

## Factors in the Formation of Isomerically and Optically Pure Alkyl Halides. Part XI.<sup>1</sup> Vilsmeier Reagents for the Replacement of a Hydroxy-group by Chlorine or Bromine

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Vilsmeier reagents,  $[\text{Me}_2\text{NCHX}]^+ \text{X}^-$  ( $\text{X} = \text{Cl}$  or  $\text{Br}$ ), interact with alcohols to give good yields of the corresponding alkyl halides. Isolation of the product is facilitated by the use of water-soluble solvents. Little or no rearrangement of the alkyl group occurs, except in the case of a branched-chain secondary alcohol, e.g. 3-methylbutan-2-ol. In dioxan or acetonitrile, (+)-octan-2-ol yields the optically pure chloride with inversion of configuration, although some racemisation occurs in dimethylformamide. 2-Bromo-octane is obtained with no detectable rearrangement and with an optical purity of ca. 75% by reaction in dioxan.

VILSMEIER-HAACK reagents,  $[\text{Me}_2\text{N}^+\text{CHX}] \text{Y}^-$  ( $\text{X} =$  halogen;  $\text{Y} = \text{X}, \text{SO}_2\text{X}, \text{PO}_2\text{X}_2$ , etc.) are obtained by the interaction of dimethylformamide with one of a number of inorganic halides, and have long been used for formylation.<sup>2</sup> A recent application has been for the introduction of alkyl groups, *via* the iminium or the formyl derivative.<sup>3</sup> Chloromethylenedimethylammonium chloride ( $\text{X} = \text{Y} = \text{Cl}$ ) has also been shown to replace the hydroxy-groups of acids<sup>4</sup> and of alcohols<sup>5</sup> by chlorine, but the reaction has received only limited application<sup>6</sup> and has not been developed as a method for alkyl halide preparation.

We now report the reactions of the Vilsmeier reagents ( $\text{X} = \text{Cl}$  or  $\text{Br}$ ) with a range of saturated alcohols, branched at the 1-, 2-, or 3-position; we have found the method<sup>7</sup> to be in many ways superior to other halogeno-dehydroxylation procedures. High yields of alkyl halides can be obtained and the complication of carbocation rearrangement is in most cases avoided (Tables 1 and 2). By use of water-soluble solvents such as dioxan, acetonitrile, dimethylformamide (DMF), and hexamethylphosphoric triamide (HMPT), the final isolation of the product is particularly easy.

The chloro-reagent was most conveniently made by

<sup>1</sup> Part X, H. R. Hudson and G. R. de Spinoza, *J.C.S. Perkin I*, 1976, 104.

<sup>2</sup> G. Hazebrucq, *Ann. pharm. franç.*, 1966, **24**, 793.

<sup>3</sup> D. Burn, *Chem. and Ind.*, 1973, 870.

<sup>4</sup> H. H. Bosshard, R. Mory, M. Schmid, and Hch. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653.

<sup>5</sup> H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, 1960, **72**, 836; *Chem. Ber.*, 1963, **96**, 2671.

addition of phosphorus pentachloride to DMF, although other procedures can be used.<sup>4</sup> The bromo-reagent was prepared by treatment of the chloro-analogue with an excess of hydrogen bromide,<sup>8</sup> or better by the reaction of triphenylphosphine with bromine and DMF. Both reagents gave isomerically pure alkyl halides (>99.9%) from all types of primary alcohol, including 2,2-dimethylpropan-1-ol, although in the case of this sterically hindered alcohol prolonged heating under reflux was necessary for the reaction to proceed to completion. Other types of alcohol gave good yields of product after a short period of heating at 50–100 °C. Straight-chain secondary alcohols, which give mixtures of isomers by many standard procedures,<sup>9</sup> were converted into the corresponding chlorides with no detectable rearrangement and into the bromides with <1% rearrangement. Rearrangement in the latter case might be due to some addition between hydrogen bromide and the olefinic by-products, a reaction shown to occur under the conditions used. By addition of pyridine to the reaction mixture, the extent of rearrangement in the preparation of 3-bromopentane was reduced to 0.1%, although the yield of product thus obtained was poorer. The branched-chain secondary alcohol, 3-methylbutan-2-ol, is known to

<sup>6</sup> S. Hanessian and N. R. Plessas, *Chem. Comm.*, 1967, **22**, 1152; R. F. Dods and J. S. Roth, *Tetrahedron Letters*, 1969, 165; G. Ferre and A. L. Palomo, *Anales de Quim.*, 1969, **55**, 163.

