

## Synthesis of Esters from Alcohols or Alcohols and Aldehydes with *t*-Butyl Hypoiodite

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From studies of the reaction of an aldehyde with an alcohol in the presence of *t*-butyl hypoiodite (generated from *t*-butyl hypochlorite, iodine, and potassium *t*-butoxide), it is proposed that the ester derived from an alcohol and *t*-butyl hypoiodite in the dark is formed *via* a polar process in which the intermediate is not the acyl iodide. The acceleration of ester formation when the reaction mixture is irradiated is suggested to be due to hydrogen abstraction from the aldehyde to form the acyl iodide, which then reacts with the alcohol.

IN the hope of obtaining a homogeneous reaction system to pursue our study of the reactions of alcohols with vicinal substituents<sup>1</sup> in the presence of 'positive' iodine species, we investigated the reactions of alcohols with *t*-butyl hypochlorite-iodine. *t*-Butyl hypochlorite reacts rapidly with iodine to produce *t*-butyl hypoiodite<sup>2</sup> and iodine monochloride, and the latter reacts with diols to give oxidation products, substitution products, and esters.<sup>3</sup> It was thus deemed necessary to avoid the production of iodine monochloride. *t*-Butyl hypoiodite has been prepared from potassium *t*-butoxide<sup>4</sup> and iodine in benzene, but the results obtained were of a non-quantitative nature. We have found<sup>5</sup> that *t*-butyl hypoiodite is more successfully prepared from potassium *t*-butoxide in *t*-butyl alcohol-benzene by treatment with iodine monochloride.

We therefore studied the reactions of alcohols with *t*-butyl hypoiodite prepared from *t*-butyl hypochlorite and iodine with potassium *t*-butoxide in the molar ratio 1 : 1.5 : 2, expecting that the excess of iodine would react



with the even larger excess of potassium *t*-butoxide to give more 'positive' iodine reagent while the remaining excess of potassium *t*-butoxide could serve as a trap for any acids produced from the reaction with alcohols. The results are summarised in Table 1.

These results differ completely from those obtained for the reactions of alcohols with lead tetra-acetate,<sup>6</sup> mercury(II) oxide-iodine<sup>2</sup> and nitrosyl chloride.<sup>7</sup> 2-

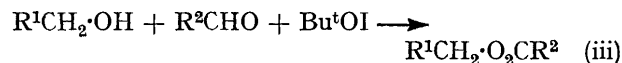
<sup>1</sup> A. Goosen and H. A. H. Laue, *J. Chem. Soc. (C)*, 1969, 383; *J. Chem. Soc. (B)*, 1969, 995; *J. S. African Chem. Inst.*, 1971, **14**, 126.

<sup>2</sup> (a) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1964, **86**, 1528; (b) A. Goosen and C. W. McClelland, *J.C.S. Chem. Comm.*, 1975, 655.

<sup>3</sup> A. Goosen and C. W. McClelland, submitted to *J. S. African Chem. Inst.*

Phenoxyethanol with mercury(II) oxide-iodine in the dark quantitatively produced *p*-iodophenoxyethanol,<sup>2b</sup> and the thermal reaction with lead tetra-acetate resulted in oxidation, fragmentation, and intramolecular cyclisation. Upon treatment with *t*-butyl hypoiodite, phenoxyethanol gave 2-phenoxyethyl phenoxyacetate as major product. All the primary alcohols gave esters as major products with the exception of benzyl alcohol which, like secondary alcohols, gave mainly oxidation products.

By analogy with ester formation with iodine monochloride,<sup>3</sup> it seemed probable that the *t*-butyl hypoiodite promoted ester formation between the initially formed aldehyde and unchanged alcohol. This postulate [equation (iii)] was confirmed by the reactions of alcohols with



aldehydes in excess in the presence of *t*-butyl hypoiodite (Table 2).

In order to establish whether the aldehyde was first being converted into an acyl hypoiodite, the reactions of heptanal and benzaldehyde with *t*-butyl hypoiodite were investigated (see Figure). Whereas benzaldehyde was stable to *t*-butyl hypoiodite in the dark, but was rapidly consumed under irradiation to give *t*-butyl benzoate, heptanal reacted with the *t*-butoxy species present to form *t*-butyl heptanoate. The formation of *t*-butyl heptanoate was accelerated by irradiation. In contrast to the slow formation of *t*-butyl heptanoate from heptanal and *t*-butyl alcohol in the dark, heptanal reacts

<sup>4</sup> D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 1965, 2438; D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *ibid.*, p. 181.

