Optimized Procedures for One-Pot Conversion of Alkyl Bromides into Amines via the Staudinger Reaction

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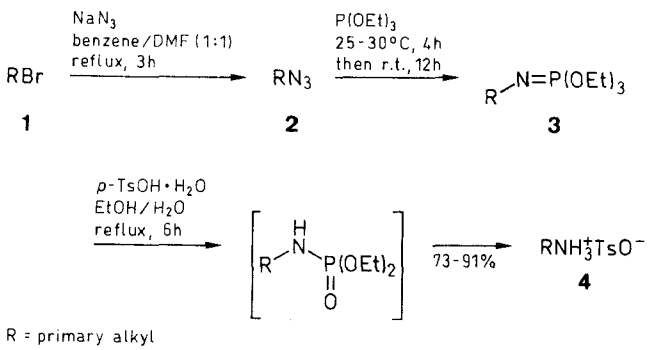
New optimized procedures for transforming primary and secondary alkyl bromides into the corresponding primary amine salts have been elaborated. Essential modifications of azidation and deprotection of intermediate triethoxyphosphine alkylimides resulted in substantial improvement of the overall yields. Conversion of ammonium tosylates and hydrochlorides into free amines in a nonaqueous medium is described.

In recent years organic azides received considerable attention as potential precursors of primary amines.[1] Among the spectrum of various reduction procedures reported for azides the chemoselective Staudinger reaction evidently plays an important role. The phosphinimine route based on the application of relatively expensive triphenylphosphine has been so far notoriously utilized.[2] Some years ago we reported on the possible replacement of this reagent by substantially cheaper and more reactive triethyl phosphite.[3]

Despite its simplicity, relatively inexpensive materials used, and satisfactory overall yields of amine hyrochlorides obtained our procedure suffered however, from some significant drawbacks: (a) – relatively long azidation times were recommended; (b) – no uniform workup procedure for isolation of the amine salts was given; (c) – only moderate yields of *sec*-alkylamine hydrochlorides were obtained. All these disadvantages, obviously diminishing the preparative value of the reported methodology, can be at least partially circumvented. It is a purpose of this paper to disclose our attempts in this matter. In the light of our findings the following procedure offers the simplest and the most effective way of transforming primary alkyl bromides into the corresponding ammonium tosylates (Scheme 1).



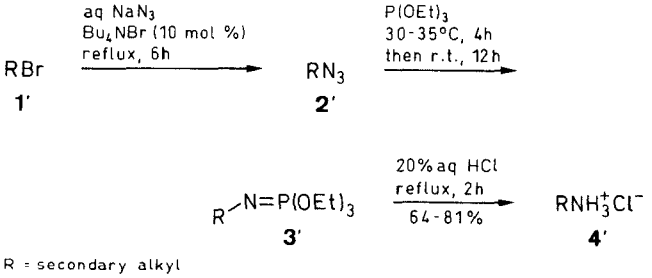
Scheme 1

It was well established that the solid–liquid PTC variant used previously for azidation[3] can be effectively replaced by conventional nucleophilic displacement with sodium azide suspended in benzene/dimethylformamide (1 : 1, v/v).

Relatively low concentration of an azide anion in such systems seems to be quite sufficient for a reasonable rate of azidation which is practically complete after 3 hours at reflux temperature.[4] The benzene solution of crude azide **2** obtained after aqueous workup of the reaction mixture is then treated with triethyl phosphite at 25–30°C for 4 hours to give the corresponding triethoxyphosphine alkylimides **3**. Acidolysis of crude **3** by means of *p*-toluenesulfonic acid monohydrate in refluxing ethanol is in our opinion the deprotection method of choice when primary alkylammonium tosylates **4** are the final products. They can be easily isolated in pure form by evaporation of solvent and diluting the residue with an excess of diethyl ether. Analytically pure samples of **4** can be obtained by recrystallization from the suitable solvent (see Table 1). Overall yields and melting points of ammonium tosylates **4** are given in Table 1. All compounds reported give IR and ^{1}H NMR spectra (see Table 2) fully compatible with the expected structures.