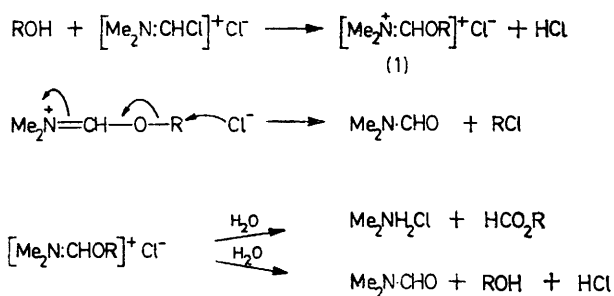
<sup>7</sup> D. R. Hepburn and H. R. Hudson, *Chem. and Ind.*, 1974, 664.

<sup>8</sup> Z. Arnold and A. Holy, *Coll. Czech. Chem. Comm.*, 1961, **26**, 3059.

<sup>9</sup> W. Gerrard and H. R. Hudson, *Chem. Rev.*, 1965, **65**, 697

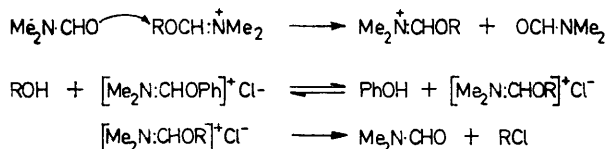
be difficult to convert into the corresponding halides without formation of the *t*-pentyl isomers.<sup>10</sup> Although use of the chloro-reagent gave varying degrees of rearrangement with this alcohol in all the solvents used, it was possible to obtain a product of over 99% purity in 41% yield by reaction in HMPT. Conversion into the bromide was less successful, the best product (97.7% pure) being obtained in only 19% yield. Cyclohexanol gave mainly cyclohexene.

Alkyl halide formation occurs *via* an alkoxymethylene-ammonium intermediate (1), which yields the corresponding alkyl formate together with some alcohol, if the reaction mixture is treated with water before alkyl halide formation is complete (Scheme 1). The intermediate can be isolated if R = phenyl. The initial formation of the intermediate (1) was shown to be rapid, the i.r. OH band of the alcohol disappearing immediately



SCHEME 1

the reagents were mixed. Rate-determining dealkylation then occurs by what appears to be  $\text{S}_{\text{N}}2$  attack of halide ion, except perhaps in the case of branched-chain secondary alcohols such as 3-methylbutan-2-ol and tertiary alcohols for which a carbocation mechanism is more likely. Thus, 2,2-dimethylpropan-1-ol gave the corresponding halides without rearrangement, whilst (+)-octan-2-ol gave 2-chloro-octane with 99–100% net inversion<sup>11</sup> if the reaction was carried out in dioxan or acetonitrile. Some loss of optical purity occurred in DMF, although no rearrangement was observed, and it was shown that the product itself underwent gradual racemisation under reaction conditions in this solvent. It is also possible that the intermediate (1) might racemise by interaction with DMF:



(+)-2-Bromo-octane was obtained without rearrangement but with some loss of optical purity in dioxan.

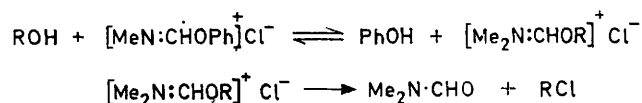
The stable solid intermediate (1; R = Ph) which is

<sup>10</sup> R. A. Arain and M. K. Hargreaves, *J. Chem. Soc. (C)*, 1970, 67.

<sup>11</sup> H. R. Hudson, *Synthesis*, 1969, 1, 112; H. M. R. Hoffmann, *J. Chem. Soc.*, 1964, 1249.

<sup>12</sup> A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' Longmans, London, 1956, 3rd edn., p. 177.

obtained from phenol can also be used for the replacement of a hydroxy-group by halogen, since exchange with an alcohol occurs readily (Scheme 2). This method could



SCHEME 2

be of use in systems in which it is important that free hydrogen halide should not be present, although phenol is thereby introduced and might complicate the work-up procedure.