<sup>5</sup> S. A. Glover and A. Goosen, unpublished result.

<sup>6</sup> M. Lj. Mihailović, Z. Ceković, V. Andrejević, R. Matic, and D. Jeremić, *Tetrahedron*, 1968, **33**, 2767.

<sup>7</sup> D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1960, **82**, 2640; 1961, **83**, 4076.

rapidly with n-butanol in the dark to produce n-butyl heptanoate.

The pronounced increase in the rate of formation of t-butyl ester upon irradiation indicates that the overall rate of esterification does not represent the reaction of the, initially rapidly formed, acyl iodide with the alcohol, since irradiation above 300 nm would not be expected to have an influence on this process. Furthermore, the

esterification carried out in the dark, was the stability of benzaldehyde to t-butyl hypoiodite under these conditions, whereas it reacted with n-butanol in the presence of t-butyl hypoiodite, albeit inefficiently, to form n-butyl benzoate.

The formation of t-butyl benzoate and the increased rate of formation of t-butyl heptanoate from the reactions of benzaldehyde and heptanal, respectively, under

TABLE 1  
Reaction of alcohols with t-butyl hypochlorite-iodine-potassium t-butoxide

Alcohol	Time (h)	Starting material	Products (%) *		
			RCHO(R <sub>2</sub> CO)	RCO <sub>2</sub> -CH <sub>2</sub> R ‡	Others §
PhCH <sub>2</sub> -OH	0.05	30 (4)	72 (4)	2 (5)	
	0.30	23 (4)	78 (4)	3 (5)	
	0.30 †	22 (4)	80 (4)	3 (5)	
<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> -OH	2.00	29	8	26	<i>p</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -CO <sub>2</sub> But, 1
	0.30 †	22 (4)		22 (A6)	
Ph[CH <sub>2</sub> ] <sub>2</sub> -OH	1.10 †	20 (4)		22 (A6)	
	0.30	51 (5)	0	23 (5)	
PhO-[CH <sub>2</sub> ] <sub>2</sub> -OH	1.30 †	19 (5)	0	40 (5)	
	0.30 †	50 (5)	0	22 (5)	
	2.00 †	4 (5)	0	48 (5)	
Ph[CH <sub>2</sub> ] <sub>4</sub> -OH	2.00 †	0		46	2-Ph-THF, (4)
PhCH <sub>2</sub> -O-[CH <sub>2</sub> ] <sub>2</sub> -OH	0.10 †	0		36	2-Ph-1,3-DXL, 18
Bu <sup>n</sup> OH	0.05	23 (4)		36 (4)	
	0.20	13 (4)		41 (4)	
	0.20 †	10 (4)		42 (4)	
Me[CH <sub>2</sub> ] <sub>6</sub> -OH	0.05	0	26 (4)	38 (4)	Me[CH <sub>2</sub> ] <sub>5</sub> -CO <sub>2</sub> But { 0 (4) 2 7
	1.00	0	21	37	
	4.30	0	14	38	
Ph <sub>2</sub> CH-OH	1.00	0	100		
[CH <sub>2</sub> ] <sub>5</sub> CH-OH	0.05	0	97 (4)		
PhCH <sub>2</sub> -OH + Me[CH <sub>2</sub> ] <sub>5</sub> -OH	0.10	41 (4)	51 (3)	Trace	PhCO <sub>2</sub> But <sup>n</sup> , 2 (4)
		65 (4)		8 (4)	Me[CH <sub>2</sub> ] <sub>5</sub> -CO <sub>2</sub> -CH <sub>2</sub> Ph, 6 (3) γ-Lactone, 79 (4)
HO-CH <sub>2</sub> -[CH <sub>2</sub> ] <sub>2</sub> -CH <sub>2</sub> -OH	1.5	10 (10)			

\* Figures in parentheses indicate the g.l.c. column used for analysis. All other analyses were carried out by n.m.r. spectroscopy.  
† With irradiation. ‡ Where the maximum yield possible is 50%. § THF = tetrahydrofuran; DXL = dioxolan.

