

Synthesis of Tertiary 1-Naphthylamines via the Enamine

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ABSTRACT

A series of tertiary 1-naphthylamines has been synthesised by the reaction of 1-tetralone with secondary amines. The intermediate enamines are aromatised by treatment with palladium on charcoal in a high-boiling solvent, preferably limonene. This method is particularly successful with cyclic amines, leading to heterocycle-substituted naphthalenes, whilst the acyclic analogues are best obtained by alkylation of the anion derived from a secondary 1-naphthylamine. © 1998 Elsevier Science Ltd

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INTRODUCTION

N-Substituted naphthylamines have been widely used in the dyestuffs industry for over a century and yet there is no firmly established route to these compounds. Examples are scattered throughout the literature in which the most common synthetic approach consists of the direct *N*-alkylation of 1-naphthylamine (naphthalen-1-amine). *N,N*-Dimethyl-1-naphthylamine [1] as well as its diethyl [2] and diisobutyl [3] analogues have been made in moderate yields using the appropriate trialkylphosphate reagents and other methylating agents [1,4]. The 1-(1-naphthyl) derivatives of pyrrolidine and piperidine have been prepared in low yields from 1,4-dichlorobutane and 1,5-dichloropentane, respectively, utilising the nucleophilic property of 1-naphthylamine in ring formation reactions [5,6]. However, in addition to its apparently low reactivity, 1-naphthylamine is recognised as a highly toxic and carcinogenic compound [7] and its use in synthesis should be avoided.

The few alternative methods are rather tedious [8] or are low yielding [9,10], and we now describe a two-step synthesis to some tertiary 1-naphthylamines from 1-tetralone via enamines.

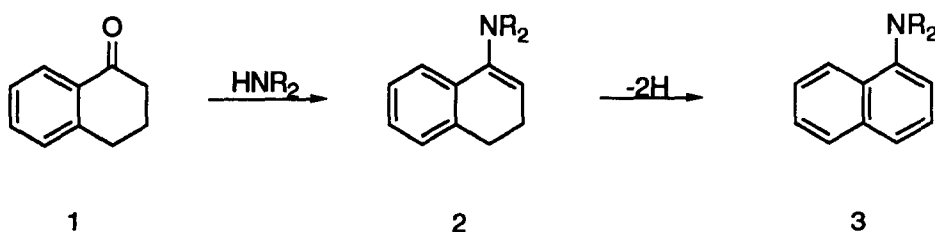
RESULTS AND DISCUSSION

The formation and reactions of enamines is well documented [11] and 1-(3,4-dihydro-1-naphthyl)pyrrolidine (2, $\text{NR}_2 = \text{pyrrolidino}$) has been prepared from 1-tetralone, pyrrolidine and a trace of 4-toluenesulfonic acid in refluxing benzene [12,13]. However, preliminary experiments confirmed the literature indications that this reaction is rather unpredictable, giving yields which vary from 45 to 79%.

A more reliable route to enamines uses titanium tetrachloride as catalyst [14] under conditions which have since been optimised [15]. Many enamines have been made in high yields using morpholine, pyrrolidine and dimethylamine as the secondary amine component [15,16].

This method gave high yields of the pyrrolidino and morpholino enamines of 1-tetralone (Structure 1, Table 1). However, yields of the piperidine analogue were lower, but were significantly improved when dry hexane was used as solvent. In the case of diethylamine, the enamine was obtained in a much lower yield, even in hexane, and the diisopropylamine analogue could not be

TABLE 1
Synthesis of Tertiary Naphthylamines from Tetralone



Amine	Enamine %	Naphthylamine % ^a
Pyrrolidine	85 ^b	55
Piperidine	62 ^c (45 ^b)	53
Morpholine	90 ^b	66
Diethylamine	25 ^c	20 ^d

^aBased on the enamine

^bin toluene

^cin hexane

^dsealed tube.

formed. This may be a result of the larger steric requirements of flexible, non-cyclic amines, although the basicity of the amine is also believed to play a critical role [15]. Optimisation studies were not undertaken, but it may be possible to improve the yields by varying the amine/TiCl₄ ratio. Other reagents, such as the recently proposed unsymmetrical tin(II) amides, may also offer advantages [17].

