A Simple Conversion of Alcohols into Amines

Emmanuel Fabiano, Bernard T. Golding,* Majid M. Sadeghi

Department of Organic Chemistry, Bedson Building, The University, Newcastle upon Tyne, NE1 7RU, United Kingdom

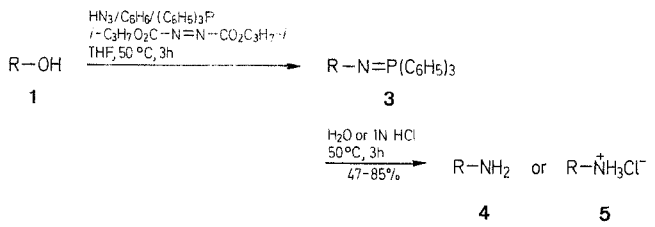
In a convenient one-pot sequence, treatment of alcohols and α-hydroxyesters with hydrazoic acid, di-isopropyl azodicarboxylate and an excess of triphenylphosphine in tetrahydrofuran, followed by addition of water or aqueous acid, yields amines or amino-acid esters in moderate to good overall yields.

Various methods[1-4] have been used to convert hydroxy groups into amino groups in the synthesis of amines and amino acids. A popular method[3] first converts the alcohol into an alkyl halide or sulfonate, which is then reacted with a metal azide to give an alkyl azide. This is reduced to the amine by one of a variety of reagents.[5] In most cases the intermediates have to be isolated and this means that extra time is taken, and all the problems associated with handling toxic and potentially explosive (alkyl azide) intermediates are encountered. Recently a convenient one-pot transformation of alkyl bromides into primary amines *via* the Staudinger reaction[6] was described, which avoids the problem of isolating the intermediate alkyl azide.[7]

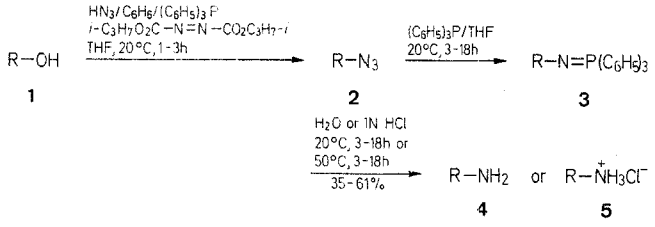
We have devised a one-pot method for converting alcohols into amines by the judicious combination of three known reactions. Thus, the Mitsunobu reaction[2] to convert an alcohol into an azide[8] as shown in the Scheme (**1** → **2**) is followed by an *in situ* Staudinger reaction[6] of the azide with triphenylphosphine to produce, after loss of nitrogen, an iminophosphorane intermediate **3**. This is hydrolysed by addition of an excess of water or dilute hydrochloric acid to give, after work-up, the free amine **4** or its hydrochloride **5**. The reactions are done at room temperature or at 50 °C depending either on the reactivity of the substrate, or its stability, or that of the azide formed. The representative examples in the Table are of primary and secondary alcohols. As expected, an attempt to convert *t*-butyl alcohol into the corresponding amine failed.

Under the conditions of Method C, methyl (*S*)-mandelate gave a racemic azide, and hence a racemic amino acid hydrochloride. On the other hand, ethyl (*S*)-lactate gave optically pure (*R*)-

Method A



Method B and C



alanine, and (*S*)-octan-2-ol gave (*R*)-2-amino-octane. Inversion of configuration in the Mitsunobu reaction has previously been established.[2] The method described[7] for converting bromides into amines presumably involves an overall inversion of configuration, but this was not confirmed. The racemisation of the azide from methyl (*S*)-mandelate probably occurs *via* a stabilised carbanion intermediate, formed by loss of the α-hydrogen. It was found that the pure isolated azide undergoes base-catalysed exchange of the α-hydrogen for deuterium when incubated in [$^2H_4$]methanol. Thus, a 0.52 molar solution of methyl 2-azido-2-phenylacetate in [$^2H_4$]methanol containing 0.2 molar of 1,4-diazabicyclo[2.2.2]octane showed exchange of the α-hydrogen ($\tau_{\frac{1}{2}} \sim 45$ min. at 41 °C; monitoring by ^{1}H-NMR spectroscopy). Under similar conditions, optically pure ethyl (*S*)-2-azidopropionate did not show any deuterium exchange.

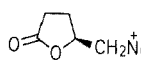
The alcohols used were commercial products except that for entry 3 which was prepared from (*S*)-methyloxirane by analogy to a literature procedure,[9] and for entry 11 which was made from (*S*)-glutamic acid as described.[10]

Amine 4 or Amine Hydrochloride 5; General Procedure:

Method A: To a solution of the alcohol (10 mmol) in tetrahydrofuran (5 ml) is added a 1 molar solution of hydrazoic acid in benzene[11] (12 ml) followed by a solution of di-isopropyl azodicarboxylate (2.22 g, 11 mmol) in tetrahydrofuran (5 ml). To the resulting mixture is added a solution of triphenylphosphine (5.77 g, 22 mmol) in tetrahydrofuran (30 ml) with stirring. The reaction is exothermic and the temperature of the solution (≥ 30 °C) depends on how fast the triphenylphosphine is added. After 1 h at room temperature the reaction mixture is heated at 50 °C for 3 h. Water (1 ml) is added and the temperature is maintained at 50 °C for another 3 h. The solvents are removed *in vacuo* and the residue is partitioned between dichloromethane (40 ml) and 1 normal hydrochloric acid (40 ml). The aqueous phase is extracted with more dichloromethane (3 × 40 ml). Removal of the water under reduced pressure (40 °C) gives the amine hydrochloride, which is recrystallized from a suitable solvent (e.g. methanol-ether). Alternatively, the aqueous phase is neutralised to pH 8 with a saturated aqueous solution of sodium hydrogen carbonate. Extraction with dichloromethane (at least 5 × 100 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* gives the pure amine.

