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A CONVENIENT AND PRACTICAL METHOD FOR CONVERSION OF PRIMARY ALKYL CHLORIDES TO HIGHLY PURE BROMIDES (≥99%)

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ABSTRACT: Repeated treatment (second after the aqueous work-up) of primary alkyl chlorides with ten equivalents (each) of lithium bromide in 3-pentanone at 120 °C for a total of five hours gave the corresponding bromides in excellent yield (86-96%) and with high chemical purity (≥99%).

Alkyl bromides are prepared not only for study of their chemical properties but also for their use as synthetic intermediates, such as in the preparation of organometallic halide complexes.[1] Moreover, due to their biological implications,[2,3] the synthesis of alkyl halides with high chemical purity has drawn attention from chemists during the recent years.

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During the course of synthesis of compounds aimed at specific biological properties, we needed a method that could convert alkyl chlorides to alkyl bromides with high chemical purity (≥99%). A series of available reports indicated methods for the preparation of alkyl halides (RX, X = Cl, Br, I).[1-15] A number of methods have also been developed for the conversion of alkyl chlorides to the corresponding bromides[1,6-16] either in homogeneous solutions under S_N1 conditions,[1,6,8,12] or in two phase systems under classical phase transfer catalysis conditions[7,9,10,11,14-16] or by a more specific approach.[13] Most of these reactions,[7-16] however, could not provide the alkyl bromides with high chemical purity. In fact, 3-4% of unreacted alkyl chloride was left and its removal from the mixture was usually cumbersome.

It should be indicated that a few conversions reported to date are efficient. As example, the well known Willy's method[1] utilizes alkali metal halides, N-methylpyrrolidone as solvent, and an excess (20-100 mol) of ethyl or 2-propyl bromide as regenerating agent for the nucleophile, thus yielding about 99% chemically pure bromides although at least 3 days are needed for completion of the reaction. On the other hand, the Babler's procedure[6] uses one equivalent of sodium bromide as the nucleophile in a solvent mixture of N,N-dimethylformamide/dibromomethane (2/1:v/v) for several hours to yield bromide at a 94 to 99% purity. However, not every alkyl chloride can be converted by this method to its corresponding bromide with the purity equal to or above 99%, and it has been reported[6] that there were about 3% of other components present in the product mixture.

It thus clearly appears that there is a need for an improvement of the method(s) for generating alkyl halides. The present study describes an efficient and general method for the conversion of primary alkyl chlorides to primary alkyl bromides with high chemical purity (≥99%).

It is well known that the reaction under study is reversible in nature and that the inverse reaction is much faster than the desired one.[7] The conversion is generally

accomplished by the exchange with a metal salt (M^+Br^-) in a polar homogeneous solution. In the present report, we investigated the following in order to achieve our final aim: first, optimal equilibrium conditions were assessed for the chosen metal bromide and solvent, and, secondly, the removal of the metal chloride formed in the reaction was achieved by easy means in order to shift the equilibrium towards the right in a second step (Eq.). In order to establish optimal equilibrium conditions,

$$RCl + LiBr \rightleftharpoons RBr + LiCl \xrightarrow[\text{(work-up)}]{LiBr} RBr + LiCl \quad (\geq 99\%) \quad \text{(Eq.)}$$

lithium bromide was chosen since it is considered as being the best salt of metal bromides for such transformation[7,9] and 3-pentanone was selected as the solvent since it is a polar, high boiling, non-toxic and easy to manipulate component during the work-up.