Free amines can be liberated from the ammonium tosylates **4** in a nonaqueous medium by employing a specific solid–liquid PTC process similar to that reported previously.[5] This procedure can be also applied for transforming amine hydrochlorides into free bases. It is noticeable that deprotection of iminophosphoranes **3** can be arrested at the intermediate stage of diethyl *N*-alkylphosphoramidates when neutral hydrolysis with water in benzene is employed.[6] Such phosphoryl-protected amine derivatives, which are not available when triphenylphosphine is used for the Staudinger reaction, are valuable starting materials for the preparation of secondary amines.[7]

The synthetic procedure recommended for primary alkyl bromides was found, however, unsuitable for secondary substrates. In this case the slightly modified liquid–liquid PTC system described before[8] was found superior for azidation of *sec*-alkyl bromides **1'**. Moreover, a different deprotection procedure involving hydrolysis of triethoxyphosphine *sec*-alkylimides **3'** by refluxing with 20% hydrochloric acid appeared preferable for such intermediates. The synthetic protocol for *sec*-alkyl bromides is outlined in Scheme 2. The products **4'** were purified via free amines and finally characterized as pure amine hydrochlorides **4'** (see Table 1).



Scheme 2

Table 1. Ammonium Tosylates **4** and Hydrochlorides **4'** Prepared

Product	R	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)
4a	Bu	91 (73)	119–119.5 (EtOH)	115–117[9]
4b	*n*-C_6H_{13}	73 (60)	124–125 (EtOH)	$C_{13}H_{23}NO_3S$ (273.4)
4c	$Ph(CH_2)_2$	84 (77.5)	171–172 (EtOH)	$C_{15}H_{19}NO_3S$ (293.4)
4d	$Ph(CH_2)_3$	79 (69)	169–170 (EtOH)	$C_{16}H_{21}NO_3S$ (307.4)
4e	$CH_2=CHCH_2$	81[d]	96–97 (EtOAc)	$C_{10}H_{15}NO_3S$ (229.3)
4f	$CH\equiv CCH_2$	92 (80)[d]	152–153 (EtOH/Et_2O)	$C_{10}H_{13}NO_3S$ (227.3)
4g	$PhCH=CHCH_2$	74 (60)[d]	203–204 (EtOH)	$C_{16}H_{19}NO_3S$ (305.4)
4'a	*s*-Bu	64[e] (64.5)	145–146 (EtOH/Et_2O)	144–145[10]
4'b	2-pentyl	76 (51)	148.5–149 (EtOH/Et_2O)	147.5–148[11]
4'c	2-octyl	81	90–91 (hexane)	90–91[12]
4'd	*c*-C_6H_{11}	68 (51)	206–207 (EtOH/Et_2O)	206–207.5[13]

[a] Yield of isolated product **4** or **4'** based on **1** or **1'**. Yields of amine hydrochlorides prepared by the previously described procedure[3] are shown in parenthesis.
[b] Uncorrected, measured in capillaries.
[c] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.15, N ± 0.30, S ± 0.20.
[d] The azidation was carried out for 6 h at 35–40 °C.
[e] The solution of crude amine hydrochloride obtained after hydrolysis of **3'** was evaporated to dryness, the residue treated with Et_2O, and refrigerated for 24 h.

Both optimized sequences for the one-pot conversion of alkyl bromides into amines offer relatively high overall yields and thus constitute an attractive and inexpensive alternative to the Gabriel synthesis.

Conversion of Primary Alkyl Bromides into Ammonium Tosylates 4; General Procedure:

A mixture of RBr (1; 0.05 mol), NaN_3 (6.5 g, 0.1 mol), benzene (15 mL), and DMF (15 mL) was refluxed with stirring for 3 h. The product was cooled to r.t. and poured into H_2O (200 mL).

The organic phase was separated. The H_2O layer was extracted with benzene (3 × 15 mL) and the extracts were combined with the organic phase. The solution of **2** was dried ($MgSO_4$) and $P(OEt)_3$ (8.3 g, 0.05 mol) was added dropwise with stirring. The temperature of the slightly exothermic reaction was maintained at 25–30 °C for 4 h. The solution of **3** was left overnight (12 h) at r.t. and then the solvent was evaporated in vacuo. The residue was diluted with anhydr. EtOH (30 mL) containing H_2O (0.9 mL, 0.05 mol) treated with TsOH · H_2O (9.51 g, 0.05 mol), and refluxed for 6 h. Solvent was then evaporated, the residue diluted with Et_2O (75 mL) and left in a refrigerator for 12 h. Crystalline ammonium tosylate **4** was filtered off, washed with Et_2O, and crystallized from a suitable solvent, if necessary.

