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A CONVENIENT METHOD OF ANION EXCHANGE IN QUATERNARY SALTS

J. J. KAMINSKI, K. W. KNUTSON and N. BODOR*
INTERx Research Corporation, 2201 West 21st Street, Lawrence, KS 66044, U.S.A.

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Abstract—A convenient and efficient method for the preparation of anion exchanged quaternary salts has been developed. The method involves treatment of quaternary halides with methanolic solutions of suitable protic acids. The process is effective for aromatic and aliphatic quaternary halides with no loss of alkyl group integrity in the quaternary salt.

The Menschutkin reaction, the process of converting a tertiary amine to its quaternary salt by reaction with an alkylating agent, is a synthetic procedure which has been investigated thoroughly.[1a–k] In some instances, the low reactivity of the tertiary amine to be quaternized requires the use of more reactive alkylating agents such as the alkyl fluorosulfonates, alkyl tosylates or the alkyl iodides. Under these circumstances, the alkylating agent used inherently determines the identity of the gegen ion in the quaternary salt. Exchange of the gegen ion in the quaternary salt has been accomplished most frequently using an anion exchange resin.[2] This procedure involves conversion of the quaternary salt to its hydroxide form and subsequent neutralization using the conjugate acid of the desired base.

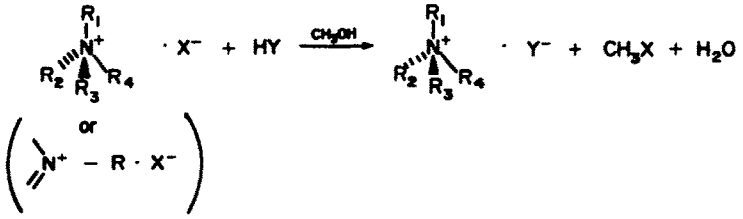
The present work reports a different and, in most cases, more convenient procedure for the exchange of gegen ions in quaternary salts. The general scheme of the exchange is as shown in Scheme 1.

In other words, a methanolic solution of an HY acid will react with a quaternary ammonium halide to produce the methyl halide and the corresponding quaternary ·Y salt. The methyl halide (CH_3I, CH_3Br, CH_3Cl) formed during the exchange is removed from the reaction mixture. One related reaction has previously been reported[3] as a commercial synthesis of 1-methyl-2-pyridiniumaldoxime chloride, 2-PAM·Cl, (1) from the corresponding iodide (1a) by evaporating a solution of 1a in methanolic hydrogen chloride. The methyl iodide formed could then be recycled.

The mechanism of the reaction was first elucidated. Treatment of 1a with methanolic hydrogen chloride to product 1 can proceed via two possible mechanistic pathways. In the first case, the iodide ion can react with the protonated methanol solvent to produce water, methyl iodide and the product, 1. On the other hand, the iodide ion could also dealkylate the quaternary salt, 1a, to produce methyl iodide and 2-pyridinealdoxime. In this case, subsequent reaction of 2-pyridinealdoxime with methyl chloride generated *in situ* from methanolic hydrogen chloride could also produce 1. Distinction between these two mechanistic possibilities becomes increasingly important since the latter process could lead to loss of alkyl group integrity in the quaternary salt to be anion exchanged when a potentially labile alkyl group in the quaternary salt and the alkyl group of the alcohol solvent are different. In order to distinguish between these two possible pathways, the reaction of 1a with hydrogen chloride in methanol and d^4-methanol was examined. In each case, the reaction products isolated were identical by melting point, mixed m.p., IR and PMR. This observation supports the first mechanistic pathway and demonstrates that the integrity of the alkyl group in the quaternary salt is conserved and no alkyl group exchange with the alcohol solvent is anticipated.

Further support for the first mechanistic pathway is obtained by the lack of anion exchange capability when organic acids of low pK_a are utilized in the process. Treatment of 1a with methanolic solutions of acetic and/or lactic acid gave quantitative recovery of the starting material, 1a. Furthermore, the presence of a catalytic amount of a strong acid, such a p-toluenesulfonic acid, in the presence of the weaker organic acid did not facilitate the reaction. In addition, when a 1:1 mixture of p-toluenesulfonic acid and the weaker organic acid was reacted with 1a, only the 2-PAM salt of the strong acid, 4, was isolated.

