Selective Reduction of Azides. Improved Preparation of α,α-Disubstituted Benzylamines

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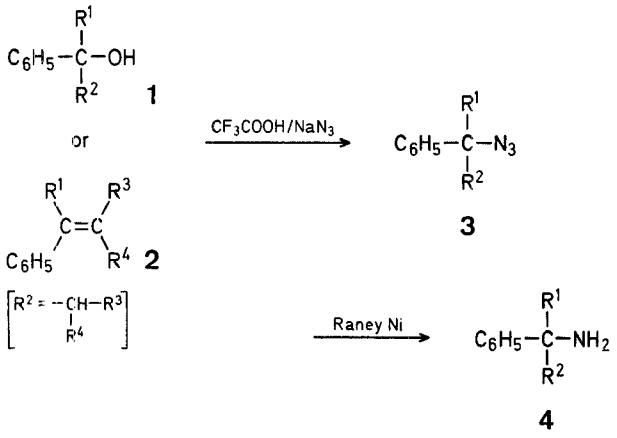
1-Phenylcycloalkylamines are compounds of interest as potential drugs or starting materials for physiologically active compounds of the phencyclidine series[1,2,3].

The compounds were prepared usually: (a) from 1-phenylcycloalkanols or -cycloalkenes and an organic nitrile in sulfuric acid (Ritter reaction[4]) with subsequent hydrolysis of the acylamide; or (b) by the Hofmann or Curtius rearrangement of 1-phenylcycloalkylcarboxamides or -azides[5].

Method (a) gives poor results with cycloalkyl derivatives except cyclohexyl, whereas Method (b) requires relatively expensive starting materials.

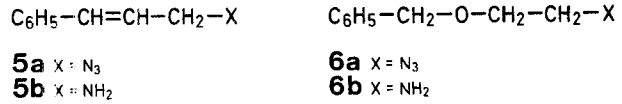
Tertiary alcohols or their corresponding olefins can be converted to azides, e.g. α-methylbenzhydrylazide was prepared from α-methylbenzhydrol or 1,1-diphenylethene, and sulfuric acid/sodium azide[6,7]. It has been reported recently that 1-phenylcyclohexanol and its 2-methyl derivative gave, with sodium azide and trichloroacetic acid, the corresponding azides[3]. Their reduction yielded the desired amines[8].

We have found that the use of trifluoroacetic acid and sodium azide in this reaction permits the preparation of tertiary azides in high yield.



The azides could be simply reduced with active Raney nickel in an open vessel to afford a satisfactory yield of the tertiary amines. The catalyst contains sufficient hydrogen required for the reduction. The present method is general, and particularly suitable for compounds that fail to give amides in the Ritter reaction.

It was of interest to check whether this reduction is applicable in the presence of other functional groups. Corey et al. found that double bonds or benzyloxy groups were unaffected during reduction of azides in ethanol with hydrogen and a Lindlar catalyst at atmospheric pressure[9]. Consequently, cinnamyl azide (**5a**) and 2-benzyloxyethyl azide (**6a**) were prepared and selectively reduced to the corresponding amines, **5b** and **6b**.



5a X = N_3
5b X = NH_2

6a X = N_3
6b X = NH_2

The required 1-phenylcycloalkanols or 1-phenylcycloalkenes are either expensive, or not available commercially. They were prepared from phenylmagnesium bromide, and an appropriate ketone, and added to the mixture of trifluoroacetic acid/sodium azide, after decomposition of the Grignard complex, and removal of the solvent.

Preparation of 2-Azido-2-phenylpropane (3; $R^1 = R^2 = CH_3$):
Freshly distilled α-methylstyrene (Fluka; 23.6 g, 0.2 mol), and sodium azide (26 g) in chloroform (200 ml) are cooled to −5°. A solution of trifluoroacetic acid (80 ml) in chloroform (200 ml)

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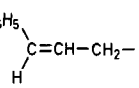
Table. Preparation of Azides ($R—N_3$) and Amines ($R—NH_2$)