The figure shows the percentage of primary alkyl bromide formed with respect to time at various concentrations of LiBr at 120 °C. From the Figure, it is clear that the position of the equilibrium is highly dependent upon the concentration of LiBr and to a lesser extend upon time. For instance, one molar eq. of LiBr gave a 1:4 mixture of RCH_2Br:RCH_2Cl after 5 h, and even after 20 h of reflux, this ratio did not change appreciably. However, when 5 molar eq. of LiBr was used, after 8 h the ratio improved to 3:1 and increased to 7:1 after 20 h of reaction. Nearly 80% of RCH_2Br was obtained after 2 h of reaction, when 10 molar eq. of LiBr was used and a small yield improvement was found after 20 h. Further changes on the reaction conditions failed to improve the results significantly. For instance, the use of a large excess of LiBr (20 molar eq.) pushed the reaction to 96% completion after 20 h of reflux (Figure). Undoubtedly, an equilibrium is rapidly established between RCH_2Cl and RCH_2Br. Due to the greater nucleophilicity of the chloride

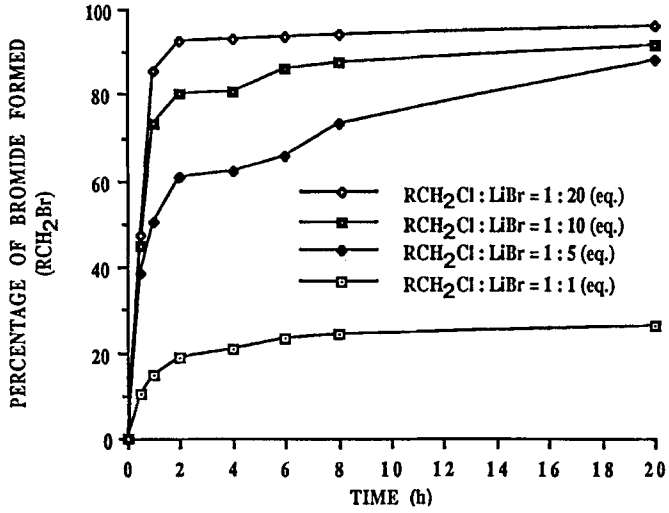

Figure. Plot of the Percentage of Primary Alkyl Bromide Formed Versus Time at the Indicated Concentrations of Lithium Bromide at 120 °C.

The reaction was carried out as described under standard procedure, where RCH_2Cl is 17β-Hydroxy-17α-(5'-chloro-1'-pentynyl)-4-methyl-4-aza-5α-androstan-3-one in each reaction. The percentage of bromide formed was calculated from a ratio of the clear triplet signals of the chloride (5'-CH_2Cl at 3.65 ppm) to that of its bromide (5'-CH_2Br at 3.52 ppm) in the ^{1}H-NMR spectra of the reaction mixture. The chemical shifts between 3.40 and 3.80 ppm were expanded and integrated. The bromide was used after standard work-up and without further purification. A sample of the reaction mixture (1.0 mL of each time interval) was withdrawn via the syringe at reaction time 0.5, 1, 2, 4, 6, 8 and 20 h. Four concentrations (1, 5 10 and 20 molar eq.) were investigated. Lithium bromide (99%$^+$) was purchased from Aldrich Chemical Company, Inc., U. S. A.

ion, a small amount (4%) of RCH_2Cl remained present despite the use of directed conditions. Since a large excess of LiBr did not force the reaction to completion, we decided to use 10 molar eq. of LiBr in the reaction.

The next step was the removal of lithium chloride from the mixture before starting with second treatment of LiBr. Since we did not want to use a cancerogenic reagent as scavenger of LiCl, such as dibromomethane,[1,6] bromoethane and 2-bromopropane,[1] we decided to do quick aqueous work-up to remove LiCl after first

treatment of LiBr. Indeed, first exposure of RCH_2Cl to 10 molar eq. of LiBr for 2 h at 120 °C and removal of LiCl by aqueous work-up gave nearly 80% of RCH_2Br. Second treatment with another 10 molar eq. of LiBr for 3 h at 120 °C led to a chemically pure alkyl bromide (≥99%, HPLC) product. The whole process was complete within 5 h. All the chlorides tested gave chemically pure products. This approach is safe for other functional groups that are present, such as primary, secondary and tertiary hydroxyl groups, cyano groups, as well as ketals and amides (Table).

