A Simple, One-Pot Transformation of *t*-Alkyl Chlorides Into (*t*-Alkyl)amines

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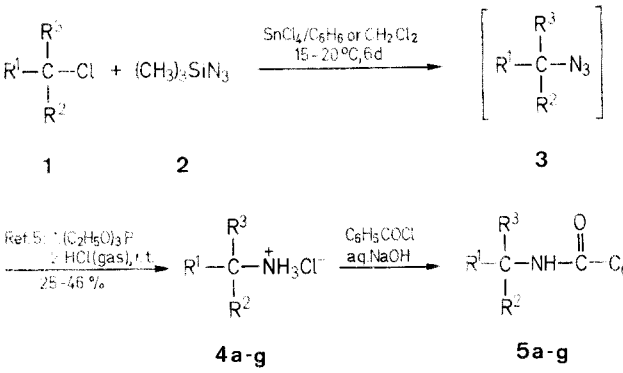
t-Alkyl chlorides are readily azidated using trimethylsilyl azide in the presence of tin tetrachloride. Tertiary azides can be transformed without isolation into the corresponding (*t*-alkyl)amine hydrochlorides in a one-pot procedure employing the Staudinger reaction.

Several primary amines in which an amino group is linked directly with a tertiary carbon atom deserve attention as important starting materials for the pharmaceutical industry. Despite considerable interest in the preparation of these compounds, they are still not easily accessible at present. Two general approaches – the Ritter reaction[1] and the Haaf reaction[2] – suffer from several inconveniences and do not secure high yields. Specific procedures, like the synthesis of *t*-butylamine by the alkaline hydrolysis of *t*-butylurea[3] or hydrogenolysis of 2,2-dimethylethyleneimine,[4] are tedious, not very efficient (overall yields of *t*-butylamine are 24% and 38%, respectively), and not adaptable for the preparation of higher analogues. No direct amination of *t*-alkyl halides was so far possible because, due to steric hindrance and/or prevailing elimination, these compounds fail to undergo nucleophilic substitution either by the S_N2 or the S_N1 mechanism.

Recently, we have devised a simple, one-pot procedure for the transformation of primary and secondary alkyl bromides into the corresponding amine hydrochlorides.[5] The crucial step of this method is the azidation of the respective halide occurring *via* nucleophilic displacement. Looking for an effective azidation of *t*-alkyl chlorides **1** we reasoned that the reaction of these compounds with trimethylsilyl azide **(2)** yielding the corresponding tertiary azide **3** and trimethylsilyl chloride should be possible, provided that the use of a suitable catalyst would make the process kinetically feasible. Such procedure employing titanium tetrachloride as catalyst has been proposed for effective azidation of adamantyl chloride,[6] but its general applicability for other *t*-alkyl chlorides, which are susceptible to competing elimination, was never proved. It appeared reasonable to try tin tetrachloride, the catalyst which has been successfully applied recently for the cyanotrimethylsilane–promoted cyanation of *t*-alkyl chlorides.[7] Optimizing the reaction conditions, we found that *t*-alkyl azides **3** are formed in reasonable yields when the solutions of *t*-alkyl chlorides **1** in benzene (Method A) or dichloromethane (Method B) are treated with trimethylsilyl azide **(2)** in 20% excess. Catalytic amounts (25 mol-%) of tin tetrachloride mediate this transformation effectively. Concurrent elimination is hampered most successfully when the reaction is carried out at 15–20°C for 6 days. The use of higher temperatures and/or different catalysts, i.e. ferric chloride, zinc chloride, boron trifluoride etherate or titanium tetrachloride gives inferior results. The resulting solutions of tertiary azides **3** can be transformed in workable overall yields into (*t*-alkyl)amine hydrochlorides **4** *via* the previously described one-pot procedure utilizing the Staudinger reaction.[4] The results presented in Table 1 illustrate the synthetic scope of the procedure. Simple *t*-alkyl chlorides **1** devoid of additional functionalities (entries 1–7) react readily. *t*-Alkyl chlorides **1** with considerable bulk at the reaction center (entries 8–10) cannot be, however, transformed into the corresponding amine hydrochlorides **4** by this method. In majority of cases crude (*t*-alkyl)amine hydrochlorides **4** tend to decompose on heating in ethanolic solution. Therefore they were purified by dissolving in cold ethanol, filtration of the resulting solution, and reprecipitation with ether. Due to serious analytical difficulties, the amine hydrochlorides **4** were converted into the corresponding *t*-alkylbenzamides **5** by standard treatment with benzoyl chloride



