Synthesis of Alkyl Iodides

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Hindered alkyl iodides may be prepared conveniently by treatment of the corresponding chlorides with sodium iodide in carbon disulphide in the presence of an inorganic catalyst, such as zinc chloride. The reactions appear to be dependent upon electrophilic catalysis, and *in situ* trapping of carbenium species by iodide ion.

ALKYL iodides are considerably more reactive than their halogen analogues and consequently are often used in synthesis in preference to other halides. Their preparation normally presents no great difficulty if the alkyl group is primary or secondary, since the exchange of iodide for other displaceable functions is a well established reaction.[1] Tertiary iodides, however, are considerably more awkward to prepare,[1] largely because of the ease with which competing reactions, such as β-elimination, may occur during, or subsequent to, the attempted introduction of iodide. Moreover, once formed, these iodides are sensitive to thermolysis, photolysis, and ionising conditions, and they can be difficult to isolate and purify.

One of the attractions of the halogen-exchange pro-

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[1] A. Roedig in ' Methoden der Organischen Chemi ' (Houben-Weyl), ed. E. Muller, Thieme Verlag, Stuttgart, 1960, vol. V/4, p. 595.

cedure (Finkelstein reaction) for non-hindered iodides is its simplicity and mildness, and it was with this in mind that it was decided to examine the effect of inorganic salts upon exchanges at tertiary centres. It is recognised that typical Lewis acids, such as aluminium trichloride, are capable of co-ordination to halogen atoms, particularly those of tertiary halides, to generate species which behave as carbenium ions.* If this interaction could be produced in a non-ionising and non-solvolysing medium, it seemed that a potential nucleophile like iodide ion might trap the carbenium-type species. This paper is concerned with the preparative and mechanistic aspects of our attempts to achieve this end—as indicated in equation (i).

$$R^tCl + I^- \longrightarrow R^tI + Cl^- \qquad (i)$$

Scope of Reaction.—Initial experiments were carried out in carbon disulphide, partly because of its lack of protons, but largely because of its low dielectric constant. When t-butyl chloride and sodium iodide (2 mol. equiv.) were stirred at room temperature in carbon disulphide, in the presence of iron(III) chloride (trace, anhydrous), t-butyl iodide was formed fairly rapidly, and apparently in very high yield, as judged by n.m.r. Further experiments in acetone, methanol, bis-(2-methoxyethyl) ether, and dimethylformamide yielded no t-butyl iodide under similar conditions. At this stage, only one other solvent, carbon tetrachloride, was found suitable for the synthesis of t-butyl iodide, although the exchange was much slower and its efficiency less than with the carbon disulphide system. For this, and all other exchanges, control experiments showed that exchange did not occur in the absence of catalyst.

The scope of the iron(III) chloride-catalysed exchange was then investigated in some detail; the main results are reported in Table 1. Two general trends emerge. The first is that in the simple alkyl series, chlorides must be tertiary in order to be exchanged. Thus n-butyl and cyclohexyl chlorides do not react, whereas 1-methyl-1-chlorocyclohexane reacts fairly readily. This last reaction showed that no β-elimination was occurring during the exchange, since the possible olefinic product(s) derived from this would certainly accumulate in carbon disulphide at room temperature—with isobutene this could not be taken for granted.

The second feature of these reactions is that phenyl or acyl groups attached to the halogen-bearing carbon atom also facilitate exchange. Thus the primary chlorides benzyl chloride and phenacyl chloride were exchanged under our heterogeneous conditions. Most noteworthy was the exchange leading to the unstable benzylidene iodide, which seems not to have been reported previously. α-Chlorocumene (1) produces 1,1,3-trimethyl-3-phenyl-

indane (2), a well known dimer of α-methylstyrene;[3] our evidence indicates that the corresponding iodide (3) is an intermediate in the formation of at least some of (2).
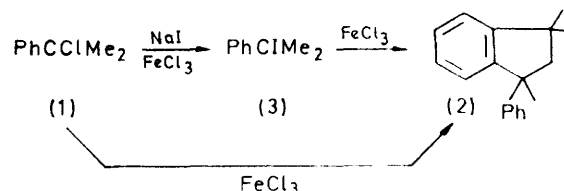
Attempts to extend the exchange to prepare tertiary bromides were not so successful; the reaction leading to t-butyl bromide, which was the only one studied in any detail, appears to approach equilibrium at about 70% conversion, but the attainment of equilibrium is extremely sluggish.