The enamines proved somewhat unstable in air and they were characterised mainly by their ¹H nmr spectra. Incorporation of the amine functionality was apparent from the multiplets at *ca* 3 ppm associated with the methylene units adjacent to the nitrogen and the upfield signals (1.6–2.2 ppm) for the remaining methylene moieties. In the case of the morpholino derivative, the O-CH₂ absorptions were at 3.86 ppm, whilst the methyl component of the diethylamino compound absorbed at *ca* 1 ppm as the expected triplet. In all of the examples, the alkenic proton appeared as a triplet at 5.19–5.28 ppm, whilst the two methylene groups of the 3,4-dihydronaphthalene unit showed as multiplets in the range 2.2–2.7 ppm. Further structural confirmation was provided by measurement of the *m/z* values of the molecular ions.

Many reagents can effect the aromatisation of hydroaromatic compounds by dehydrogenation, often at high temperatures [18]. A relevant example is the synthesis of 1-phenylnaphthalene from 1-phenyl-3,4-dihydronaphthalene [19], whilst the aromatisation of 1-(3,4-dihydro-2-naphthyl)pyrrolidine to the corresponding 2-naphthylamine has been reported using cyanogen bromide in dioxan [12]. However, in our hands, when applied to 1-(3,4-dihydro-1-naphthyl)pyrrolidine and its analogues, this method yielded only 2-bromo-1-tetralone.

Palladium on charcoal (Pd/C) was chosen for the dehydrogenation because it is easier and often safer to handle than are other dehydrogenating agents. Various solvents were used in an attempt to optimise the reaction. The high boiling diglyme and sulfolane both afforded the starting tetralone, whilst a low yield of the impure naphthylamine was obtained using diphenyl ether. In the much lower boiling solvent, cyclohexene, the reaction proceeded cleanly but very slowly and the unreacted enamine showed signs of decomposition with time. When limonene, a higher-boiling solvent which can act as a dihydrogen acceptor like cyclohexene, was used, the naphthylamines were formed cleanly and in reasonable yields (Table 1) within a short period of time. *N,N*-Diethyl-1-naphthylamine proved difficult to synthesise via this route, probably because of the very low stability of the corresponding enamine, and the best yield was obtained by the use of limonene and Pd/C in a sealed tube. The reaction produced several by-products including tetralin and naphthalene.

As the yield of *N,N*-diethyl-1-naphthylamine was disappointingly low, direct ethylation of *N*-ethyl-1-naphthylamine was examined. The low

reactivity of the secondary amino group made the reactions with triethyl phosphate and iodoethane difficult. However, treatment with *n*-BuLi in dry THF and reaction of the resulting lithium salt with bromoethane gave the *N,N*-diethyl compound in 89% yield.

As with the enamines, the naphthylamines tended to decompose in air at room temperature and they too were characterised by nmr and mass spectral data. The amine moiety exhibited the usual signals in the range 1–4 ppm and the remaining signals were all in the aromatic region, with the absorptions for H-5 and H-8 being downfield of and separated from the other signals.

The use of the enamine route is limited to the synthesis of tertiary amines, but a recent synthesis of primary 1-naphthylamines using a similar method has been reported [20], illustrating the potential of tetralones as a source of naphthylamines.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WM250 instrument for CDCl₃ solutions. Mass spectral data were obtained using a Perkin Elmer 8500. Distillations were performed using a bulb-to-bulb (Kügelrohr) apparatus (Büchi GKR-50 glass tube oven) and all boiling points quoted relate to the oven temperature at which distillation commenced. Melting points are uncorrected. Flash chromatography was performed on silica gel (Sorbisil C60, MPD 60Å, 40–60 microns).