#### EXPERIMENTAL

*Starting Materials.*—Alcohols were obtained commercially, dried (BaO), redistilled, and checked for purity by g.l.c. on polyethylene glycol 400. Dioxan was purified as described<sup>12</sup> and other solvents were purified by distillation.

*Analytical Methods.*—Alkyl halides were identified by b.p., refractive index, halogen analysis, and g.l.c.,<sup>13</sup> by which 0.1% or less of isomeric impurities could be detected. Optically active products were purified by preparative g.l.c. on polyethylene glycol 400.<sup>14</sup> Optical rotations were measured for samples in thermostatted cells with a Perkin-Elmer 141 photoelectric polarimeter. Neopentyl formate was identified by g.l.c. on the silicone oil column used for alkyl halide analysis<sup>13</sup> and by <sup>1</sup>H n.m.r. [ $\tau$  9.04 (Me<sub>3</sub>C, s), 6.15 (CH<sub>2</sub>, s), and 1.91 (CHO, s)].

*Chloromethylenedimethylammonium Chloride.*—Phosphorus pentachloride (50.0 g, 0.24 mol) was added in small portions and with thorough mixing (30 min) to DMF (140.0 g, 1.92 mol) in a flask fitted with a reflux condenser, the temperature being allowed to rise to 120 °C. After a further 15 min the mixture was cooled to 0 °C and filtered in the absence of moisture to yield white crystals, which were washed successively with DMF (25 cm<sup>3</sup>) and anhydrous ether (3 × 50 cm<sup>3</sup>) to give chloromethylenedimethylammonium chloride (27.0 g, 88%) (Found: C, 28.4; H, 5.9; Cl, 55.0; N, 10.0. Calc. for C<sub>3</sub>H<sub>7</sub>Cl<sub>2</sub>N: C, 28.1; H, 5.5; Cl, 55.5; N, 10.9%), m.p. (sealed tube) 136–138 °C (decomp.).

*Bromomethylenedimethylammonium Bromide.*—(a) *From hydrogen bromide and the chloro-reagent.* Anhydrous hydrogen bromide was passed in excess (20 min) through a sintered-glass bubbler immersed in a solution of chloromethylenedimethylammonium chloride (27.0 g, 0.21 mol) in dry chloroform (96 cm<sup>3</sup>), at 0 °C. The mixture was then allowed to warm to room temperature and was evaporated almost to dryness at 15 mmHg. The residue was dissolved in chloroform (100 cm<sup>3</sup>) and then anhydrous ether was added in excess to cause precipitation of bromomethylenedimethylammonium bromide (41.4 g, 90%) (Found: C, 17.4; H, 4.0; Br, 71.7; N, 6.5. Calc. for C<sub>3</sub>H<sub>7</sub>Br<sub>2</sub>N: C, 16.6; H, 3.2; Br, 73.7; N, 6.5%), m.p. (sealed tube) 149–151 °C (decomp.).

(b) *From triphenylphosphine and bromine.* Bromine (6.4 g, 0.04 mol) was added dropwise (5 min) to a solution of triphenylphosphine (10.5 g, 0.04 mol) in DMF (36.0 g, 0.49 mol), in a flask fitted with a reflux condenser. The temperature was allowed to rise to 60 °C. After cooling of the

<sup>13</sup> D. R. Hepburn and H. R. Hudson, *J. Chromatog.*, 1975, 103, 166.

<sup>14</sup> H. R. Hudson, A. R. Qureshi, and D. Ragoonanan, *J.C.S. Perkin I*, 1972, 1595.

product to 0 °C, filtration in the absence of moisture yielded crystals which were washed successively with DMF (10 cm<sup>3</sup>) and anhydrous ether (2 × 20 cm<sup>3</sup>) to give pale yellow bromomethylenedimethylammonium bromide (6.2 g, 71%) (Found: C, 16.9; H, 3.4; Br, 72.9; N, 6.9%), m.p. 151—152 °C (decomp.).