TABLE

Conversion of Primary Alkyl Chlorides into the Corresponding Bromides[a]

Starting Alkyl chloride	Alkyl Bromide product	
	Conversion[b] (%)	Yield[c] (%)
4-chlorobutyronitrile	99.4	88
10-chloro-1-decanol	99.1	96
5-chloro-2-pentanone ethylene ketal	99.4	86
3-chloropropionamide	99.7	91
17α-(5'-chloro-1'-pentynyl)-1,3,5(10)-estratrien-3,17β-diol	99.6	94
17α-5'-chloro-1'-pentynyl)-5-androsten-3β,17β-diol	99.2	91
17α-(5'-chloro-1'-pentynyl)-17β-hydroxy-4-methyl-4-aza-5α-androstan-3-one	99.1	93

[a]All experiments were conducted using the standard procedure described in this communication. [b]All conversions were determined by a Bruker Aspect-3000 (300 MHz) NMR and by a Waters Model 600E HPLC equipment. Detection limit of the HPLC equipment is 40 ng/mL. [c]All yields were uncorrected for trace amounts of alkyl chloride present in the reaction products.

The presented double-refluxing procedure[18] is time-saving and produces highly pure primary alkyl bromides[17] in excellent yield for all kinds of primary alkyl

chlorides, especially for solid RCH_2Cl. Thus, it offers an alternative method for the quantitative conversion of primary alkyl chlorides to their corresponding bromides.

EXPERIMENTAL PROCEDURE

General. Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer 1600 Series FT Infrared Spectrometer. ^1H NMR spectra were determined on a Bruker Aspect-3000 (300 MHz) apparatus, ^{13}C NMR spectra were measured at 75.14 MHz with a Bruker Aspect - 3000. Chemical shifts are expressed in parts per million (ppm, δ) downfield from internal tetramethylsilane (TMS) for ^1H and ^{13}C. Significant ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant(s) (in hertz), number of protons. Low resolution mass spectra were obtained with a Varian Model 3700 Gas Chromatography/Micromass 16F Mass Spectrometer. Mass spectral data are tabulated as m/s (intensity expressed as percent of total ion current). High resolution mass spectra were analyzed in the Department of Chemistry, University of Montreal, Montreal, Québec, Canada. Chemical purity of the formed primary alkyl bromides was determined by high performance liquid chromatography (HPLC) on a Waters Model 600E (Millipore) equipped with a Waters 600E System Controller, a Waters 991 Photodiode Array Detector, a Waters automated Switching valve, a Computer NEC Power Mate SX/16 and a NEC Pinwriter P6200, using a C_{18}-Nova-Pak 4.0 μm column or a Nova-Pak CN HP 4.0 μm column with (a) CH_3CN : CH_3OH (80% : 20%) and (b) CH_3CN : H_2O (50% : 50%) as mobile phases at a flow rate of 1 mL/min.

General Procedure for Preparation of 17β-Hydroxy-17α-(5'-Chloro-1'-Pentynyl)-Steroids. To a solution of *n*-butyllithium (6.90 mmol) (2.5 M in

hexanes) in tetrahydrofuran (anhydrous, 75 mL) at -40 °C was added 5-chloro-1-pentyne (6.60 mmol) dropwise and the mixture was stirred under argon for 1 h at -40 °C. A solution of 17-oxosteroids (3.30 mmol) in tetrahydrofuran (75 mL) was added to the above reaction mixture and stirred at -60 °C for 1 h. The reaction was quenched with sat. aq. ammonium chloride (5 mL) and water (80 mL). The mixture was extracted with ethyl acetate (3 X 80 mL). The combined organic phase was dried ($MgSO_4$), filtered and evaporated to give the crude product, which was purified by flash column chromatography (C_6H_{14}:CH_3COCH_3:EtOAc, 75:10:15 to 55:30:15) to give 17β-hydroxy-17α-(5'-chloro-1'-pentynyl)-steroidal analogues.