TABLE 2  
Reactions of alcohols with aldehydes in the presence of t-butyl hypoiodite

Alcohol R <sup>1</sup> OH	Aldehyde R <sup>2</sup> CHO	Time (h)	Products (%) *			
			R <sup>1</sup> OH	R <sup>2</sup> CO <sub>2</sub> R	RCHO(R <sub>2</sub> CO)	Other esters
Me[CH <sub>2</sub> ] <sub>2</sub> -CH <sub>2</sub> -OH	Me[CH <sub>2</sub> ] <sub>2</sub> -CHO	0.30	13 (4)	82 (4)		
PhO-CH <sub>2</sub> -CH <sub>2</sub> -OH	Me[CH <sub>2</sub> ] <sub>2</sub> -CHO	0.10	19 (5)	81 (5)		
		1.10	12	83		
Me[CH <sub>2</sub> ] <sub>2</sub> -CH <sub>2</sub> -OH	PhCHO	1.00	17 (4)	11 (4)		Me[CH <sub>2</sub> ] <sub>2</sub> -CO <sub>2</sub> But <sup>n</sup> , 36; and PhCO <sub>2</sub> But <sup>t</sup> , trace
PhCH <sub>2</sub> -OH	Me[CH <sub>2</sub> ] <sub>2</sub> -CHO	1.00	6 (5)	57 (3)	34 (5)	
Me[CH <sub>2</sub> ] <sub>2</sub> -CH <sub>2</sub> -OH	<i>p</i> -O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -CHO	1.00		53		
MeCH <sub>2</sub> -CH(OH)Me	Me[CH <sub>2</sub> ] <sub>2</sub> -CHO	1.00		20 (4)		
[CH <sub>2</sub> ] <sub>5</sub> CHOH	Me[CH <sub>2</sub> ] <sub>5</sub> -CHO	0.10	0	8 (4)	89 (3)	
[CH <sub>2</sub> ] <sub>5</sub> CHOH	Me[CH <sub>2</sub> ] <sub>5</sub> -CHO †	0.10	0	17 (4)	80 (4)	
Bu <sup>t</sup> OH	<i>p</i> -O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub> -CHO	2.00		4		
		6.00		11		

\* Figures in parentheses indicate g.l.c. columns used for analysis. All other analyses were carried out by n.m.r. spectroscopy.  
† 4 mol excess.

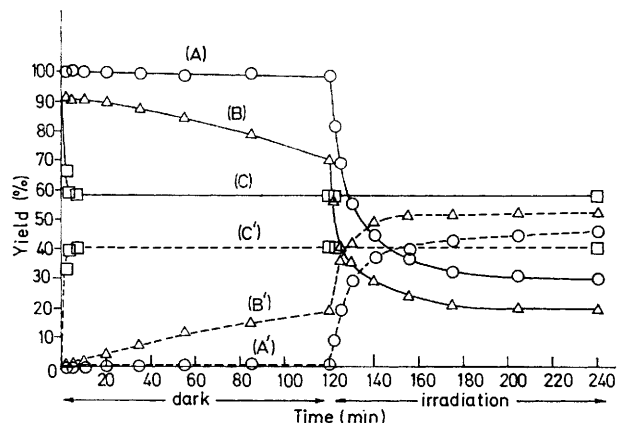
dark reaction to produce esters cannot involve formation of acyl iodide, since the rapid formation of n-butyl heptanoate, from heptanal with n-butanol in the presence of t-butyl hypoiodite suggests that formation of acyl iodide is fast, whereas the dark reaction of heptanal with t-butyl alcohol is much slower. It therefore appears that the reaction of an alcohol and an aldehyde, initiated by t-butyl hypoiodite, is a polar process (A), possibly taking place *via* a concerted mechanism (B). Further evidence that acyl iodides are not intermediates in the

irradiation are best accounted for by the hydrogen abstraction process. Under irradiation, the aldehydic hydrogen atom is probably abstracted by a t-butoxyl radical, producing an acyl radical which is trapped by iodine as acyl iodide; this then reacts with the t-butyl alcohol present.