Preparation of enamines

1-(3,4-Dihydro-1-naphthyl)pyrrolidine

A solution of pyrrolidine (34 cm³; 0.41 mol) in dry toluene (50 cm³) was added under an inert atmosphere to a solution of 1-tetralone (10 g; 68.4 mmol) in dry toluene (75 cm³). The flask contents were cooled to –10°C with an ice-ethanol bath and TiCl₄ (3.75 cm³; 34.2 mmol) in 45 cm³ of dry toluene was added dropwise, at such a rate that the temperature did not reach 0°C. The orange slurry was stirred at –10°C for 1 h and then at room temperature for two days. Filtration through Celite and evaporation of the solvent yielded an orange residue which was distilled (b.p. 150°C/1.3 mm) to afford 11.65 g (85%) of a clear yellow oil. δ_{H} : 1.90–1.96 (4H, m, (CH₂)₂), 2.22–2.27 (2H, m, 3-H), 2.65–2.71 (2H, m, 4-H), 2.96–3.01 (4H, m, N(CH₂)₂), 5.19 (1H, t, 2-H), 7.16–7.18 (3H, m, Ar-H), and 7.43–7.46 (1H, m, Ar-H); (*m/z*) 199 (M⁺). C₁₄H₁₇N requires 199.

The following enamines were also obtained by this method.

1-(3,4-Dihydro-1-naphthyl)piperidine

(62%) from 1-tetralone (10 g), piperidine (41 cm³; 0.41 mol) and TiCl₄ (3.75 cm³) in dry n-hexane (150 cm³) as a pale yellow oil, b.p. 135°C/0.15 mm. δ_{H} : 1.58–1.60 (2H, m, CH₂), 1.68–1.74 (4H, m, (CH₂)₂), 2.19–2.25 (2H, m, 3-H), 2.65–2.68 (2H, m, 4-H), 2.71–2.78 (4H, m, N(CH₂)₂), 5.26 (1H, t, 2-H), 7.13–7.25 (3H, m, Ar-H), and 7.45 (1H, m, Ar-H); (*m/z*) 213 (M⁺) C₁₅H₁₉N requires 213.

4-(3,4-Dihydro-1-naphthyl)morpholine

(90%) as a clear yellow oil from 1-tetralone (10 g), morpholine (35.75 g; 0.41 mol), TiCl₄ (3.75 cm³) and dry toluene (150 cm³), b.p. 150°C/0.2 mm which solidified when refrigerated m.p. 52°C. δ_{H} : 2.26 (2H, m, 3-H), 2.70 (2H, m, 4-H), 2.84 (4H, m, N(CH₂)₂), 3.86 (4H, m, O(CH₂)₂), 5.28 (1H, t, 2-H), 7.16–7.24 (3H, m, Ar-H), and 7.45 (1H, m, Ar-H); (*m/z*) 215 (M⁺). C₁₄H₁₇NO requires 215.

1-Diethylamino-3,4-dihydronaphthalene

(25%) as a yellow oil b.p. 110°C/7 mm from 1-tetralone (10 g), diethylamine (42 cm³; 0.41 mol), TiCl₄ (3.75 cm³) and dry n-hexane (170 cm³). δ_{H} : 0.98 (6H, t, (CH₃)₂), 2.22–2.26 (2H, m, 3-H), 2.65–2.71 (2H, m, 4-H), 2.81 (4H, q, (CH₂)₂), 5.21 (1H, t, 2-H), 7.15–7.18 (3H, m, Ar-H), and 7.43–7.45 (1H, m, Ar-H); (*m/z*) 201 (M⁺). C₁₄H₁₉N requires 201.