17β-Hydroxy-17α-(5'-chloro-1'-pentynyl)-4-methyl-4-aza-5α-androstan-3-one (0.94 g, yield 71%) was obtained from its corresponding starting material 4-methyl-4-aza-5α-androstan-3-one: mp 102-104 °C. IR (KBr, cm^{-1}) 3376, 2944, 2870, 1625. ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H, 18-CH_3), 0.90 (s, 3 H, 19-CH_3), 0.77-0.98 (m, 2 H), 1.24-1.51 (m, 6 H), 1.57-1.70 (m, 4 H), 1.77-2.09 (m, 5 H), 2.21 (dddd, J = 3.9,4.4, 5.2, 5.7 Hz, 1 H), 2.44 (t, J = 6.7, 6.9 Hz, 2 H, 3'-H), 2.48 (dd, J = 4.8, 9.6 Hz, 2 H), 2.94 (s, 3 H, 4-NCH_3), 3.05 (dd, J = 3.5, 12.6 Hz, 1 H, 5α-H), 3.65 (t, J = 6.2, 6.4 Hz, 2 H, 5'-H). ^{13}C NMR ($CDCl_3$) δ 171.1, 84.7, 84.3, 79.8, 65.8, 51.8, 50.1, 47.0, 43.7, 39.2, 36.5, 35.0, 32.8, 32.7, 31.4, 29.8, 29.3, 28.9, 25.3, 22.9, 20.8, 16.3, 12.9, 12.4. EI-MS *m/s* (relative intensity) 406 (M^+, 22), 391 (14), 343 (17), 328 (36), 270 (25), 262 (64), 248 (55), 148 (29), 124 (34), 112 (36), 83 (100), 70 (42), 55 (73). HRMS Calcd for $C_{24}H_{36}O_2N_1Cl_1$, 406.0069; found 406.0081.

17α-(5'-Chloro-1'-pentynyl)-androst-5-en-3β,17β-diol (0.67 g, yield 99%) was obtained from its corresponding starting material 5-androsten-3β-ol-17-one: mp 65-67 °C. IR (KBr, cm^{-1}) 3384, 2937, 2869, 1462, 1439, 1379, 1051, 1025. ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H, 18-CH_3), 1.01 (s, 3 H, 19-CH_3), 0.89-1.14 (m, 2 H), 1.22-1.53 (m, 5 H), 1.57-1.69 (m, 5 H), 1.71-1.89 (m, 5 H), 1.91-

2.08 (m, 4 H), 2.11-2.35 (m, 3 H), 2.44 (t, J = 6.8, 7.1 Hz, 2 H, 3'-H), 3.51 (m, 1 H), 3.63 (t, J = 6.2, 6.5 Hz, 2 H, 5'-H), 5.35 (dd J = 5.2, 12.8 Hz, 1 H, 6-H). ^{13}C NMR ($CDCl_3$) δ 140.9, 121.3, 84.9, 84.1, 80.0, 71.7, 58.8, 49.9, 46.7, 43.7, 42.3, 39.2, 37.3, 36.5, 32.8, 32.6, 31.6, 31.5 (2 C), 23.2, 20.8, 19.4, 16.3, 12.8. EI-MS *m/s* (relative intensity) 390 (M^+, 18), 375 (29), 357 (26), 339 (46), 328 (33), 288 (40), 255 (31), 229 (32), 213 (59), 185 (27), 159 (52), 145 (67), 105 (100), 91 (91), 79 (66), 67 (66). HRMS Calcd for $C_{24}H_{36}O_2Cl_1$, 390.0002.; found 390.0016.