The absence of 2,3-dihydro-1,4-benzodioxin, which is considered<sup>8</sup> to be formed by an intramolecular free

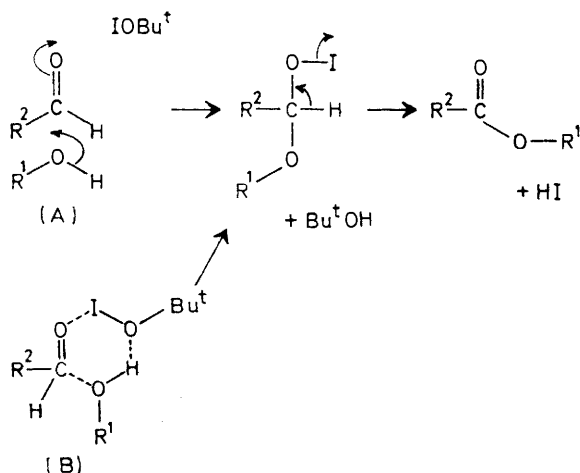
<sup>8</sup> M. I. J. Mihailović and M. Miloradović, *Tetrahedron*, 1966, **22**, 723.

radical cyclisation process from phenoxyethanol and *t*-butyl hypoiodite under irradiation, indicates that the radical cyclisation process cannot compete with the oxidative and esterification process. In an effort to obtain an alkoxy radical process which could compete with oxidation to the aldehyde and hence with ester formation, the reactions of 4-phenylbutan-1-ol and 2-benzyloxyethanol with *t*-butyl hypoiodite were investigated. Only a trace of 2-phenyltetrahydrofuran was



Stability of aldehydes towards *t*-butyl hypoiodite; (A) benzaldehyde, (A') *t*-butyl benzoate, (B) heptanol, (B') *t*-butyl heptanoate, (C) heptanol in the presence of *n*-butanol, (C') *n*-butyl heptanoate

formed from 4-phenylbutan-1-ol and 2-phenyl-1,3-dioxolan was a minor product (18%) from the reaction of 2-benzyloxyethanol. In both cases the corresponding ester was the major product. These product distributions demonstrate that free radical intramolecular cyclisation does not effectively compete with oxidation



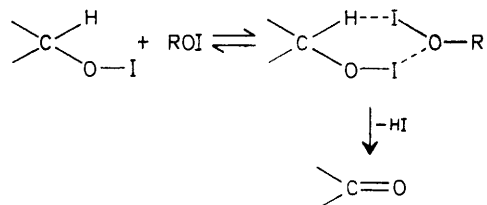
of the alcohols to the aldehydes, which subsequently form esters.

The oxidation can be accounted for by two pathways. Either the alcohol first forms a hypoiodite, which is

<sup>9</sup> Y. Ogata and K. Nagura, *J. Org. Chem.*, 1974, **39**, 3680.

<sup>10</sup> I. R. L. Barker, W. G. Overend, and C. W. Rees, *J. Chem. Soc.*, 1964, 3263; L. Kaplan, *J. Amer. Chem. Soc.*, 1954, **76**, 4645; 1958, **80**, 2638.

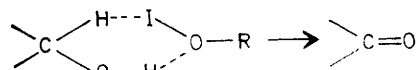
oxidised by another hypoiodite molecule, assisting the removal of a hydride ion from the  $\alpha$ -carbon atom (Scheme 1),<sup>9</sup> or the alcohol could be oxidised by the



SCHEME 1

hypoiodite in a process analogous to that generally accepted for oxidation of alcohols by bromine in aqueous acidic media (Scheme 2).<sup>10</sup> Since the products obtained from the reaction of alcohols with mercury(II) oxide-iodine were mainly those formed by an abstraction process,<sup>1</sup> and those derived from the same alcohols with *t*-butyl hypoiodite were esters, it is unlikely that both reagents initially generate hypoiodites from the alcohols.

These results can be rationalised on the basis of hypoiodite formation with *t*-butyl hypoiodite being an



SCHEME 2

equilibrium process (iv) well over to the left; hence the free radical process arising from the alkyl hypoiodite



competes ineffectively with the fast oxidation of the alcohol according to Scheme 2. A similar equilibrium was proposed<sup>11</sup> for the reaction of alcohols with *t*-butyl hypochlorite. Only in the case of 2-benzyloxyethanol is any significant amount of product produced from the free radical process. In their study of steroidal alcohols with *t*-butyl hypochlorite-iodine and with potassium *t*-butoxide-iodine, Akhtar and Barton<sup>2</sup> obtained mainly oxidation products in the dark, and mainly products derived from alkoxy radicals from the irradiated reaction mixture. The difference is probably due to the smaller entropy factor in the rigid steroidal system.

The alcohols must initially be oxidised to the aldehyde or ketone by the hypoiodite. However, in order for esters to be formed from the aldehydes the esterification reaction must be much faster than the oxidation since there is sufficient hypoiodite present to oxidise all the alcohol.