Although the reactions with iron(III) chloride as catalyst are ' clean ' in terms of the organic components, the same cannot be said of the physical appearance of the reaction mixture or of the work-up procedure. The undesirable features are due to the redox reaction between iodide ion and iron(III) chloride. Under heterogeneous conditions, this has been found to be quite slow, but nevertheless it generates iodine, which certainly does not enhance the stability of the tertiary iodides. Accordingly, attempts were made to find a more suitable catalyst.

Aluminium chloride did not catalyse exchange, and copper(II) chloride only yielded small amounts of t-butyl iodide from the chloride. Similarly silver nitrate was not very successful, although it did bring about partial exchange of either one or both chlorine atoms of benzylidene chloride. However the group 2B chlorides were adequate, with zinc chloride being superior in terms of reaction rate. The principal advantage of zinc chloride over iron(III) chloride is that the reaction mixtures remain clear and colourless, and the inorganic material stays granular and easy to filter off. Thus the zinc chloride-catalysed reactions permit a simple filtration and evaporation to yield almost pure iodides. Moreover the exchangeability of alkyl chlorides shows exactly the same organic group dependence as that with iron(III) chloride. However, iron(III) chloride exchanges were several times faster, *e.g.* ten-fold for t-butyl chloride. Table 2 records the yields obtained by use of various catalysts.

We then extended our studies to a number of other hindered chlorides, as shown in Table 3. 1-Chloroadamantane underwent exchange rather slowly, but nevertheless quite cleanly. On the other hand 3-chloro-3-methylbut-1-ene (4) exchange is the fastest that we have observed, and it leads to the rearranged iodide (5), also formed from the corresponding primary allylic chloride (6).

* This co-ordination is an essential feature of the isotopic exchange of halogens in organic halides by metal halides [2a] and of the Friedel–Crafts reaction.[2b]

[2] (a) Reviewed by M. F. A. Dove and D. B. Sowerby in ' Halogen Chemistry,' ed. V. Gutmann, Academic Press, London, 1967, vol. 1, pp. 116—117; (b) reviewed by G. A. Olah, ' Friedel–Crafts Chemistry,' Wiley, New York, 1973, pp. 229—305.

[3] (a) H. Staudinger and F. Breusch, *Chem. Ber.*, 1929, **62**, 442; (b) L. Schaap and H. Pines, *J. Amer. Chem. Soc.*, 1957, **79**, 4967; (c) J. M. Barton and D. C. Pepper, *J. Chem. Soc.*, 1964, 1573; (d) R. Gelin and B. Chantegral, *Bull. Soc. chim. France*, 1971, 2527.

Pathway to Exchange.—The structural limitations on the organic residue in these exchanges are distinct, and show that ability to sustain some degree of positive charge is important. This behaviour suggests that the

catalysts are indeed acting as Lewis acids, although at one stage consideration was given to radical pathways. The redox reaction with iron(III) chloride produces iron(II) chloride, which has been implicated in a number of electron-transfer processes by other workers.[4] However we were never able to detect radical intermediates, or possible products of radical dimerisation or disproportionation, and the catalytic properties of zinc chloride offer little scope for rationalisation based on redox pathways.

With regard to the nature of the catalysed reaction pathway, a number of results suggest that the catalyst, organic halide, and iodide source are involved in a fairly intimate sequence of events. First indications of this came from our work in which benzene was used instead of carbon disulphide. When t-butyl chloride was stirred in benzene with sodium iodide and iron(III) chloride for 4 h, the major product (95 ± 2%) was t-butyl iodide. Very small amounts of t-butylbenzene are produced, despite the fact that it is formed quantitatively in minutes from t-butyl chloride and catalytic amounts of iron(III) chloride in benzene.[5]

