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THE INTERCONVERSION OF PRIMARY ALKYL HALIDES

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Summary: Using tetra-alkylammonium halides dissolved in alkyl halides as reagents a variety of halogen exchange reactions can be carried out conveniently in high yield. In particular, it becomes practicable to use $-CH_2Cl$ as a protected equivalent of $-CH_2Br$.

In work on the synthesis of aliphatic compounds of very long chain-length[1,2] two antithetical problems arose. The first was the undesired conversion of primary bromides to chlorides; as these are some 250 times less reactive to triphenylphosphine,[3] yields in the next step of the synthesis[1] were reduced. Formation of chlorides could be monitored by g.l.c. with C_{12} or C_{24} intermediates, or by the appearance of a triplet at $\delta 3.53$ near the $-CH_2CH_2Br$ triplet at $\delta 3.40$. It emerged that (a) the source of Cl^- was the (carefully purified) dichloromethane; (b) the reaction was promoted by traces of phase-transfer catalysts such as the alkyltriphenylphosphonium salts used in the synthesis,[1] which are hard to remove completely from glassware; and (c) this catalysis was inhibited by hydroxylic species.[4] It then became possible to avoid these unwanted reactions.

If, however, the $RCH_2Cl \rightleftarrows RCH_2Br$ conversion could be effected in high yield in either direction the $-CH_2Cl$ group would become, effectively, a protected equivalent of $-CH_2Br$. For example, in Wittig reactions between ω-bromoaldehydes and ω-2-dioxalenylalkyltriphenylphosphonium salts[1] using the excellent method of R.M. Boden[5] yield was reduced by attack by K_2CO_3 and 18-crown-6 on $-CH_2Br$, but the chloro-analogue, unintentionally introduced, underwent the desired condensation with negligible displacement of halogen. The advantages of this strategy have been reviewed by Willy *et al.*,[6] who have published much the best procedure so far, involving alkali metal halides, N-methylpyrrolidone as solvent, and an excess (20-100 mol) of an ethyl or 2-propyl halide as regenerating agent for the nucleophile. For 1-bromo-octane → 1-chloro-octane they obtained a 91% yield in 32 days, and (sodium bromide being more soluble than the chloride) an excellent yield in the reverse direction after 3 days. However, even the latter reaction time is inconveniently long. It seemed that use of tetra-alkylammonium salts would allow more rapid reactions and a wider range of solvents. Parker has shown[7] that with tetra-ethylammonium counter-ions the displacement of Br^- by Cl^- is *ca.* 150 times faster than the reverse reaction; use of 1,2-dichloroethane, more reactive than dichloromethane, as solvent should approximately equalise the rates of the two stages of the redistribution reaction, the low bimolecular rate-constant for $Br^- + RCH_2Cl \rightarrow Cl^- + RCH_2Br$ being counterbalanced by the high concentration of $-CH_2Cl$. Indeed, even with only 0.1 mol of halide ion as turntable (we used tetrabutylammonium bromide) alkyl bromides were converted to chlorides in >99% yield in 4h at the boiling point. In the converse process, however, the two factors reinforce each other, so that although regeneration of Br^- by the solvent is very rapid, the displacement of Cl^- by the bromide ion initially present is slow. Again, however, the use of tetrabutylammonium bromide (2 mol) in refluxing 1-bromopropane (30 mol) led to an improvement, modest this time; after 24h reaction was incomplete, but after 42h conversion was 97.5%, near to the calculated equilibrium ratio.

1-Bromobutane led to a faster reaction and slight darkening, but with bromoethane several days would be needed. Addition of N-methylpyrrolidone (1 vol to 2 vol of 1-bromopropane) did not increase the reaction-rate significantly. In this mixture the use of sodium bromide, less soluble than in the 4:3 ratio used earlier,[6] led to a very slow exchange. Normal drying of solvents and reaction under reflux maintained adequately dry conditions, no improvement being observed when exceptional care was employed. Attainment of extremely high ratios $[R.CH_2Br]:[R.CH_2Cl]$ naturally requires either the displacement of the equilibrium by volatilising, e.g. chloroethane (which we did not effect) or the use of a large excess of e.g. bromoethane as solvent.

Iodides are occasionally needed in synthesis, especially as precursors to radicals, although more often the formation of molecular iodine by oxidation or photolysis leads to unwanted side-reactions, e.g. olefine stereomutation and double-bond shift.[8] The conversion of primary chlorides and bromides to iodides using sodium iodide in acetone, a method based on ion-pairing interactions and solubility factors, is well known, but the reverse processes are not.[6] Using tetra-alkylammonium counter-ions, the work of Parker[4] indicates equilibrium constants favouring this change of _ca._ 10^4 and 10^2, respectively. Indeed, tetrabutylammonium chloride (1.2 mol) in 1,2-dichloroethane and the corresponding bromide (2 mol) in 1-bromopropane converted 1-iodododecane to the lower halides in >99% yield in 1h in each case.

Typical Procedure for Preparation of 12-Chlorododecanal Ethylene Acetal

A mixture of 12-bromododecanal ethylene acetal[2] (25 g), tetrabutylammonium bromide (2.63 g), 2,2-dimethyl-1,3-dioxalane (0.83 g), and 1,2-dichloroethane (dried, redistilled and stored over molecular sieve, 650 ml) was heated under reflux for 20h. The solvent was removed under reduced pressure, light petroleum (b.p. 30-40°; 200 ml) was added, and the solution was washed with water (4 x 50 ml), dried and evaporated, giving the chloro-acetal (21.0 g, 98%), m.p. 22-23° (Found: C, 63.9; H, 10.45; Cl, 13.6. $C_{14}H_{27}ClO_2$ requires C, 64.0; H, 10.35; Cl, 13.5%). By g.l.c. analysis the purity was 98.8%, identified contaminants being the starting material (0.7%) and 12-chlorododecanol (0.3%), formed from the corresponding bromine compound present in the starting acetal. Omission of the dimethyldioxalane led to appreciable deprotection of the acetal. The halogen exchange reaction reaches equilibrium in _ca._ 4h, according to g.l.c.

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