*Reactions of Alcohols with Halogenomethylenedimethylammonium Halides.*—The alcohol was added dropwise with

ammonium chloride (4.8 g, 0.037 mol), and DMF (16.2 g). After 4 h (100 °C) the products were isolated and separated by preparative g.l.c. to give 2-chloro-octane (0.9 g),  $\alpha_D^{20} -3.14^\circ$  (l 1).

*Reaction of Chloromethylenedimethylammonium Chloride with Phenol.*—The chloride (4.6 g, 0.036 mol) was suspended in anhydrous ether (30 cm<sup>3</sup>) and phenol (3.2 g, 0.034 mol) was added. After the mixture had been heated under

TABLE 1  
Reactions of alcohols with chloromethylenedimethylammonium chloride

| ROH   |                  | Me <sub>2</sub> NCHCl <sub>2</sub><br>(mol. equiv.) | Solvent |      | Temp.<br>(°C) | Time<br>(h) | Yield of RCl<br>(mol. equiv.) <sup>a</sup> | Rearrangement<br>(%) |
|---|------------------|---|---------|------|---------------|-------------|--|----------------------|
| R   | g                |   |         | g    |               |             |  |                      |
| Me[CH <sub>2</sub> ] <sub>3</sub> ·CH <sub>2</sub>    | 4.0              | 1.4   | Dioxan  | 26.5 | 100           | 1           | 0.77                                       | 0                    |
| Me[CH <sub>2</sub> ] <sub>3</sub> ·CH <sub>2</sub>    | 3.8              | 1.2   | MeCN    | 21.8 | 80            | 1           | 0.89                                       | 0                    |
| Me <sub>3</sub> CH·CH <sub>2</sub> ·CH <sub>2</sub>   | 6.3              | 1.2   | Dioxan  | 35.6 | 100           | 1           | 0.78                                       | 0                    |
| EtMeCH·CH <sub>2</sub>                                | 3.8              | 1.4   | Dioxan  | 25.1 | 100           | 1           | 0.74                                       | 0                    |
| Me <sub>3</sub> C·CH <sub>2</sub>                     | 4.7              | 1.2   | Dioxan  | 26.8 | 100           | 12          | 0.72 <sup>b</sup>                          | 0                    |
| Me <sub>3</sub> C·CH <sub>2</sub>                     | 7.2              | 1.2   | DMF     | 40.0 | 150           | 6           | 0.73                                       | 0                    |
| cyclo-C <sub>6</sub> H <sub>11</sub> ·CH <sub>2</sub> | 6.5              | 1.1   | Dioxan  | 28.4 | 100           | 1.5         | 0.85                                       | 0                    |
| Pr <sup>n</sup> MeCH                                  | 9.1              | 1.2   | Dioxan  | 51.5 | 100           | 0.5         | 0.82                                       | 0                    |
| Pr <sup>n</sup> MeCH                                  | 3.8              | 1.2   | MeCN    | 21.4 | 80            | 1           | 0.85                                       | 0                    |
| Pr <sup>n</sup> MeCH                                  | 4.4              | 1.1   | HMPT    | 20.0 | 75            | 0.75        | 0.71                                       | 0                    |
| Et <sub>2</sub> CH                                    | 7.9              | 1.2   | Dioxan  | 44.6 | 100           | 0.5         | 0.76                                       | 0                    |
| Et <sub>2</sub> CH                                    | 4.4              | 1.2   | HMPT    | 20.0 | 75            | 0.75        | 0.65                                       | 0                    |
| n-C <sub>8</sub> H <sub>17</sub> MeCH                 | 7.1 <sup>c</sup> | 1.2   | Dioxan  | 27.4 | 100           | 3           | 0.88 <sup>d</sup>                          | 0                    |
| n-C <sub>8</sub> H <sub>17</sub> MeCH                 | 4.8 <sup>e</sup> | 1.2   | MeCN    | 18.3 | 80            | 3           | 0.84 <sup>e</sup>                          | 0                    |
| n-C <sub>8</sub> H <sub>17</sub> MeCH                 | 4.9 <sup>c</sup> | 1.2   | DMF     | 18.8 | 100           | 3           | 0.70 <sup>f</sup>                          | 0                    |
| Pr <sup>i</sup> MeCH                                  | 3.2              | 1.2   | Dioxan  | 18.7 | 100           | 1           | 0.51 <sup>g</sup>                          | 54 <sup>h</sup>      |
| Pr <sup>i</sup> MeCH                                  | 5.7              | 1.2   | Dioxan  | 34.2 | 100           | 1           | 0.46 <sup>g</sup>                          | 39 <sup>h</sup>      |
| Pr <sup>i</sup> MeCH                                  | 4.8              | 1.2   | MeCN    | 21.2 | 80            | 1           | 0.34 <sup>g</sup>                          | 68 <sup>h</sup>      |
| Pr <sup>i</sup> MeCH                                  | 1.9              | 1.2   | DMF     | 10.4 | 100           | 1           | 0.56 <sup>g</sup>                          | 41 <sup>h</sup>      |
| Pr <sup>i</sup> MeCH                                  | 11.1             | 1.2   | HMPT    | 50.0 | 75            | 1           | 0.41 <sup>i</sup>                          | 0.3 <sup>h</sup>     |
| cyclo-C <sub>6</sub> H <sub>11</sub>                  | 6.2              | 1.0   | Dioxan  | 30.9 | 20            | 1           | 0.005 <sup>j</sup>                         |                      |
| EtMe <sub>2</sub> C                                   | 5.3              | 1.2   | Dioxan  | 29.8 | 100           | 0.25        | 0.53                                       | 0                    |

