiodite occurs by a heterolytic pathway, since the dark reaction of pentanoic acid with

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[7] S. A. Glover and A. Goosen, unpublished result.

1-iodobutane in the presence of t-butyl hypochlorite and iodine carried out in different solvents, *viz.* carbon tetrachloride and nitrobenzene, afforded n-butyl pentanoate at different rates. With nitrobenzene as solvent the maximum yield (40%) was reached within 5 min, whereas the reaction in carbon tetrachloride gave a maximal yield (37%) after 90 min.

studies have shown that bridgehead substituents cannot be replaced in an S_N2 process.[8] As expected, the reaction with 1-iodoapocamphane did not produce 1-apocamphyl phenylacetate, as the bridgehead apocamphyl carbocation [9] is not readily formed. Interestingly the reaction with ethyl iodoacetate did not produce phenylacetoxyacetate. The electron-withdrawing

TABLE 1

Effect of reactant molar ratios and reaction times in dark reactions of carboxylic acids with alkyl halides in the presence of t-butyl hypochlorite and iodine or bromine upon ester yields $R^1CO_2H + R^2Y + 2.2X_2 \xrightarrow[\text{dark}]{2\ Bu^tOCl} R^1CO_2R^2$

R^1	R^2	Y	Molar ratio (R^2Y to R^1CO_2H)	X_2	Reaction time (h)	Yield (%) * of $R^1CO_2R^2$
Benzyl	1-Adamantyl	I	2.4 : 1	I_2	8	84
Benzyl	1-Apocamphyl	I	2.4 : 1	I_2	8	0
Benzyl	Benzyl	Cl	4.0 : 1	I_2	2	0
Benzyl	n-Butyl	I	4.0 : 1	I_2	4.5	50
Benzyl	Cholestan-3β-yl	I	2.4 : 1	I_2	24	80
Benzyl	Ethoxycarbonylmethyl	I	4.0 : 1	I_2	5	0
Benzyl	Isopropyl	I	2.0 : 1	I_2	4	76
n-Butyl	n-Butyl	I	4.0 : 1	I_2	2	39
4-Methylbenzyl	Benzyl	I	4.0 : 1	I_2	2	76
Phenyl	n-Butyl	Br	4.0 : 1	Br_2	6	0
Phenyl	n-Butyl	Br	4.0 : 1	I_2	4	0
Phenyl	n-Butyl	I	4.0 : 1	Br_2	2.5	23
Phenyl	n-Butyl	I	4.0 : 1	I_2	1	23
Phenyl	t-Butyl	I	4.0 : 1	I_2	4	47
Phenyl	Ethyl	I	4.0 : 1	I_2	4	30

* Yield based on R^1CO_2H.

TABLE 2

Effect of reactant molar ratios on the yield of n-butyl phenylacetate (based on phenylacetic acid)

$PhCH_2\cdot CO_2H$	Bu^nI	Bu^tOCl	I_2	ICl	$KOBu^t$	$Bu^nO_2C\cdot CH_2Ph$
1	1			1	1	Trace
1	1			2	2	0
1	1			4	4	Trace
1	4			2		Trace
1	4			1 (+2) *	1	0.12
1				1	1	0 †
1				2	2	0 †
1				4	2	Trace †
1	1	1	1			0.2
1	1	2	2			0.15
1	1	4	4			0.09
1	4	1	1			0.25
1	4	2	2			0.5
1	10	2	2			0.5
1	4	5	5			0.30
1	4	9	9			0.15
1	4	2				0.5
1	4	1				0.35
1	2	4				0.1
1	2	2				0.1
1	4			1	1	†
1	4			2	2	†
1	4			4	2	0.05 †

* Added after the alkyl iodide. † Irradiated reaction mixture.

Extending the scope of the esterification reaction we found that, in the presence of t-butyl hypochlorite and iodine, phenylacetic acid reacted with 3β-iodocholestane and 1-iodoadamantane to give cholestan-3α-yl phenylacetate (80%) and 1-adamantyl phenylacetate (84%), respectively (Table 1). The product of the former reaction presumably results from an S_N2 reaction, but that of the latter from an S_N1 reaction, since solvolytic ethoxycarbonyl group would not favour the formation of a carbocation on the α-position, and it probably also prevents complexation with iodine monochloride, which facilitates the S_N2 esterification process.

We also found that n-butyl phenylacetate is produced when a solution of phenylacetic acid and n-butyl iodide in carbon tetrachloride is treated with only t-butyl hypochlorite. However this mode of esterification

[8] P. D. Bartlett and L. H. Knox, *J. Amer. Chem. Soc.*, 1939, **61**, 3184; G. J. Gleicher and P. von R. Schleyer, *ibid.*, 1967, **89**, 582.

[9] U. Schollkopf, *Angew. Chem.*, 1960, **72**, 147; E. H. White, R. H. McGirk, C. A. Aufdermarsh, H. P. Tiwari, and M. J. Todd, *J. Amer. Chem. Soc.*, 1973, **95**, 8107.

cannot be occurring in the decarboxylation reactions since the t-butyl hypochlorite does not effect decarboxylation of acids to alkyl chlorides. Further, no n-butyl phenylacetate was formed when n-butyl chloride was used instead of n-butyl iodide in the reaction of phenylacetic acid with t-butyl hypochlorite. In addition we have established that t-butyl hypochlorite reacts rapidly with iodine [3] and thus would not exist for any appreciable time in the relatively slower decarboxylation reactions which are carried out in the presence of an excess of iodine.