The next objective was to examine the scope of the process. Since a wide variety of 2-PAM salts have been described in the literature,[4] the anion exchange reaction was corroborated using 1a. In each case, the yield of the product obtained was not optimized. Treatment of 1a with methanolic solutions of hydrogen bromide, methanesulfonic acid, *p*-toluenesulfonic acid and 5-sulfosalicylic acid gave the corresponding anion exchanged 2-PAM salts, 2–6. Similarly, the synthesis of



Scheme 1.

alternative salt forms of other N-alkyl pyridiniumaldoximes were desired.[5] In this regard, treatment of 1-n-dodecyl-3-pyridiniumaldoxime iodide, 3-PAD·I, with methanolic solutions of hydrogen chloride, hydrogen bromide, methanesulfonic acid, *p*-toleunesulfonic acid and 5-sulfosalicylic acid gave the corresponding 3-PAD salts, 7–11.

The aldoxime group in the quaternary salts studied is a very reactive nucleophile.[5] It also undergoes relatively facile dehydration and other reactions. However, the fact that it remained intact during the anion exchange process indicates that the method is quite general and should be easily extended to other simple pyridinium and other heteroaromatic quaternary salts.

An important point to clarify was the possible involvement of the well-known charge transfer complexes[6] formed between pyridinium and iodide ions. The fact that 2, as well as 1a, could easily be exchanged to 4 indicates that the iodide is not necessary. This result implies that the procedure could possibly be extended to aliphatic quaternary salts.

Quinuclidine, a simple, structurally rigid tertiary amine, was chosen as the basis for the model compound of an aliphatic quaternary salt, N-methylquinuclidinium iodide. It is expected that all the other simple aliphatic quaternary salts will behave similarly.

Indeed, treatment of quinuclidinium iodide, 12, with methanolic solutions of hydrogen chloride, hydrogen bromide and *p*-toluenesulfonic acid gave the corresponding anion exchanged quinuclidinium salts, 13–15.

It is evident that when quaternary iodides are the salts utilized in the anion exchange, the conjugate acids selected must not possess a sufficient oxidation potential to initiate the iodide ⇌ iodine oxidation. Treatment of quaternary iodides with methanolic solutions of sulfuric acid and nitric acid resulted in the formation of iodine.

In conclusion, the treatment of quaternary halides with methanolic solutions of suitable protic acids appears to be a convenient and efficient method for the preparation of anion exchanged quaternary salts. The process is effective for aromatic as well as aliphatic, quaternary halides with no loss of alkyl group integrity in the quaternary salt. This observation suggests the process may be more advantageous than the anion exchange resin method for example, in the synthesis of radiolabelled quaternary salts. It is quite possible that under appropriate conditions, other alcohols could also be used.

EXPERIMENTAL

1-Methyl-2-pyridiniumaldoxime chloride (1)

1-Methyl-2-pyridiniumaldoxime iodide 2.65 g (0.01 mol) was dissolved in 50 ml MeOH containing 2.7 g (0.075 mol) anhyd. HCl. The soln was concentrated to 10 ml by distillation. Addition of approximately an equal volume of acetone gave a white ppt which was isolated by filtration and washed thoroughly with anhyd. ether. Recrystallization from EtOH/ether gave 1.38 g (0.008 mol), 80%, 1, m.p. 225–226°, Lit.[3] m.p. 235–237°, IR (KBr) 2900, 1615, 1570, 1490, 1310, 1170, 1010 and 800 cm^{-1}; PMR (D_2O) δ 7.6–8.6 (m, 5H) and 4.2 (s, 3H) ppm. (Found: C, 48.28; H, 5.18; N, 16.03; Cl, 20.63. Calc. for $C_7H_9ClN_2O$: C, 48.71; H, 5.26; N, 16.23; Cl, 20.54%).