17α-(5'-Chloro-1'-pentynyl)-1,3,5(10)-estratrien-3,17β-diol (0.69 g, yield 98%) was obtained from its corresponding starting material 1,3,5(10)-estratrien-3-ol-17-one: mp 56-58 °C. IR (KBr, cm^{-1}) 3364, 2930, 2868, 1611, 1585, 1501, 1444, 1287, 1247, 1019. ^1H NMR ($CDCl_3$) δ 0.88 (s, 3 H, 18-CH_3), 0.92-1.54 (m, 5 H), 1.62-1.90 (m, 5 H), 1.93-2.03 (m, 3 H), 2.05-2.37 (m, 4 H), 2.46 (t, J = 6.7, 6.9 Hz, 2 H, 3'-H), 2.72-2.91 (m, 2 H), 3.66 (t, J = 6.5, 6.5 Hz, 2 H, 5'-H), 6.58 (d, J = 2.6 Hz, 1 H, 4-H), 6.64 (dd, J = 2.6, 8.4 Hz, 1 H, 2-H), 7.15 (d, J = 8.5 Hz, 1 H, 1-H). ^{13}C NMR ($CDCl_3$) δ 153.5, 138.2, 132.5, 126.5, 115.3, 112.8, 84.8, 84.4, 80.2, 49.6, 47.2, 43.7, 39.5, 39.2, 33.0, 31.4, 30.9, 29.7, 27.3, 26.5, 22.8, 16.3, 12.9. EI-MS *m/s* (relative intensity) 373 (M^+, 12), 372 (M^+-1, 44), 357 (15), 310 (11), 270 (57), 239 (20), 228 (57), 213 (79), 185 (31), 172 (36), 160 (100), 146 (32), 133 (46), 83 (48). HRMS Calcd for $C_{23}H_{29}O_2Cl_1$, 372.9339.; found 372.9332.

Standard Halogen Exchange Procedure. A mixture containing 0.2 mmol of primary alkyl chloride and 174 mg (2.0 mmol) of lithium bromide in 20 mL of 3-pentanone was heated at 120 °C (external temperature, preheated oil bath) for 2 h. The reaction mixture was then cooled to room temperature and the solvent was removed by a flash-rotavaper under water aspiration at 50 °C. The residue in ethyl acetate (20 mL) was washed with 20 mL of water. The organic phase was then

evaporated to give a mixture of RCH_2Br:RCH_2Cl, which was once more treated with lithium bromide (174. mg, 2.0 mmol) in 10 mL of 3-pentanone. The mixture was subsequently refluxed for 3 h at 120 °C, after which the aq. work-up described above, drying ($MgSO_4$) and removal of the solvent afforded the alkyl bromide with high chemical purity.

17β-Hydroxy-17α-(5'-bromo-1'-pentynyl)-4-methyl-4-aza-5α-androstan-3-one (0.36 g, yield 93%) was obtained from its corresponding 5'-chloride: mp 119-121 °C. IR (KBr, cm^{-1}) 3342, 2939, 2873, 1622. ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H, 18-CH_3), 0.89 (s, 3 H, 19-CH_3), 0.80-0.98 (m, 2 H), 1.24-1.47 (m, 7 H), 1.56-1.69 (m, 4 H), 1.77-1.91 (m, 2 H), 1.93-2.09 (m, 2 H), 2.05 (t, *J* = 6.6, 6.7 Hz, 2 H, 4'-H), 2.20 (dddd, *J* = 4.2, 4.6, 5.0, 5.4 Hz, 1 H), 2.43 (t, *J* = 6.7, 6.9 Hz, 2 H, 3'-H), 2.40-2.48 (m, 2 H), 2.92 (s, 3 H, 4-NCH_3), 3.04 (dd, *J* = 3.6, 12.5 Hz, 1 H, 5α-H), 3.52 (t, *J* = 6.3, 6.5 Hz, 2 H, 5'-H). ^{13}C NMR ($CDCl_3$) δ 170.9, 84.9, 84.1, 79.8, 65.7, 51.8, 50.1, 47.1, 39.2, 36.5, 35.0, 32.9, 32.8, 32.6, 31.5, 29.8, 29.2, 29.1, 25.3, 22.9, 20.9, 17.6, 12.9, 12.5. EI-MS *m/s* (relative intensity) 451 (M^+, 12), 453 (M^++2, 14), 436 (38), 438 (39), 420 (9), 370 (26), 343 (31), 328 (8), 270 (24), 262 (78), 248 (28), 234 (9), 149 (29), 124 (44), 112 (42), 83 (100), 70 (42), 55 (55). HRMS Calcd for $C_{24}H_{36}O_2N_1Br_1$, 450.4579.; found 450.4566.