The role of iodine monochloride in the esterification reaction thus accounts for the difference in yields of alkyl iodides when the decarboxylation reaction is carried out with t-butyl hypoiodite generated from potassium t-butoxide and iodine [5] or iodine monochloride, as opposed to t-butyl hypoiodite generated from t-butyl hypochlorite and iodine.[3]

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Silica gel for preparative t.l.c. was type HF 254 + 366 (Merck; nach Stahl). I.r. spectra were determined with Unicam SP 200G and SP 1000 spectrometers. N.m.r. spectra were determined with a Perkin-Elmer R12A spectrometer, with tetramethylsilane as internal standard. G.l.c. analysis was carried out with a Packard–Becker 420 gas chromatograph with flame ionization detector. Yields of products were determined by means of calibration graphs correlating peak areas of the esters with that of a standard.

Dark Reactions of Carboxylic Acids with Alkyl Halides in the Presence of t-Butyl Hypochlorite and Iodine or Bromine.—General procedures. (*a*) A mixture of the carboxylic acid (*ca.* 0.006 mol), iodine or bromine, the alkyl halide, and t-butyl hypochlorite in carbon tetrachloride (200 ml) was stirred in the dark at room temperature. The solution was washed (aqueous sodium thiosulphate and aqueous sodium carbonate), dried (Na_2SO_4), and concentrated. The products were separated (t.l.c.) and their spectra (i.r. and n.m.r.) compared with those of authentic esters. Except for those described below, the esters were all known compounds. The reaction mixtures were analysed by n.m.r.[10] or g.l.c. with added internal standards. Results are given in Tables 1 and 2.

(*b*) Iodine monochloride was added to potassium t-butoxide in carbon tetrachloride and the mixture shaken in the dark for 10 min. The carboxylic acid was added and the mixture shaken for 5 min, after which the alkyl halide was added. Work-up and analysis were carried out as described above. The results are summarised in Table 2.

(i) Phenylacetic acid (0.80 g, 0.005 9 mol) and 1-iodoadamantane (3.70 g, 0.014 2 mol) gave a solid which was purified on silica gel preparative t.l.c. plates (developed with cyclohexane) to give 1-adamantyl phenylacetate (1.343 g, 0.004 98 mol), m.p. 42—43°, identical (i.r. and n.m.r.) with an authentic specimen.

(ii) Phenylacetic acid (0.49 g, 0.003 6 mol) and 3β-iodocholestane (4.33 g, 0.008 7 mol) gave a product which was separated on silica gel preparative t.l.c. plates (developed in cyclohexane) to yield cholestan-3α-yl phenylacetate (1.50 g, 0.002 96 mol), m.p. 111—114° (leaflets from methanol), identical (i.r., n.m.r., and m.p.) with an authentic specimen. The half-height width of the 3β-H n.m.r. signal was 8 Hz.

A portion of the ester in diethyl ether was reduced with lithium aluminium hydride to give, after work-up with dilute hydrochloric acid and crystallisation from ethanol, cholestan-3α-ol, m.p. 179—183° (lit.,[11] m.p. 188°), identical (i.r. and n.m.r.) with an authentic specimen.

Rate of Ester Formation in the Dark Reaction of Carboxylic Acids with Alkyl Iodides in the Presence of t-Butyl Hypochlorite–Iodine.—The procedure was as described above, except that samples (2 ml) were withdrawn and washed with water before n.m.r. analysis.[8]

Phenylacetic acid and 1-iodobutane in carbon tetrachloride gave n-butyl phenylacetate (60%) after 10 min. Benzoic acid and 1-iodobutane in carbon tetrachloride gave n-butyl benzoate (23%) after 30 min. Pentanoic acid and 1-iodobutane in carbon tetrachloride gave n-butyl pentanoate (37%) after 90 min. Pentanoic acid and 1-iodobutane in nitrobenzene gave n-butyl pentanoate (40%) within 5 min.

1-Adamantyl Phenylacetate.—Adamantan-1-ol (10.0 g, 0.066 mol) was added to a solution of ethylmagnesium bromide [from ethyl bromide (7.52 g, 0.069 mol) and magnesium (1.65 g, 0.069 mol) in diethyl ether (200 ml)]. The mixture was refluxed for 0.5 h, a solution of phenylacetyl chloride (11.0 g, 0.07 mol) in ether (100 ml) was added, and the mixture was then refluxed for 12 h, cooled, washed (aqueous sodium carbonate), dried (Na_2SO_4), and concentrated to an oil. Chromatography on silica gel gave *1-adamantyl phenylacetate* (7.70 g, 0.028 mol), m.p. 43—44°; M^+ 270; δ ($CDCl_3$) 1.61 (6 H, s), 2.08 (9 H, s), 3.40 (2 H, s), and 7.18 (5 H, s) (Found: C, 79.9; H, 8.0. $C_{18}H_{22}O$ requires C, 80.0; H, 8.2%).

Cholestan-3α-yl Phenylacetate.—A solution of cholestan-3α-ol (2.21 g, 0.0056 mol) and phenylacetyl chloride (3.40 g, 0.02 mol) in carbon tetrachloride (30 ml) was left at room temperature for 17 h, washed (aqueous sodium carbonate), dried (Na_2SO_4), and concentrated. Chromatography on silica gel preparative t.l.c. plates (developed in benzene) gave *cholestan-3α-yl phenylacetate* (1.66 g, 0.003 3 mol), m.p. 115—117° (from ethyl acetate); M^+ 506; δ ($CDCl_3$) 4.95 (1 H, s, $W_{\frac{1}{2}}$ 8 Hz) (Found: C, 82.9; H, 10.7. $C_{35}H_{54}O_4$ requires C, 82.95; H, 10.7%).

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