Only in the case of benzyl and secondary aliphatic alcohols is the oxidation faster than the esterification. Even the reaction of benzyl alcohol and an excess of butanal with *t*-butyl hypoiodite gave, in addition to benzyl butanoate, a significant amount of benzaldehyde. A competitive reaction of benzyl alcohol and *n*-butanol gave mainly benzaldehyde with the yields of ester in the order: *n*-butyl butanoate, benzyl butanoate, and *n*-butyl

<sup>11</sup> C. Walling and M. J. Mintz, *J. Amer. Chem. Soc.*, 1967, **89**, 1515.

benzoate, indicating rapid oxidation of benzyl alcohol and a lower rate of ester formation from benzaldehyde. This was confirmed by the reaction of n-butanol with benzaldehyde in the presence of t-butyl hypoiodite. The yield of n-butyl butanoate was more than three times that of n-benzyl benzoate. In the reactions of secondary aliphatic alcohols with aldehydes in the presence of t-butyl hypoiodite, oxidation of the alcohols to ketones occurred more readily than esterification. The lack of reactivity of benzaldehyde, as compared with aliphatic aldehydes, is due to interaction of the aromatic ring with the carbonyl group which lowers its susceptibility to nucleophilic attack. In support of this, *p*-nitrobenzaldehyde was much more reactive and more readily produced the ester, n-butyl *p*-nitrobenzoate, upon treatment with n-butanol and t-butyl hypoiodite in the dark. Further, under the same conditions in which benzaldehyde was stable, *p*-nitrobenzaldehyde reacted with t-butyl alcohol in the presence of t-butyl hypoiodite to give a significant amount of t-butyl *p*-nitrobenzoate.

The above trends in the esterification of aldehydes are reflected in the formation of hemiacetals from aldehydes and alcohols.<sup>12,13</sup> Benzaldehyde did not form hemiacetals, and in the case of aliphatic aldehydes the rate of hemiacetal formation decreased markedly with increased branching around the hydroxy-group. If the aldehyde contained a strongly electronegative substituent (*e.g.* *p*-nitrobenzaldehyde) the extent of hemiacetal formation was more substantial.

These results represent an extension and improvement of the one-stage synthesis<sup>12</sup> of esters from an alcohol or

<sup>12</sup> J. C. Craig and E. C. Horning, *J. Org. Chem.*, 1960, **25**, 2098.

<sup>13</sup> N. C. Melchior, *J. Amer. Chem. Soc.*, 1949, **71**, 3651; J. M. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *J. Org. Chem.*, 1965, **30**, 4284.

a mixture of an aldehyde and an alcohol, *via* oxidation of the intermediate hemiacetal with acid dichromate.

#### EXPERIMENTAL

G.l.c. analyses were carried out with a Becker Packard 420 gas chromatograph fitted with an Autolab 6 300 digital integrator, by use of the following columns: (4) 15% Carbowax 20M on Chromosorb M(80—100 mesh), (5) 1% Silicone Dow 11 on Carbowax XXX (60—70 mesh), (A6) 1% Silicone on Chromosorb P (80—100) mesh, and (10) 4% ethofat and 2% isophthalic acid on Chromosorb T (40—60 mesh). Yields of products were obtained from calibration graphs of the peak areas against concentration of substrate. N.m.r. analyses were carried out with a Perkin-Elmer R12A instrument.

*Reaction of Alcohols (and/or Aldehydes) with t-Butyl Hypoiodite-Iodine-Potassium t-Butoxide.*—Iodine (7.5—12 mmol) and t-butyl hypochlorite (5.5 mmol) in either benzene (30 ml) or a 50% solution of t-butyl alcohol in benzene were stirred in the dark at room temperature for 10 min. Potassium t-butoxide (10 mmol) was then added and stirring was continued for 10 min. The alcohol (5 mmol) [and/or aldehyde (5 mmol)] was then added and either irradiation (1 000 W tungsten lamp) was commenced immediately, or the mixture was first stirred in the dark and irradiation was begun later. Samples (2 ml) were withdrawn, quenched (aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>), dried (Na<sub>2</sub>SO<sub>4</sub>), and analysed (g.l.c. or n.m.r.). All products were fully characterised by comparison with authentic materials.

The Figure illustrates the reactivity of benzaldehyde and heptanal in the dark and under irradiation with t-butyl hypoiodite.

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