17α-(5'-Bromo-1'-pentynyl)-androst-5-en-3β,17β-diol (0.079 g, yield 91%) was obtained from its corresponding 5'-chloride: mp 61-63 °C. IR (KBr, cm^{-1}) 3388, 2937, 2868, 1462, 1434, 1378, 1247, 1051, 1025. ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H, 18-CH_3), 1.02 (s, 3 H, 19-CH_3), 0.93-1.15 (m, 2 H), 1.23-1.70 (m, 11 H), 1.81-1.90 (m, 4 H), 1.92-2.11 (m, 4 H), 2.16-2.31 (m, 3 H), 2.42 (t, *J* = 6.7, 6.7 Hz, 2 H, 3'-H), 3.48-3.53 (m, 1 H), 3.51 (t, *J* = 6.5, 6.6 Hz, 2 H, 5'-H), 5.34 (dd *J* = 5.2, 12.5 Hz, 1 H, 6-H). ^{13}C NMR ($CDCl_3$) δ 140.8, 121.3, 85.0, 84.0, 80.0, 71.7, 58.8, 49.9, 46.7, 42.3, 39.2, 37.3, 36.4, 32.8, 32.6,

31.4, 31.6, 31.5 (2 C), 23.2, 20.8, 19.4, 16.3, 12.8. EI-MS *m/s* (relative intensity) 436 (M^+, 22), 421 (41), 385 (25), 355 (32), 328 (45), 237 (25), 229 (44), 213 (77), 185 (26), 171 (36), 159 (52), 147 (35), 131 (50), 119 (52), 105 (100), 91 (92), 81 (81), 67 (74). HRMS Calcd for $C_{24}H_{36}O_2Br_1$, 436.4512; found 436.4529.

17α-(5'-Bromo-1'-pentynyl)-1,3,5(10)-estratrien-3,17β-diol (0.80 g, yield 94%) was obtained from its corresponding 5'-chloride: mp 60-62 °C. IR (KBr, cm^{-1}) 3376, 2930, 2868, 1611, 1585, 1501, 1451, 1286, 1247, 1019. ^1H NMR ($CDCl_3$) δ 0.88 (s, 3 H, 18-CH_3), 0.92-1.54 (m, 5 H), 1.62-1.89 (m, 5 H), 1.97-2.10 (m, 3 H), 2.16-2.37 (m, 4 H), 2.46 (t, *J* = 6.7, 6.8 Hz, 2 H, 3'-H), 2.74-2.92 (m, 2 H), 3.53 (t, *J* = 6.4, 6.5 Hz, 2 H, 5'-H), 6.57 (d, *J* = 2.3 Hz, 1 H, 4-H), 6.64 (dd, *J* = 2.2, 8.3 Hz, 1 H, 2-H), 7.16 (d, *J* = 8.4 Hz, 1 H, 1-H). ^{13}C NMR ($CDCl_3$) δ 153.5, 138.2, 132.5, 126.5, 115.3, 112.8, 84.9, 84.3, 80.2, 49.6, 47.3, 43.7, 39.5, 39.2, 33.0, 32.4, 30.9, 29.7, 27.3, 26.5, 22.8, 17.6, 12.9. EI-MS *m/s* (relative intensity) 417 (M^+, 6), 416 (M^+-1, 21), 418 (M^++1, 19), 403 (15), 401 (14), 310 (16), 270 (21), 239 (26), 228 (56), 213 (100), 185 (20), 159 (58), 146 (32), 133 (49), 83 (20). HRMS Calcd for $C_{23}H_{29}O_2Br_1$, 417.3849; found 417.3833.

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17. The IR, ^{1}H- and ^{13}C-NMR and EI-MS or HRMS spectral properties of each of these alkyl bromide products were consistent with the assigned structures.
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