Furthermore, the sources of the iodide ion and the iron(III) ion are critical: use of iron(III) sulphate results in inhibition of the exchange, as does use of tetrabutylammonium iodide, which is moderately soluble in carbon disulphide. Thus these exchanges appear to involve some degree of co-ordination of the tertiary chloride to the catalyst, followed by trapping of the developing carbenium ion by iodide ion. That the iodide is able to do this without being in solution suggests that it too has become co-ordinated to the catalytic centre. This might well be the result of either substitution in the catalyst [equation (ii)] or co-ordination to the catalyst giving an

anionic species[6] [equation (iii)], although it does not seem likely that such a complex anion would be an efficient

Lewis acid. On the other hand, metals such as zinc form[6] polyhalogeno-dianions, as in Na_2ZnCl_4, and it is therefore conceivable that an organic chloride could provide the fourth ligand around a zinc atom. The thermodynamics of these zinc complexes are known[7] to be highly solvent-dependent, which makes it difficult to apply data on solutions in aqueous solvents to the present reactions.

The failure of the Friedel–Crafts t-butylation of benzene to compete with the much slower production of t-butyl iodide must surely mean that the catalyst, iron(III) chloride (generally 3×10^{-4} mol) or zinc chloride (generally 6.6×10^{-3} mol), has been altered in some way by the iodide ion present (generally 2×10^{-2} mol), and that insufficient catalyst remains to bring about the Friedel–Crafts reaction. It is not clear at this stage why the nature of the iodide source is critical, and whether it is pertinent to the way in which the Friedel–Crafts activity of the initial Lewis acid is inhibited.

A number of related functional group exchanges have been described recently, and certain of these make interesting comparisons with the present work. For example, alkyl derivations of both aluminium[8] and zinc[9] are known to alkylate t-butyl chloride. The reaction with alkylaluminium derivatives has been the subject of several recent studies, from which it appears[10] that these reactions involve the formation of an ion pair (7). It was also found[10] that reactivity decreases across the series $Bu^tCl > Bu^tBr > Bu^tI$, and this order

is in agreement with the inertness of t-butyl iodide to our exchange conditions. Rearrangements have also been observed[11] in the organic system during the reactions of the homoallylic halide (8). From our own work, the observed allylic rearrangement of 3-chloro-3-methylbut-1-ene (4) appears to be similar in general features, although the alkylation reactions of trimethylaluminium occur in homogeneous solution.

Electrophilic catalysis has also been used in several recent syntheses of alkyl halides. For example, magnesium iodide has been shown to convert primary or secondary tosylates into iodides in ether at room

[4] R. B. Allen, R. G. Lawler, and H. R. Ward, *J. Amer. Chem. Soc.*, 1973, **95**, 1692; M. Tamura and J. Kochi, *J. Organometallic Chem.*, 1971, **31**, 239.

[5] F. Drahowzal in ' Friedel–Crafts and Related Reactions,' ed. G. A. Olah, Interscience, New York, 1963, vol. 2, ch. 8, p. 417.

[6] B. J. Aylett in ' Comprehensive Inorganic Chemistry,' ed. A. F. Trotman-Dickenson, Pergamon, London, 1973, vol. 3, p. 187.

[7] E. Y. Gorenbein, M. N. Vainshtein, E. P. Skorobogatko, A. K. Trofimchuk, *J. Gen. Chem.* (*U.S.S.R.*), 1974, **44**, 1527.

[8] J. P. Kennedy, *J. Org. Chem.*, 1970, **35**, 532.

[9] G. R. Noller, *J. Amer. Chem. Soc.*, 1929, **51**, 594.

[10] J. P. Kennedy, N. V. Desai, and S. Sivaram, *J. Amer. Chem. Soc.*, 1973, **95**, 6386.

[11] E. G. Melby and J. P. Kennedy, *J. Org. Chem.*, 1974, **39**, 2433.

temperature,[12] and to induce ring opening of the cyclopropylmethanols (9) in ether.[13] The latter reaction fails for the primary alcohol, and is easiest when R = Me, a trend which is again shown in the present exchanges. Other examples come from work on the exchange of 1-adamantyl halides with aluminium tribromide [14] or zinc fluoride [15] as catalyst.