Conversion of *sec*-Alkyl Bromides into Amine Hydrochlorides 4'; General Procedure:

A mixture of RBr **1'** (0.05 mol), NaN_3 (6.5 g, 0.1 mol), Bu_4NBr (1.61 g, 0.005 mol), and H_2O (20 mL) was refluxed with efficient stirring for 6 h. The product was cooled to r.t. and the organic phase was separated. The H_2O layer was extracted with benzene (3 × 10 mL) and the extracts were combined with the organic phase. The resultant solution of **2'** was dried ($MgSO_4$) and $P(OEt)_3$ (8.3 g, 0.05 mol) was added dropwise with stirring. The temperature of the slightly exothermic reaction was kept at 30–35 °C for 4 h and the resultant solution was left overnight (12 h) at r.t.

Crude **3'** obtained after removal of benzene was treated with 20% HCl (40 mL) and refluxed for 2 h. The solution of amine hydrochloride **4'** was cooled to r.t. and extracted with Et_2O (2 × 15 mL). The extracts were discarded and the aqueous solution was made alkaline with 50% NaOH aq. (30 mL) with stirring and external cooling. The free amine was extracted with Et_2O (3 × 20 mL). The extracts were stirred with conc. HCl (5 mL) for 15 min and then evaporated to

Table 2. Spectrometric Data of Ammonium Tosylates **4**

Product	IR (KBr)[a] ν (cm^{-1})	^1H NMR (D_2O/$TMS_{ext.}$)[b] δ, J (Hz)
4a	3056, 2992, 2960, 1640, 1188, 1140, 1124, 1036, 1008	0.93 (t[c], 3H), 1.14–1.89 (m, 4H), 2.39 (s, 3H), 2.98 (br t, 2H, J = 7.3), 7.26–7.82 (AA'XX' system, 4H)
4b	3132, 2980, 2944, 2884, 2864, 1488, 1476, 1472, 1192, 1128, 1108, 1096, 1040, 1028, 1016, 960, 944, 816, 686	0.90 (t[c], 3H), 1.05–1.88 (m, 8H), 2.42 (s, 3H), 3.00 (br t, 2H, J = 7.1), 7.30–7.90 (AA'XX' system, 4H)
4c	3128, 3050, 1492, 1180, 1156, 1150, 1128, 1116, 1100, 1036, 1012, 942, 900, 814, 776, 720, 696, 692, 688	2.40 (s, 3H), 2.91–3.48 (m, 4H), 7.28–7.90 (m, 9H)
4d	3064, 2948, 1480, 1468, 1452, 1174, 1148, 1140, 1134, 1126, 1036, 1012, 816, 758, 688	1.82–2.27 (m, 2H), 2.45 (s, 3H), 2.70 (t, 2H, J = 7.6), 2.97 (t, 2H, J = 7.8), 7.26–7.87 (m, 9H)
4e	3036, 2972, 2944, 1492, 1188, 1140, 1124, 1036, 1012, 934, 812, 686	2.37 (s, 3H), 3.60 (br d, 2H, J = 5.7), 3.83–6.27 (m, 3H), 7.24–7.86 (AA'XX' system, 4H)
4f	3288, 3228, 3040, 2140, 1220, 1196, 1152, 1138, 1124, 1036, 1012, 816, 688	2.40 (s, 3H), 2.95 (t, 1H, J = 2.5), 3.86 (d, 2H, J = 2.5), 7.25–7.85 (AA'XX' system, 4H)
4g	3028, 2956, 2920, 1480, 1194, 1180, 1170, 1154, 1148, 1124, 1116, 1108, 1036, 1012, 972, 816, 738, 688	2.44 (s, 3H), 3.84 (dd, 2H, J = 6.5, 1.0), 6.37 (dt, 1H, J = 16.0, 6.5), 6.99 (dt, 1H, J = 16.0, 1.0), 7.32–7.86 (m, 9H)

[a] Recorded on a Specord M 80 (C. Zeiss) spectrophotometer.
[b] Recorded at 80 MHz with a Tesla BS 587 FT spectrometer.
[c] Distorted triplet.

dryness. The amine hydrochloride **4'** was dried in vacuo (P_2O_5 and solid NaOH) till constant weight. Analytical samples were obtained by crystallization from the suitable solvent.

Conversion of the Amine Salts 4 and 4' into Free Amines; General Procedure:

A mixture of the amine salt **4** or **4'** (0.05 mol), $KHCO_3$ (10.0 g, 0.1 mol), K_2CO_3 (11.0 g, 0.08 mol), Bu_4NBr (1.61 g, 0.005 mol), and CH_2Cl_2 (100 mL) was stirred vigorously at 20–25 °C for 4 h. The suspension was then filtered and the filtrate was evaporated under reduced pressure to give the amine contaminated only with Bu_4NBr in quantitative yield. Analytically pure sample could be obtained by distillation.

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