Following the procedure described above, 2.65 g (0.01 mol) 1-methyl-2-pyridiniumaldoxime iodide was treated with 11.7 g (0.325 mol) anhyd. HCl in 25 ml d^4-MeOH to give 1.36 g (0.0079 mol), 79%, 1, m.p. 225–226°, IR (KBr) 2900, 1615, 1570, 1490, 1310, 1170, 1010 and 800 cm^{-1}; PMR (D_2O) δ 7.6–8.6 (m, 5H) and 4.2 (s, 3H) ppm. (Found: C, 48.76; H, 5.29; N, 15.91; Cl, 20.79. Calc. for $C_7H_9ClN_2O$: C, 48.71; H, 5.26; N, 16.23; Cl, 20.54%).

Using the procedure described for the preparation of 1, the following 1-methyl-2-pyridiniumaldoxime salts were prepared. The percentage yield refers to the isolated product, which in every case studied appeared to be of high quality, based on their m.ps and PMR spectra. One recrystallization from the solvent described gave the analytically pure material.

1-Methyl-2-pyridiniumaldoxime bromide (2). Yield 2.00 g (0.0092 mol), 92%. Recrystallization from MeOH/acetone gave 2, m.p. 232–234°, IR (KBr) 2900, 1615, 1570, 1490, 1310, 1170, 1010 and 780 cm^{-1}; PMR (D_2O) δ 7.6–8.6 (m, 5H) and 4.4 (s, 3H) ppm. (Found: C, 38.72; H, 3.92; N, 12.63; Br, 36.52. Calc. for $C_7H_9BrN_2O$: C, 38.73; H, 4.18; N, 12.91; Br, 36.82%).

1-Methyl-2-pyridiniumaldoxime methanesulfonate (3), yield 1.6 g (0.007 mol), 70%. Recrystallization from acetone/petroleum ether (30–60°) gave 3, m.p. 149–152°, Lit.[7] m.p. 155°, IR (KBr) 2900, 1615, 1570, 1490, 1310, 1170, 1050, 1010 and 780 cm^{-1}; PMR (D_2O) δ 7.6–8.6 (m, 5H), 4.4 (s, 3H) and 2.8 (s, 3H) ppm. (Found: C, 41.10; H, 5.45; N, 12.06. Calc. for $C_8H_{12}N_2O_4S$: C, 41.37; H, 5.21; N, 12.06%).

1-Methyl-2-pyridiniumaldoxime p-toluenesulfonate (4), yield 2.94 g (0.0095 mol), 95%. Recrystallization from EtOAc gave 4, m.p. 134–135° IR (KBr) 2900, 1615, 1570, 1500, 1320, 1170, 1000, 810 and 680 cm^{-1}; PMR (D_2O) δ 7.1–8.8 (m, 9H), 4.4 (s, 3H) and 2.4 (s, 3H) ppm. (Found: C, 54.36; H, 5.04; N, 9.11. Calc. for $C_{14}H_{16}N_2O_4S$: C, 54.53; H, 5.23; N. 9.08.%).

1-Methyl-2-pyridiniumaldoxime p-toluenesulfonate (from 2) (4)

1-Methyl-2-pyridiniumaldoxime bromide 2.2 g (0.01 mol) was dissolved in 100 ml MeOH containing 17.1 g (0.1 mol) *p*-toluenesulfonic acid. The soln was concentrated to 10 ml by distillation. Addition of EtOAc gave the crystalline product, 4. 2.2 g (0.007 mol), 70%. Recrystallization from EtOAc gave 4, m.p. 138–140° IR (KBr) 2960, 1620, 1570, 1500, 1320, 1230, 1150, 1020, 1000, 810 and 680 cm^{-1}; PMR (D_2O) δ 7.1–8.8 (m, 9H), 4.3 (s, 3H) and 2.3 (s, 3H) ppm. (Found: C, 54.73; H, 5.39; N, 8.85. Calc. for $C_{14}H_{16}N_2O_4S$: C, 54.52; H, 5.24; N, 9.09%).

1-Methyl-2-pyridiniumaldoxime dihydrogenphosphate (5), yield 2.05 g (0.0088 mol), 87%. Recrystallization from acetone gave 5, m.p. 210–211°, lit.[4] m.p. 214–215°, IR (KBr) 3600, 2000, 1615, 1570, 1500, 1450, 1330, 1250, 1150, 1040, 950, 880 and 780 cm^{-1}; PMR (D_2O) δ 7.9–8.9 (m, 5H) and 4.4 (s, 3H) ppm. (Found: C, 35.87; H, 4.51; N, 11.97; P, 13.08. Calc. for $C_7H_{11}N_2O_5P$: C, 35.90; H, 4.73; N, 11.97; P, 13.23%).