In conclusion, there is considerable current evidence that inorganic salt catalysts can be usefully employed to promote functional group exchanges. We hope to establish details of the mechanism of these exchanges, and also to examine their efficiency in the presence of relatively polar organic functions.

EXPERIMENTAL

I.r. spectra were run with a Perkin-Elmer 157 G spectrometer for liquid films. N.m.r. spectra were determined for solutions in carbon disulphide (unless stated otherwise) with tetramethylsilane as internal standard, by using a Perkin-Elmer R 10 spectrometer operating at 60 MHz. Solvent grade carbon disulphide was used throughout. Inorganic salt catalysts were reagent grade, anhydrous, and no special precautions were taken with their use. Anhydrous iron(II) chloride was prepared from iron(III) chloride and chorobenzene,[16] and stored under nitrogen.

Alkyl Iodides from Alkyl Chlorides by Use of Iron(III) *Chloride as Catalyst.*—In a typical reaction, the alkyl chloride (0.01 mol) was dissolved in carbon disulphide (10 ml). Sodium iodide (anhydrous; 0.02 mol) was added, followed by iron(III) chloride (anhydrous), and the reactants were gently ground together under the solvent, by which time a strong iodine colour was apparent. The mixture was then stirred at room temperature, and monitored periodically by n.m.r. spectroscopy. The alkyl chlorides used are indicated in Table 1, together with the yields (estimated by n.m.r. integrals) of iodide, the catalyst–alkyl chloride ratio, and the reaction time. The reaction of t-butyl chloride was also followed by e.s.r., but no evidence of radical intermediates was found. Furthermore the reactions were not sensitive to atmospheric oxygen. Control experiments were set up in each case, and these showed that no significant halogen exchange had occurred within the reaction times shown in the Table when iron(III) chloride was omitted.

The iodides were isolated by filtration to remove inorganic salts and evaporation of the solution in a current of dry nitrogen at room temperature. Liquid iodides were then distilled, but the isolated yields were usually low, and the product rapidly became discoloured, even in the dark under nitrogen. With solid iodides, the residue was taken up in petroleum (b.p. 40—60°), and the chilled solution was partially evaporated by a current of dry nitrogen, until precipitation occurred. Attempted recrystallization in more conventional fashion yielded tarry oils. The only new iodide isolated in this way was *benzylidene iodide* (22%), m.p. 28—32 °C (Found: M^+, 343.8857. $C_7H_6I_2$ requires M, 343.8859), τ 2.4—3.0 (5 H, m, aryl), and 3.85 (1 H, s, CH). Otherwise the iodides were identified by comparison of their i.r. and n.m.r. spectra with those of samples prepared by standard routes.

[12] J. Gore, P. Place, and M. L. Roumestant, *J.C.S. Chem. Comm.*, 1973, 821.

[13] J. P. McCormick and D. L. Barton, *J.C.S. Chem. Comm.*, 1975, 303.

Effect of Catalyst Change on the Exchange Reaction.—The reaction of t-butyl chloride (0.93 g, 0.01 mol) and sodium iodide (anhydrous; 3.0 g, 0.02 mol) in carbon disulphide (10 mol) was studied on account of its convenience and sensitivity of analysis, and because of the relatively favourable rate of the analogous iron(III) chloride-catalysed reaction. Table 2 shows the amounts of catalysts, and the

TABLE 1

Alkyl iodides from alkyl chlorides by use of sodium iodide and iron(III) chloride in carbon disulphide at 20 °C

Chloride	Iodide yield (%)	$FeCl_3$: chloride (mol)	Reaction time (h)
1-Methylcyclohexyl	96	1 : 16	22
1-Ethyl-1,5-dimethylhexyl	98	1 : 20	72
Benzyl	95	1 : 13	10
Benzylidene	100	1 : 20	28
t-Butyl	99	1 : 40	2
Cyclohexyl	0	1 : 16	120
2-Chloroethyl	0	1 : 6	120
n-Butyl	0	1 : 20	120
Acetyl	100	1 : 13	32
Phenacyl	95	1 : 53	44

TABLE 2

Catalysts used in attempted synthesis of alkyl iodides from alkyl halides and sodium iodide in carbon disulphide at 20 °C

