

One-Pot Transformation of Alkyl Bromides into Primary Amines via the Staudinger Reaction

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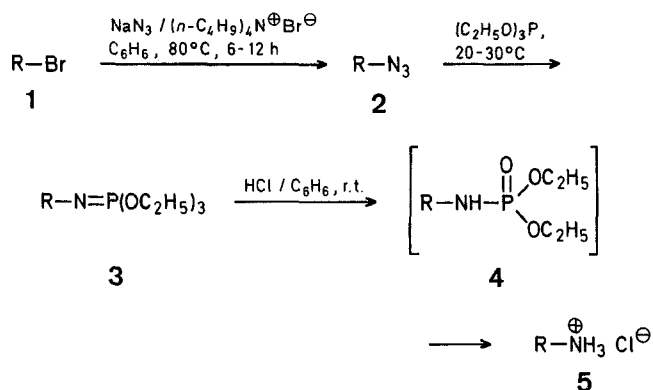
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Among the various synthetic methods leading to primary amines the reduction of azides plays an important and significant role. Classical reduction procedures, mainly based on the use of lithium aluminium hydride or catalytic hydrogenation¹, have been recently supplemented by several new reagents² and techniques³ including phase-transfer catalysis⁴.

It is well documented that triphenylphosphinimines, conveniently accessible by the Staudinger reaction⁵ between triphenylphosphine and organic azides, can be easily hydrolyzed to the corresponding primary amines⁶. In spite of the synthetic potential of this approach, the reduction of azides via phosphinimines has been reported only occasionally⁷ and was recommended as a general chemoselective method only recently⁸. The phosphite-azide coupling method⁹, representing the less popular variant of Staudinger reaction, was so far applied only for the preparation of monomethylanilines of high purity from the respective phenyl azides¹⁰ and for transforming some 5'-azidonucleosides into the corresponding amines¹¹.

The reduction with trialkyl phosphites seems to be the method of choice for transforming organic azides into primary amines. This assumption is based on the recognized relatively high reactivity of trialkyl phosphites towards azides⁹ and the easy deprotection of the phosphazo compounds produced by Staudinger reaction⁵. The use of more expensive and less reactive triphenylphosphine is not justified from the economic point of view unless some special demands have to be met. Since alkyl azides can be readily obtained from the corresponding bromides by nucleophilic displacement under phase-transfer catalysis conditions¹², it seemed feasible to use them in crude form in solution for the reaction with trialkyl phosphites. Such system avoids cumbersome and hazardous separation and purification of high-

boiling azides. With this idea in mind we have elaborated a one-pot procedure by which primary and secondary alkyl bromides can be effectively transformed into primary amines without separating any intermediately formed compounds. The procedure constitutes of: (a) – azidation of an alkyl bromide (**1**) under solid-liquid PTC conditions (vide infra); (b) – the Staudinger reaction of crude azide (**2**) with triethyl phosphite; (c) – two-step deprotection of the iminophosphorane (**3**) by means of hydrogen chloride at room temperature.



It was reasonable to assume that the yield of the azidation step is crucial for the final result of the whole transformation. So, we decided to optimize the reported reaction conditions by changing the liquid-liquid PTC system to the solid-liquid one. With respect to the literature methods^{4,12} this approach shows the novelty of using an anhydrous system consisting of solid sodium azide suspended in benzene (Methods A and B) or benzene/dimethylformamide (1:1) (Method C) in the presence of 5–10 mol% of tetrabutylammonium bromide as catalyst. When the displacement is carried out at 80 °C for 6 h (primary bromides) or 12 h (secondary bromides) the con-

version to the corresponding azides (**2**) is generally higher than by using a liquid-liquid PTC system according to the reported procedure^{4,12}. It is probably not the case only for some alicyclic bromides when better yields of the respective amine hydrochlorides (**5**) are obtained by employing for azidation the liquid-liquid PTC system (Method D). After removal of inorganic salts by filtration the solutions of azides (**2**) are used directly for further transformation, the temperature of the slightly exothermic reaction with triethyl phosphite being kept below 30 °C. Crude iminophosphoranes (**3**) treated in solution with gaseous hydrogen chloride at room temperature undergo stepwise degradation via diethyl *N*-alkylphosphoroamidates (**4**) to give the corresponding amine hydrochlorides (**5**) which can be routinely isolated (Methods A, C and D) in good yield by precipitation with ether. Low yields obtained for some secondary bromides are evidently due to high solubility of the respective amine hydrochlorides (**5**) in solutions obtained after degradation of **3**. They can be, however, effectively improved by isolation and purification of the free amines and their subsequent treatment with gaseous hydrogen chloride in ether (Method B). Overall yields and melting points of amine hydrochlorides (**5**), which are compiled in the Table, illustrate the scope and preparative utility of the procedure.

The reported procedure offers a simple and inexpensive alternative to the Gabriel synthesis. It deserves recommendation especially for such cases when nucleophilic displacement is accompanied by extensive elimination (compounds **5c** and **5m**) and/or when drastic deprotection conditions should be avoided (compound **5q**).