Method B: To a solution of alcohol (10 mmol) in tetrahydrofuran (5 ml) is added a solution of hydrazoic acid in benzene[11] (12 ml) followed by a solution of triphenylphosphine (3.15 g, 12 mmol) in tetrahydrofuran (20 ml). To the mixture is added a solution of di-isopropyl azodicarboxylate (2.22 g, 11 mmol) in tetrahydrofuran (5 ml) with stirring. After 1–3 h a solution of triphenylphosphine (2.62 g, 10 mmol) in tetrahydrofuran (10 ml) is added and the solution is stirred for 3–18 h at room tempera-

Table. Amines Prepared

Entry[a]	Product	Method[b]	Yield[c] (%)	Data for Characterisation[d]	
				Found	Reported
1	$C_6H_5CH_2\overset{+}{N}H_3\ Cl^-$	A	68	m.p. 261–262 °C (dec)	260 °C (dec)[13]
2	*rac.*-$CH_3(CH_2)_5CH(\overset{+}{N}H_3)CH_3\ Cl^-$	A	82	m.p. 89–90 °C	91–92 °C[14]
3	(*R*)-$CH_3(CH_2)_5CH(\overset{+}{N}H_3)CH_3\ Cl^-$	A	58	$[\alpha]_D^{23}$ + 3.9° (*c* = 9, H_2O)	−3.9° for (*S*)-isomer[15]
4	$C_2H_5(OCH_2CH_2)_2NH_2$	A	47	b.p. 68 °C/9 torr	65 °C/7 torr[16]
5	$H_2NCH_2C{\equiv}CCH_2NH_2$	A[e]	85	m.p. 37–38 °C	42–46 °C[17]
6	$HOCH(CH_2\overset{+}{N}H_3)_2\ 2Cl^-$	A[e]	56	m.p. 176–178 °C	175–177 °C[18]
7	*rac.*-$C_6H_5CH(\overset{+}{N}H_3)COOCH_3\ Cl^-$	C	61	$[\alpha]_D^{22}$ 0° (*c* = 0.1, H_2O)	−121° for (*R*)-isomer[19]
8	(*R*)-$CH_3CH(\overset{+}{N}H_3)COOH\ Cl^-$	C	45	$[\alpha]_D^{24}$ −10.2° (*c* = 8.3, H_2O)	−10.3°[20]
9	(*S*)-$H_3\overset{+}{N}CH_2CH(NHZ)COO^-$	C[f]	41	$[\alpha]_D^{25}$ −8.2° (*c* = 0.39, 1M NaOH)	−8.0°[21]
10	(*S*)-$H_3\overset{+}{N}CH_2CH(NHZ)COOCH_3\ Cl^-$	B	35	$[\alpha]_D^{21}$ −43.1° (*c* = 2.5, CH_3OH)	−43°[21]
11		C	40	$[\alpha]_D^{22}$ +80° (*c* = 0.95, CH_3OH); m.p. 172–174 °C	–[d]
12	(*Z*)-$H_3\overset{+}{N}CH_2CH{=}CHCH_2\overset{+}{N}H_3\ 2Cl^-$	A[e]	69	m.p. of *N*,*N*′-dibenzoyl derivative: 177.5–178.5 °C	178.5–179.5 °C[22]

[a] For entries 1–5, 7 and 10–12 the starting material was the corresponding alcohol or diol; for entries 6, 8 and 9 the following were used: 2-*O*-*t*-butyldimethylsilylglycerol[12] (entry 6), ethyl (*S*)-lactate (entry 8) and (*S*)-*N*-*Z*-serine methyl ester[21] (*Z* = benzyloxycarbonyl) (entry 9). Protecting groups were hydrolysed under the reaction conditions for entries 6 and 9, and by subsequent acid treatment for entry 8.

[b] Generally, Methods A and C gave higher yields than Method B.

[c] The values given are for pure isolated compounds with the exception of entry 11, which was estimated in a crude product that also contained triphenylphosphine oxide (yield of analytically pure product from entry 11 was 16%).

[d] All compounds gave spectroscopic data in accord with their assigned structures. Analysis for entry 11:

		C	H	N
$C_5H_{10}ClNO_2$ (151.5)	calc.	39.62	6.65	9.24
	found	39.51	6.57	9.11

[e] Twice the given quantities of reagents were used.

[f] Ether was used as solvent.

ture. 1 Normal hydrochloric acid (15 ml) is added and the reaction mixture is stirred for 3–18 h at room temperature, after which the tetrahydrofuran is removed *in vacuo* and the required compound is isolated as in Method A.

Method C: As for B, except that after the addition of water or hydrochloric acid the reaction is heated at 50°C for 3–18 h.

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