Halide	Catalyst	Catalyst : Halide (mol)	Iodide yield (%)	Time (h)
Bu^{t}Cl	$FeCl_2$	1 : 20	0	120
Bu^{t}Cl	$Fe_2(SO_4)_3$	1 : 40	0	120
Bu^{t}Cl	$CuCl_2$	1 : 30	2	120
Bu^{t}Cl	$CuBr_2$	1 : 30	8 (+2% Bu^{t}Br)	120
PhCHBr$_2$	$AgNO_3$	1 : 2	82	48
PhCHCl$_2$	$AlCl_3$	1 : 40	0	120
Bu^{t}Cl	$AlCl_3$	1 : 40	0	48
Bu^{t}Cl	$HgCl_2$	1 : 20	96	120
Bu^{t}Cl	HgI_2	1 : 20	3	120

TABLE 3

Alkyl iodides from alkyl halides and various iodides catalysed by zinc chloride in carbon disulphide at 20 °C

Halide	Iodide	Catalyst : Halide (mol)	Iodide yield (%)	Time (h)
Bu^{t}Cl	NaI	1 : 3	98	24
	LiI,H$_2$O	1 : 3	70	72
	ZnI$_2$	1 : 2	32	72
	(Bu$_4$N)I	1 : 3	0	96
Me$_2$C(Cl)Et	NaI	1 : 5	96	100
Me$_2$C·CH·CH$_3$Cl	NaI	1 : 5	97	2.5
Me$_2$CH·[CH$_2$]$_3$·CClMeEt	NaI	1 : 5	92	96
Me$_2$CCl·CH:CH$_2$	NaI	1 : 5	98 [of iodide (5)]	2
1-Chloroadamantane	NaI	1 : 2	>90	72

temperatures and times of reactions. Product yields were easily shown by n.m.r. since the shifts for t-butyl chloride and iodide (τ 8.41 and 8.05 in CS$_2$, respectively) are well

[14] J. W. McKinley, R. E. Pincock, and W. B. Scott, *J. Amer. Chem. Soc.*, 1973, **95**, 2030.

[15] K. S. Bhandari and R. E. Pincock, *Synthesis*, 1974, 655.

[16] P. Kovacic and N. O. Brace, *J. Amer. Chem. Soc.*, 1954, **76**, 5491.

separated. Two of the experiments in Table 2 were run with benzylidene halides, which give well separated benzylic proton signals. During the reaction of benzylidene bromide (τ 3.36) catalysed by silver nitrate, a signal at τ 3.44 appeared and then disappeared; this was presumably due to α-bromo-α-iodotoluene. [A similar intermediate signal was observed in the conversion of benzylidene chloride into benzylidene iodide with iron(III) chloride as catalyst.]

With iron(II) chloride as catalyst, further experiments were run in which the sodium iodide was replaced by iodine (0.02 mol), but this had no effect on the lack of reaction of t-butyl chloride. Similarly, further addition of aluminium trichloride (0.0005 mol) had no effect on the system.

Effect of Solvent on the Exchange Reaction.—The exchange of t-butyl chloride (0.01 mol) with sodium iodide (0.02 mol) and iron(III) chloride (0.1 g, 0.0062 mol) did not proceed (within the limits of detection by n.m.r.) in the following solvents (10 ml) over 48 h at room temperature: methanol, hexadeuterioacetone, bis-(2-methoxyethyl) ether, and dimethylformamide.

Carbon tetrachloride. The standard reaction (conditions as above) yielded t-butyl iodide in 80% yield after 20 h, and after 120 h the mixture contained no unchanged t-butyl chloride.

Benzene. The standard reaction yielded t-butyl iodide (93—97%) after 6 h at room temperature, together with small amounts of t-butylated benzenes (1—3%).