R	Azide[a] No.	Yield [%]	b.p./torr (Lit. b.p.)	Amine	Yield [%]	b.p./torr (Lit. b.p.)	n_D (temp.)	Molecular formula[b]	^{1}H-N.M.R. (CCl_4) δ [ppm]
	**3a**	–	139–140°/38	**4a**	40[c]	128–130°/20 (112–114°/9)[5]	1.5470 (15°)	$C_{11}H_{15}N$ (161.2)	7.1 (m, 5 H_{arom}); 1.8 (s, 8H); 1.1 (s, NH_2)
	**3b**[3]	–	–	**4b**	38[c]	115–120°/5 (106–107°/1.7)[11]	1.5484 (18°)	$C_{12}H_{17}N$ (175.3)	7.3 (m, 5 H_{arom}); 1.63 (s, 10H); 1.18 (s, NH_2)
	**3c**	79	90–91°/0.25	**4c**	66[d]	150–153°/23 (143–145°/20)[12]	1.5420 (18°)	$C_{13}H_{19}N$ (189.3)	7.3 (m, 5 H_{arom}); 1.58 (s, 9H); 1.3 (s, NH_2); 0.67 (q, 3H, CH_3)
	**3d**	–	153–155°/23	**4d**	45[c]	164°/25 (113°/1)[12]	1.5486 (15°)	$C_{13}H_{19}N$ (189.3)	7.1 (m, 5 H_{arom}); 1.58 (s, 12H); 1.28 (s, NH_2)
	**3e**	–	150–155°/25	**4e**	51[c,e]	163–165°/28	1.5590 (18°)	$C_{13}H_{17}N$ (187.3)	7.05 (m, 5 H_{arom}); 2.3–1.0 + 1.1 (12H, aliphatic + NH_2)
	**5a**	83	90–92°/1	**5b**	60[f]	129–130°/30 (235–237°/775)[14]	1.5825 (18°)	$C_9H_{11}N$ (133.2)	7.06 (s, 5 H_{arom}); 6.14 (m, 2H, —CH=CH—), 3.20 (d, 2H, CH_2); 0.98 (s, NH_2)
$C_6H_5—CH_2—O—CH_2—CH_2—$	**6a**[g]	93	139–141°/22	**6b**	73[h]	134–136°/31 (110–112°/7)[13]	1.5220 (17°)	$C_9H_{13}NO$ (151.2)	7.04 (s, 5 H_{arom}); 4.30 (s, 2H, $C_6H_5—CH_2$); 3.24 (t, 2H, OCH_2CH_2); 2.65 (t, 2H, CH_2NH_2); 1.43 (s, NH_2)

[a] Not isolated in the pure state, contaminated with corresponding 1-phenylalkene; all azides display a strong absorption in the I.R. spectra at 2080–2140 cm^{-1}.

[b] All amines or their hydrochlorides gave satisfactory microanalyses (C ±0.28%, H ±0.22%, Cl ±0.37, N ±0.14%).

[c] Based on ketone.

[d] Based on 1-phenylalkanol.

[e] Hydrochloride, subl. p. >250°.

[f] Based on azide.

[g] Prepared analogously to cinnamyl azide.

[h] Hydrochloride, m.p. 139–140°.

is added at such a rate that the temperature does not exceed 0°. After the addition, the cooling bath is removed, the mixture is stirred for 5–6 h, and left overnight at ambient temperature. An excess of concentrated ammonia is added to the mixture, the organic layer is separated, washed with water, dried with magnesium sulfate, and concentrated; crude yield: 50.5 g (92%). A sample is distilled at 106°/22 torr; $n_D^{16} = 1.5222$.

I.R. (neat): $\nu_{max} = 2095\ cm^{-1}$ (N_3).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.12$ (5H, arom); 1.54 ppm (6H, CH_3).

T.L.C. (silica, petroleum ether) did not reveal any impurities.

Other azides (see Table) contained the corresponding olefins as impurities.

Preparation of Cinnamyl azide (5a):

Sodium azide (38 g) in water (80 ml) is added to a solution of cinnamyl chloride (46 g) in dimethylformamide (150 ml). The temperature of the mixture rises from 20° to 45°. After stirring for 16 h at room temperature, water is added and the organic matter is extracted with benzene. The solvent is removed and the azide **5a** distilled; yield: 40.1 g (83%); b. 90–92°/1 torr; $n_D^{16} = 1.5760$.

I.R. (neat) $\nu_{max} = 2085\ cm^{-1}$ (s).

Preparation of α,α-Dimethylbenzylamine, (4; R^1, $R^2 = CH_3$):

The azide **3** (30 g) is dissolved in isopropanol (80 ml), placed in a 1 l beaker fitted with a stirrer, and heated at 70°. Activated Raney nickel (W. R. Grace Co., Chattanooga, Tenn.) is added in portions and stirred until no more foaming occurred (about 50–65 g are required). After 10 min more, the mixture is filtered *(Caution: The catalyst is pyrophoric)*, the solvent removed in a rotary evaporator, the residue dissolved in benzene (200 ml), and extracted with 20% sulfuric acid. The acid solution is separated, treated with charcoal, filtered, and the amine liberated by adding an excess of 20% sodium hydroxide. Extraction with benzene and concentration affords α,α-dimethylbenzylamine; yield: 18 g (72%); b.p. 100°/22 torr; $n_D^{16} = 1.5250$; Lit.[10], b.p. 72–73°/8 torr; $n_D^{25} = 1.5180$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 7.12$ (m, 5 H_{arom}); 1.38 (s, 6H, $2CH_3$); 1.22 ppm (s, 2H, NH_2).

Reductions of azides containing sensitive functional groups were carried out at room temperature. The results are summarized in Table.

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