Amine Hydrochlorides (**5**); General Procedures:

Method A: A mixture of sodium azide (6.5 g, 0.1 mol), the alkyl bromide **1** (0.05 mol), tetrabutylammonium bromide (5–10 mol%, Table), and benzene (30 ml) is refluxed with efficient stirring for

Table. Amine Hydrochlorides **5a–q** prepared

R	Method	Catalyst [mol %]	Duration [h]	Overall yield [%]	m. p. [°C]	
					found ^a	reported
a <i>n</i> -C ₄ H ₉	A	5	6	73	214–214.5°	195 ¹³
b <i>n</i> -C ₆ H ₁₃	C	5	6	60	219–220° (dec)	219 ¹⁴
c C ₆ H ₅ –CH ₂ –CH ₂ –	A	5	6	77.5	219–221°	217–218 ¹⁵
d C ₆ H ₅ –CH ₂ –CH ₂ –CH ₂ –	A	5	6	69	218–219°	218 ¹⁶
e –(CH ₂) ₅ –	A	10	6	80	252–256°	242–243 ¹⁷
f <i>t</i> -C ₄ H ₉ –CH ₂ –	C	10	24	0	–	–
g HC≡C–CH ₂ –	C ^b	5	8	80	177–180°	174–175 ¹⁸
h C ₆ H ₅ –CH=CH–CH ₂ –	A	5	6	60	235–238° (dec)	235–237° (dec) ¹⁸
i H ₂ C=CH–CH ₂ –CH ₂ –	C	5	6	80	178–180° ^c	–
j <i>s</i> -C ₄ H ₉	A	10	6	64.5	146–147°	144–145 ¹⁹
k 2-pentyl	B	10	12	51	153–154°	147.5–148 ²⁰
l 3-hexyl	B	10	12	60	229–230°	227–229 ²¹
m <i>c</i> -C ₆ H ₁₁	D ^f	10	12	51	206–207°	206–207.5 ²²
n <i>c</i> -C ₅ H ₉	D	10	6	79	207–208° ^d	–
o 2-octyl	B	10	12	54	– ^e	–
p <i>i</i> -C ₄ H ₉	A	5	14	35	168–171°	177–178 ²³
q H ₃ C–CH(COOC ₂ H ₅)–	A	5	6	68	65–68°	64–68 ²⁴

^a After recrystallisation from ethanol/ether.

^b The azidation was carried out at 40 °C.

^c No m. p. given.

C₄H₁₀ClN
(107.5) calc. C 44.65 H 9.30 N 13.02
 found 44.75 9.20 12.83.

^d No m. p. given.

C₅H₁₂ClN calc. C 49.38 H 9.87 N 11.52
(121.5) found 49.35 9.80 11.55.

^e Isolated as free amine; n_D^{20} : 1.4248. For
C₈H₁₉N calc. C 74.42 H 14.73 N 10.85
(129.3) found 74.40 14.55 11.18.

^f Cyclohexylamine hydrochloride was obtained in 33% and 25% yield by Methods A and C, respectively.

6–12 h (Table). The product is cooled to room temperature and filtered by suction. The precipitate of inorganic salts is washed with benzene (2 × 10 ml). The filtrate is washed with water (2 × 20 ml) and dried with magnesium sulfate. Triethyl phosphite (8.3 g, 0.05 mol) is added dropwise with stirring to the solution of organic azide **2** thus obtained. The temperature of the slightly exothermic reaction is kept below 30°C by occasional cooling. The solution is left overnight at room temperature. It is then saturated with dry hydrogen chloride for 2 h at room temperature and again allowed to stand overnight. The mixture is evaporated under reduced pressure. Dry ether (30 ml) is added to the residue and the mixture is refrigerated for 24 h. The precipitated amine hydrochloride **5** is isolated by suction, washed with ether (2 × 15 ml), and dried in vacuo over sodium hydroxide. Analytically pure samples are obtained by dissolving crude **5** in a small amount of hot ethanol, filtration of the solution, and precipitation of pure **5** with an excess of ether.

Method B: The reaction and work-up are carried out as described for Method A. The residue obtained after degradation and evaporation of solvent is mixed with water (60 ml) and steam distilled to remove the unreacted **1**. An excess of solid sodium hydroxide is added to the residue and the distillation is repeated. Solid sodium chloride and sodium hydroxide are added to the distillate and the free amine is extracted with ether (4 × 25 ml). The extract is dried with sodium hydroxide, filtered, and saturated with gaseous hydrogen chloride. The precipitated amine hydrochloride **5** is filtered by suction, washed with ether, and dried in vacuo over sodium hydroxide.

Method C: The azidation of **1** is carried out at 80°C as described for Method A using benzene (15 ml) and dimethylformamide (15 ml) as solvent instead of benzene. The product is cooled to room temperature and poured into water (150 ml). The organic phase is separated. The water layer is extracted with benzene (2 × 10 ml) and the extracts are combined with the organic phase. The solution of **2** is dried with magnesium sulfate and used for the reaction with triethyl phosphite. This reaction and work-up are carried out as described for Method A.

Method D: A mixture of sodium azide (6.5 g, 0.1 mol), **1** (0.05 mol), tetrabutylammonium bromide (1.6 g, 0.005 mol), and water (20 ml) is refluxed with stirring for 6–12 h (Table). The product is cooled to room temperature and the organic phase is separated. The water layer is extracted with ether (2 × 10 ml) and the extracts are combined with the organic phase. The resultant solution of **2** is dried with magnesium sulfate and used directly for the reaction with triethyl phosphite. This reaction and work-up are carried out as described for Method A.

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