4, 5	R^1	R^2	R^3
a	CH_3	CH_3	CH_3
b	C_2H_5	CH_3	CH_3
c	n-C_3H_7	CH_3	CH_3
d	n-C_4H_9	CH_3	CH_3
e	$-(CH_2)_5-$		CH_3
f	$-(CH_2)_4-$		CH_3
g	$C_6H_5CH_2$	CH_3	CH_3
h	C_2H_5	C_2H_5	CH_3
i	$-(CH_2)_5-$		n-C_3H_7
j	i-C_4H_9	i-C_4H_9	C_2H_5

Table 1. (*t*-Alkyl)amine Hydrochlorides **4** Prepared

Entry	Product	Method	Yield (%)[a]	m.p. (°C)		*t*-Alkylbenzamides **5**	
				found	reported	m.p. (°C)	Molecular Formula[b] or Lit. m.p. (°C)
1	**4a**	A	46	295–300	310 (cor.)[10]	135–137	134–135[10]
		B	40				
2	**4b**	A	42	193–197	–	78–80	78–79[11]
		B	19				
3	**4c**	A	32	> 300	–	83–84	$C_{13}H_{19}NO$ (205.3)
		B	9				
4	**4d**	B	25	217	–	84–85.5	$C_{14}H_{21}NO$ (219.3)
5	**4e**	A	37	270–274 (dec)	256–257[12]	100–101	101–101.5[12]
		B	21				
6	**4f**	A	27	252 (dec)	262–263[13]	122–123	$C_{13}H_{17}NO$ (203.3)
		B	30				
7	**4g**	B	36	198–199	198–198.5[10]	–	–
8	**4h**	A, B	0	–	–	–	–
9	**4i**	A, B	0	–	–	–	–
10	**4j**	A, B	0	–	–	–	–

[a] Overall yield of isolated product.

[b] Satisfactory microanalyses obtained: C, H, N ±0.4

Table 2. Spectroscopic Data of (*t*-Alkyl)amine Hydrochlorides **4** and *t*-Alkylbenzamides **5**

Compound	IR (KBr)[a] ν(cm^{-1})	^{1}H-NMR (D_2O, TMS_{ext})[b] δ(ppm)
4a	2960 ($\overset{+}{N}H_3$); 2890 (CH); 2700, 2600, 2500, 2070; 1610, 1510 (NH); 1400, 1370 (CH); 1300, 1215 (CN)	1.63 (s, 9H)
4b	2980 ($\overset{+}{N}H_3$); 2600, 2040; 1600, 1505 (NH); 1464; 1400, 1380 (CH); 1275; 1195 (CN); 1045	1.38 (t, 3H, J = 7.0 Hz); 1.75 (s, 6H); 2.09 (qt, 2H, J = 7.0 Hz)
4c	2970 ($\overset{+}{N}H_3$); 1600, 1515 (NH); 1405, 1190, 1040	1.39 (t, 3H, J = 7.0 Hz); 1.80 (s, 6H); 1.62–2.32 (m, 4H)
4d	2960 ($\overset{+}{N}H_3$); 2080, 1750; 1610, 1515 (NH); 1460, 1395, 1340 (CH); 1300, 1175	1.15–2.2 (m, 9H); 1.8 (s, 6H)
4e	2900 ($\overset{+}{N}H_3$); 2550, 2060; 1600, 1505 (NH); 1450, 1400; 1370 (CH); 1150	1.81 (s, 3H); 1.70–2.30 (m, 10H)
4f	2950 ($\overset{+}{N}H_3$); 2040, 1750, 1620, 1600, 1500, 1450, 1380; 1340 (CH); 1210, 1045, 980	1.60 (s, 3H); 1.97 (bs, 8H)
4g	2960 ($\overset{+}{N}H_3$); 2660, 2560, 2500, 2070; 1610, 1505 (NH); 1490, 1455, 1390, 1370 (CH); 1280, 1175, 1160, 1085, 1050, 1025, 990	1.72 (s, 6H); 3.01–3.15 (m, 5H); 3.30 (s, 2H)
5b	3260 (NH), 2960 (CH); 1630, 1540 (C=O); 1455, 1370 (CH); 1325, 1280, 1190	0.76 (t, 3H, J = 7.5 Hz); 1.29 (s, 6H); 1.75 (qt, 2H, J = 7.5 Hz); 6.50 (s, 1H); 7.00–7.75 (m, 5H)
5c	3280 (NH), 2960 (CH); 1640, 1545 (C=O); 1470, 1450, 1330, 1305, 1250, 1190	0.80 (t, 3H, J = 7.0 Hz); 1.30 (s, 6H); 1.02–1.88 (m, 4H); 6.38 (s, 1H); 7.00–7.75 (m, 5H)
5d	3320 (NH); 3050, 2940, 2920; 2860 (CH); 1630 (C=O); 1595, 1575; 1540 (C=O); 1490, 1465, 1450, 1435, 1380, 1375, 1360, 1325, 1315, 1295, 1290, 1230, 1180, 1095, 1070, 1020, 995, 930, 890, 870	0.62–1.87 (m, 9H); 1.3 (s, 6H); 6.55 (bs, 1H); 6.99–7.72 (m, 5H)
5e	3330 (NH); 2930; 2850 (CH); 1460 and 1535 (C=O); 1490, 1450, 1355, 1335, 1310, 1285, 1180, 930, 860	1.28 (s, 3H); 1.05–2.20 (m, 10H); 5.85 (s, 1H); 7.00–7.70 (m, 5H)
5f	3310 (NH); 2940, 2870 (CH); 1630 (C=O); 1575; 1530 (C=O); 1490, 1450, 1385, 1370, 1325, 1310, 1295, 1240, 1120, 1075, 1045, 1025, 1000, 970, 925, 875	1.25–2.29 (m, 8H); 1.42 (s, 3H); 5.96 (bs, 1H); 7.15–7.75 (m, 5H)