Alkyl Iodides from Alkyl Chlorides by Use of Zinc Chloride as Catalyst.—The alkyl chloride (0.01 mol) was dissolved in carbon disulphide (10 ml), and a source of iodide ion (0.02 mol) and zinc chloride (anhydrous powder; 0.45 g, 0.0033 mol) were added. The mixture was stirred at room temperature for the times shown in Table 3, and the iodide yields were estimated by n.m.r. Provided that the light-sensitive iodides were shielded from the light, the mixture remained clear and colourless, and the inorganic phase granular. The iodides were isolated by filtering off the inorganic material, and removing the carbon disulphide in a stream of nitrogen, and their identity was confirmed by comparison of spectra (i.r.; n.m.r.) of the distilled products with those of authentic material, prepared by standard routes. The allylic halides (4) and (6) gave the same primary iodide (5).

In the case of 1-iodoadamantane, the reaction went to >90% completion (integration of τ 7.35 absorption [17]), and the iodide was separated from the chloride by extraction of the latter from the crude solid product with cold methanol. The iodide (64%) was recrystallized from slightly aqueous methanol; m.p. 72—74 °C (lit.,[18] 74—76°).

For each of the reactions shown in Table 3, control experiments were run in which no zinc chloride was present. Apart from the reactions with allylic halides (2% reaction

in the absence of catalyst), there was no evidence of a non-catalysed exchange within the times shown.

Reactions of α-Chlorocumene (1).[19]—(a) *With sodium iodide in the presence of iron(III) chloride.* α-Chlorocumene (1.55 g, 0.01 mol) was dissolved in carbon disulphide (10 ml), and sodium iodide (3.0 g, 0.02 mol) and anhydrous iron(III) chloride (0.1 g, 0.000 62 mol) were added. The mixture was stirred for 10 h, during which time hydrogen chloride was steadily evolved. N.m.r. showed gradual loss of the signal due to the methyl groups of α-chlorocumene (τ 8.1) accompanied by the growth of singlet absorptions at τ 7.71, 8.35, 8.67, and 9.0. Of these, the first diminished as the reaction time increased, revealing an AB quartet at τ 7.53 and 7.87 (J 13.7 Hz), as well as the remaining singlets. These signals were assigned to the indane (2) after experiment (b) had been carried out. The intermediate signal was probably due to α-iodocumene (3).

(b) *With iron(III) chloride only.* The procedure was as in (a), except that sodium iodide was omitted. After the mixture had been stirred for 15 min, n.m.r. indicated complete loss of the chloride (1), and the peaks described in (a) were again observed, except that the τ 7.71 absorption did not appear. The mixture was filtered, and the filtrate evaporated. Distillation of the residue yielded pure 1,1,3-trimethyl-3-phenylindane (2) as an oil (85%), b.p. 175—177 °C at 19 mmHg (lit.,[3d] 168—170 °C at 18 mmHg), m.p. 53—54 °C (lit.,[3a] 52—53 °C); τ 2.35—3.25 (9 H, m), 7.53 and 7.87 (each 1 H, d), 8.32 (3 H, s), 8.65 (3 H, s), and 8.98 (3 H, s); $\nu_{max.}$ 2 900, 1 440, 1 024, 756, and 698 cm^{-1}.

Exchange of Chloride with Anions Other than Iodide.—(a) *With sodium cyanide.* When t-butyl chloride (0.01 mol) was stirred with a mixture of sodium cyanide (1.0 g, 0.02 mol) and anhydrous iron(III) chloride (0.1 g, 0.000 62 mol) in carbon disulphide, no reaction was observed after 1 week at room temperature. A similar observation was made with benzylidene chloride instead of t-butyl chloride.

(b) *With sodium bromide.* t-Butyl chloride (0.01 mol) was stirred at room temperature with a mixture of sodium bromide (2.08 g, 0.02 mol) and iron(III) chloride (0.1 g, 0.000 62 mol) or zinc chloride (0.54 g, 0.005 mol) in carbon disulphide for 1 week. In each system the reaction slowly came to an equilibrium mixture of t-butyl chloride and t-butyl bromide. With iron(III) chloride the conversion was 70%, whereas with zinc chloride the conversion was 68% at the end of this period.

[17] R. C. Fort and P. von R. Schleyer, *J. Org. Chem.*, 1965, **30**, 789.

[18] D. N. Kevill and F. Weitl, *J. Org. Chem.*, 1970, **35**, 2526.

[19] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, 1957, **79**, 1905.