1-Methyl-2-pyridiniumaldoxime 5-sulfosalicylate (6), yield 2.82 g (0.0080 mol), 80%. Recrystallization from acetone gave 6, m.p. 213–215°, IR (KBr) 3040, 3000, 2880, 2780, 1670, 1500, 1250, 1120, 1030, 1010, 780 and 670 cm^{-1}; PMR (D_2O) δ 7.7–8.8 (m, 7H), 7.1 (d, 1H) and 4.4 (s, 3H) ppm. (Found: C, 47.57; H, 4.04; N, 7.66. Calc. for $C_{14}H_{14}N_2O_7S$: C, 47.45; H, 3.98; N, 7.91%).

1-n-Dodecyl-3-pyridiniumaldoxime chloride (7)

1-n-Dodecyl-3-pyridiniumaldoxime iodide 4.18 g (0.01 mol) was dissolved in 50 ml MeOH containing 8.6 g (0.10 mol) anhyd. HCl. The soln was concentrated to 10 ml by distillation. Addition of approximately an equal volume of anhyd. ether gave the product 7, 2.78 g (0.0085 mol), 85%. Recrystallization from acetone-petroleum ether gave 7, m.p. 138–140°, IR (KBr) 2900, 1620, 1500, 1300 and 1010 cm^{-1}; PMR (d^6-DMSO) δ 12.4 (s, 1H), 9.5–8.0 (m, 5H), 4.7 (t, 2H) and 2.5–0.8 (m, 23H) ppm. (Found: C, 66.17; H, 9.86; N, 8.26; Cl, 11.13. Calc. for $C_{18}H_{31}ClN_2O$: C, 66.13; H, 9.56; N, 8.57; Cl, 10.85%).

Using the procedure described for the preparation of 7, the following 1-n-dodecyl-3-pyridiniumaldoxime salts were prepared.

1-n-Dodecyl-3-pyridiniumaldoxime bromide (8), yield 2.8 g (0.0075 mol), 75% Recrystallization from acetone gave 8, m.p. 141–143°, IR (KBr) 3200, 2920, 1500, 1420, 1295 and 1000 cm^{-1}; PMR (d^6-DMSO) δ 12.2 (s, 1H), 9.6–8.0 (m, 5H), 4.7 (t, 2H) and 2.7–0.7 (m, 23H) ppm. (Found: C, 58.28; H, 8.47; N, 7.47; Br, 21.66. Calc. for $C_{18}H_{31}BrN_2O$: C, 58.21; H, 8.41; N, 7.55; Br, 21.52%).

1 - n - Dodecyl - 3 - pyridiniumaldoxime methanesulfonate (9), yield 2.9 g (0.0075 mol), 75%. Recrystallization from acetone/petroleum ether (30–60°) gave 9, m.p. 118–120°, IR (KBr)

3250, 2900, 2800, 1500, 1290, 1185, 1060, 1000, 785 and 680 cm^{-1}; PMR ($CDCl_3$) δ 9.4–8.0 (m, 5H), 4.8 (t, 2H), 2.8 (s, 3H) and 2.3–0.7 (m, 23H) ppm. (Found: C, 58.98; H, 8.80; N, 7.25. Calc. for $C_{19}H_{34}N_2O_5S$: C, 59.02; H, 8.88; N, 7.25%).

1 - *n* - *Dodecyl* - 3 - *pyridiniumaldoxime* - p - *toluenesulfonate* (10), yield 3.25 g (0.007 mol), 70%. Recrystallization from acetone gave 10, m.p. 153–156°, IR (KBr) 2900, 1500, 1300, 1220, 1180, 1120, 1030, 1000, 810 and 680 cm^{-1}; PMR (d^6–DMSO) δ 12.2 (s, 1H), 9.4–8.0 (m, 5H), 7.6–7.0 (m, 4H), 4.6 (t, 2H), 2.3 (s, 3H) and 2.7–0.7 (m, 23H) ppm. (Found: C, 64.98; H, 8.28; N, 5.94. Calc. for $C_{25}H_{34}N_2O_4S$: C, 64.89; H, 8.29; N, 6.06%).