[a] The IR spectra were recorded on a Specord 71IR (C. Zeiss) Spectrophotometer.

[b] The ^{1}H-NMR spectra were measured at 80 MHz with a Tesla BS 487C spectrometer.

and sodium hydroxide solution. Spectroscopic data (Table 2) of **4** and **5** were in full agreement with the anticipated structures.

The reported procedure offers a convenient and useful alternative to the other synthetic routes to (*t*-alkyl)amines disclosed in the literature.

t-Alkyl chlorides are prepared conventionally[8] by vigorous stirring the corresponding alcohol (0.1 mol) with concentrated hydrochloric acid (24.7 ml, 0.3 mol) at room temperature for 20 min. The reaction time has to be prolonged to 45 min. for 1-propylcyclohexanol and to 3 h for 2-methyl-3-phenyl-2-propanol. Crude *t*-alkyl chlorides are separated, dried with potassium carbonate and calcium chloride, and distilled over solid potassium carbonate. The purity is controlled by IR and ^{1}H-NMR spectroscopy. Yields: 35–75%.

(*t*-Alkyl)amine Hydrochlorides 4; General Procedure:

Method A: A solution of tin tetrachloride (3.25 g, 0.0125 mol) in benzene (10 ml) is added dropwise at room temperature to a mixture of *t*-alkyl chloride (**1**; 0.05 mol), trimethylsilyl azide[9] (**2**; 6.9 g, 0.06 mol), and benzene (30 ml), and the mixture is left for 6 days at 15–20 °C. It is then poured into water (100 ml); the organic layer is separated, washed with 10% sodium hydrogen carbonate solution until neutral (2 × 30 ml), and dried with magnesium sulfate. Drying agent is removed

by filtration, triethyl phosphite (8.3 g, 0.05 mol) is added to the filtrate, and 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 solvent is evaporated under reduced pressure. Dry ether (40 ml) is added to the residue and the mixture is refrigerated for 24 h. The precipitated (*t*-alkyl)amine hydrochloride **4** is filtered, washed with ether (2 × 15 ml), and dried *in vacuo* over sodium hydroxide.

The second crop of **4** separates after refrigeration of the mother liquor for 1–2 weeks. Analytically pure samples of **4** are obtained by dissolving crude **4** in a minimum amount of cold ethanol, filtration of the solution, and reprecipitation of pure **4** with an excess of dry ether.

Method B: The reaction is performed as for Method A, using dichloromethane as solvent instead of benzene.

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