<sup>a</sup> Distilled product unless otherwise stated. <sup>b</sup> Reaction at 80 °C (1 h) gave RO·CHO (0.58 mol. equiv.) and ROH (0.23 mol. equiv.) (g.l.c.), after addition of water. <sup>c</sup>  $\alpha_D^{20} +2.71^\circ$  (l 1). <sup>d</sup>  $\alpha_D^{20} -10.53^\circ$  (l 1) after preparative g.l.c. (98.6% optical purity). <sup>e</sup>  $\alpha_D^{20} -10.64^\circ$  (l 1) after preparative g.l.c. (99.6% optical purity). <sup>f</sup>  $\alpha_D^{20} -8.60^\circ$  (l 1) after preparative g.l.c. (80.5% optical purity). <sup>g</sup> By analysis. <sup>h</sup> EtMe<sub>2</sub>CBr. <sup>i</sup> 2-Methylbut-2-ene (0.21 mol. equiv.) obtained. <sup>j</sup> Cyclohexene (0.70 mol. equiv.) obtained.

TABLE 2  
Reactions of alcohols with bromomethylenedimethylammonium bromide.

| ROH   |                  | Me <sub>2</sub> NCHBr <sub>2</sub><br>(mol. equiv.) | Solvent |      | Temp.<br>(°C) | Time<br>(h) | Yield<br>(mol. equiv.) <sup>a</sup> | Rearrangement<br>(%) |
|---|------------------|---|---------|------|---------------|-------------|-------------------------------------|----------------------|
| R   | g                |   |         | g    |               |             |                                     |                      |
| Me[CH <sub>2</sub> ] <sub>3</sub> ·CH <sub>2</sub>    | 2.5              | 1.0   | Dioxan  | 13.9 | 100           | 0.25        | 0.89 <sup>b</sup>                   | 0                    |
| Me <sub>3</sub> C·CH <sub>2</sub>                     | 10.7             | 1.1   | DMF     | 42.6 | 150           | 2           | 0.73                                | 0                    |
| cyclo-C <sub>6</sub> H <sub>11</sub> ·CH <sub>2</sub> | 4.8              | 1.1   |         | 21.2 | 100           | 0.25        | 0.82                                | 0                    |
| Pr <sup>n</sup> MeCH                                  | 1.7              | 1.5   |         | 21.3 | 100           | 1           | 0.83                                | 0.8 <sup>c</sup>     |
| Et <sub>2</sub> CH                                    | 2.7              | 1.5   |         | 33.1 | 100           | 1           | 0.82                                | 0.7 <sup>d</sup>     |
| Et <sub>2</sub> CH                                    | 2.7              | 1.1   |         | 17.0 | 20            | 24          | 0.16                                | 0.7 <sup>d</sup>     |
| Et <sub>2</sub> CH                                    | 4.8              | 1.0 <sup>e</sup>                                    | Dioxan  | 27.3 | 100           | 0.5         | 0.46                                | 0.1 <sup>d</sup>     |
| n-C <sub>8</sub> H <sub>17</sub> MeCH                 | 4.3              | 1.2   |         | 16.7 | 100           | 4           | 0.72                                | 0                    |
| n-C <sub>8</sub> H <sub>17</sub> MeCH                 | 6.1 <sup>f</sup> | 1.0   |         | 23.2 | 100           | 0.25        | 0.85 <sup>g</sup>                   | 0                    |
| Pr <sup>i</sup> MeCH                                  | 2.4              | 1.5   |         | 30.0 | 100           | 1           | 0.43                                | 26.0 <sup>h</sup>    |
| Pr <sup>i</sup> MeCH                                  | 6.6              | 1.5   | HMPT    | 53.0 | 100           | 1           | 0.13                                | 1.2 <sup>h</sup>     |