1 - *n* - *Dodecyl* - 3 - *pyridiniumaldoxime* - 5 - *sulfosalicylate* (11), yield 3.6 g (0.0071 mol), 71%. Recrystallization from acetone gave 11, m.p. 151–153°, IR (KBr) 2900, 1660, 1500, 1470, 1230, 1170, 1120, 1000 and 660 cm^{-1}; PMR (d^6–DMSO) δ 9.3–7.7 (m, 7H), 6.9–6.8 (m, 1H), 5.0 (t, 2H) and 2.6–0.7 (m, 23H) ppm. (Found: C, 58.86; H, 7.24; N, 5.56. Calc. for $C_{25}H_{36}N_2O_7S$: C, 59.03; H, 7.13; N, 5.51%).

1-Methylquinuclidinium iodide (12)

To an ethereal soln containing 3.2 g (0.029 mol) quinuclidine at 0° was added dropwise with stirrring 4.8 g (0.033 mol) MeI dissolved in ether. The suspension formed was stirred at 0° for 2 hr. The solid was isolated by filtration under N_2 and thoroughly washed with anhyd. ether. Drying *in vacuo* over $CaSO_4$ gave 6.6 g (0.026 mol), 90%, 12, m.p. >300°, IR (KBr) 2940, 2870, 1460, 1020, 950 and 835 cm^{-1}; PMR (D_2O) δ 3.8–3.3 (m, 6H), 3.0 (s, 3H) and 2.5–1.9 (m, 7H) ppm. (Found: C, 38.30; H, 6.44; N, 5.18; I, 49.91. Calc. for $C_8H_{16}NI$: C, 37.96; H, 6.37; N, 5.53; I, 50.14%).

1-Methylquinuclidinium chloride (13)

1-Methylquinuclidinium iodide, 1.0 g (0.004 mol), was dissolved in 20 ml MeOH containing 1.46 g (0.04 mol) anhyd. HCl. The soln was concentrated to 5 ml by distillation. Addition of approximately an equal volume of ether/acetone (1:1 v/v) gave the product 13, 0.48 g (0.003 mol), 75%. Recrystallization from acetone gave an extremely hygroscopic solid, m.p. >300°, IR (KBr) 2915, 1460, 1120 and 955 cm^{-1}; PMR (D_2O) δ 3.5–3.2 (m, 6H), 2.9 (s, 3H) and 2.2–1.5 (m, 7H) ppm. (Found: C, 59.25; H, 10.43; N, 8.15. Calc. for $C_8H_{16}ClN$: C, 59.42; H, 9.99; N, 8.66%).

Using the procedure described for the preparation of 13, the following 1-methylquinuclidinium salts were prepared.

1-Methyl-quinuclidinium bromide (14), yield 0.62 g (0.0030 mol), 75%. Recrystallization from acetone gave 14, m.p. >300°, IR (KBr) 2920, 1455, 1120, 955 cm^{-1}; PMR (D_2O) δ 3.5–3.0 (m, 6H), 2.8 (s, 3H) and 2.3–1.7 (m, 7H) ppm. (Found: C, 46.76; H, 8.19; N, 6.57; Br, 38.81. Calc. for $C_8H_{16}BrN$: C, 46.60; H, 7.84; N, 6.79; Br, 38.76%).

1-Methylquinuclidinium p-tosylate (15), yield 1.0 g (0.0034 mol), 84%. Recrystallization from acetone gave 15, m.p. 165–166°, IR (KBr) 2920, 1460, 1200, 1120, 1030, 1010 and 680 cm^{-1}; PMR (D_2O) δ 8.0–7.2 (m, 4H), 3.5–3.0 (m, 6H), 2.8 (s, 3H), 2.4 (s, 3H) and 2.3–1.7 (m, 7H) ppm. (Found: C, 60.49; H, 7.91; N, 4.70. Calc. for $C_{15}H_{23}NO_3S$: C, 60.56; H, 7.81; N, 4.71%).

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