<sup>a</sup> Distilled product unless otherwise stated. <sup>b</sup> By g.l.c. analysis. 2-Methylbut-2-ene (1 g) added to reactants yielded EtMe<sub>2</sub>CBr (1.1 g). <sup>c</sup> Et<sub>2</sub>CHBr. In a similar experiment the product composition remained constant during heating for 360 h. <sup>d</sup> Pr<sup>n</sup>MeCHBr. <sup>e</sup> Pyridine (1.0 mol. equiv.) added before the alcohol. <sup>f</sup>  $\alpha_D^{20} -7.27^\circ$  (l 1). <sup>g</sup>  $\alpha_D^{20} +30.81^\circ$  (l 1) after preparative g.l.c. (76.3% optical purity). <sup>h</sup> EtMe<sub>2</sub>CBr.

stirring to a suspension of the halide in the specified solvent at 0 °C. The resultant solution was then allowed to reach room temperature and was heated under reflux for the stated time (Tables 1 and 2). An excess of water was then added and the oil layer was separated, washed with water, dried (K<sub>2</sub>CO<sub>3</sub>), distilled, and analysed as described above.

*Racemisation of (—)-2-Chloro-octane under Reaction Conditions in DMF.*—2-Chloro-octane (2.0 g),  $\alpha_D^{20} -10.64^\circ$  (l 1) was added to a reaction mixture prepared as above from propan-2-ol (1.9 g, 0.032 mol), chloromethylenedimethyl-

reflux on a steam-bath (30 min) the ether layer was decanted and the residue was washed with more anhydrous ether (2 × 10 cm<sup>3</sup>). The product was dried at 0.1 mmHg to yield dimethyl(phenoxymethylene)ammonium chloride (6.2 g, 98%) (Found: C, 56.7; H, 6.5; Cl, 21.4; N, 6.8. C<sub>9</sub>H<sub>12</sub>ClNO requires C, 57.8; H, 6.4; Cl, 19.5; N, 7.5%),  $\tau$  0.3 (1 H, s, CHO), 2.55 (5 H, m, Ph), and 6.5 (6 H, d, Me<sub>2</sub>N).

*Reactions of Dimethyl(phenoxymethylene)ammonium Chloride with Alcohols.*—(a) Pentan-2-ol. The chloride (8.7 g, 0.047 mol), prepared as above, was dissolved in DMF (20 g),

and pentan-2-ol (3.5 g, 0.040 mol) was added at 0 °C. Samples (2 cm<sup>3</sup>) were placed in sealed tubes. After the given periods (*t*) at 60 °C the yields of 2-chloropentane, by analysis, were (*t*/min, %): 60, 49; 90, 55; 300, 81. No rearrangement was detectable.

(b) *3-Methylbutan-2-ol*. The alcohol (3.6 g, 0.041 mol) was added to the chloride (8.8 g, 0.047 mol) in DMF (20 g) and the mixture was heated under reflux (100 °C) for 1 h. Isolation of the product as above, including a wash with

aqueous NaOH to remove phenol, yielded chloropentanes (1.33 g, 31%), b.p. 86—91°, containing 2-chloro-3-methylbutane (70%) and 2-chloro-2-methylbutane (30%).

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