Preparation of the Naphthylamines*1-(1-Naphthyl)pyrrolidine*

To a solution of 1-(3,4-dihydro-1-naphthyl)pyrrolidine (11.46 g; 58 mmol) in limonene (80 cm³) was added 1 g of 10% Pd/C catalyst and the well-stirred mixture was refluxed gently for 24 h. The cooled reaction mixture was then filtered (Celite) and the solvent removed *in vacuo* (b.p. 80°C/0.7 mm) to afford an oily residue, elution of which from silica gel (7% ethyl acetate in hexane) and distillation (b.p. 130°C/0.2 mm) produced 6.40 g (55%) of a clear colourless oil. δ_{H} : 2.05 (4H, m, R-H), 3.40 (4H, m, R-H), 7.02 (1H, dd, 2-H), 7.40–7.49 (4H, m, 3-H, 4-H, 6-H, 7-H), 7.84 (1H, m, 5-H), and 8.25 (1H, m, 8-H); (*m/z*) 197 (M⁺). C₁₄H₁₅N requires 197.

An identical method was used to prepare the following naphthylamines.

1-(1-Naphthyl)piperidine

(53%) from 1-(3,4-dihydro-1-naphthyl)piperidine (5.85 g; 27 mmol) and 10% Pd/C (1 g) in limonene (60 cm³) as a colourless oil, b.p. 135°C/0.15 mm, which eventually solidified, m.p. 29–30°C. δ_{H} : 1.71 (2H, m, CH₂), 1.85–1.94 (4H, m, CH₂)₂), 3.10 (4H, m, N(CH₂)₂), 7.10 (1H, dd, 2-H), 7.40–7.58 (4 H,

m, 3-H, 4-H, 6-H, 7-H), 7.85 (1H, m, 5-H), 8.35 (1H, m, 8-H); (*m/z*) 211 (M^+). $C_{15}H_{17}N$ requires 211.

1-(1-Naphthyl)morpholine

(66%) as a pale yellow oil, b.p. 140°C/0.2 mm, which solidified on standing, m.p. 77–79°C from 1-(3,4-dihydro-1-naphthyl)morpholine (7.5 g; 34.9 mmol) and 10% Pd/C (1.2 g) in limonene (70 cm³). δ_H : 3.10–3.13 (4H, t, $N(CH_2)_2$), 3.97–4.00 (4H, t, R-H), 7.10 (4H, dd, 2-H), 7.39–7.59 (1H, m, 3-H, 4-H, 6-H, 7-H), 7.81–7.85 (1H, m, 5-H), and 8.19–8.23 (1H, m, 8-H); (*m/z*) 213 (M^+). $C_{14}H_{15}NO$ requires 213.

N,N-Diethyl-1-naphthylamine

Method (a). 1-Diethylamino-3,4-dihydronaphthalene (1.7 g; 8.46 mmol), 10% Pd/C (0.8 g) and toluene (30 cm³) were heated together in a sealed tube at 150°C for 24 h. The cooled reaction mixture was filtered through Celite and the toluene removed to afford the crude product. This material was purified by chromatography on silica gel (7% ethyl acetate in hexane) and distilled (b.p. 110°C/0.2 mm) to afford 0.34 g (20%) of a clear yellow oil. δ_H : 1.08 (6H, t, $(CH_3)_2$), 3.18–3.27 (4H, q, $(CH_2)_2$), 7.16 (1H, dd, 2-H), 7.39–7.49 (4H, m, 3-H, 4-H, 6-H, 7-H), 7.83 (1H, m, 5-H) and 8.34 (1H, m, 8-H); (*m/z*) 199 (M^+). $C_{14}H_{17}N$ requires 199.

Method (b). A stirred solution of *N*-ethyl-1-naphthylamine (3 g; 17.5 mmol) in dry THF (30 cm³) was treated with *n*-BuLi (2.3 M in hexane; 8.4 cm³) under an inert atmosphere. After 30 min, a solution of bromoethane (2.48 g; 22.8 mmol) in dry THF (20 cm³) was added portionwise to the brown mixture and stirring was continued overnight. The mixture was then quenched with water (150 cm³) and extracted twice with 100 cm³ portions of diethyl ether. The mixed organic layers were washed successively with water (2×50 cm³) and brine (50 cm³) and dried (Na_2SO_4) and the solvent evaporated. Distillation of the residue afforded the title compound (3.1 g; 89%) which was identical to that prepared in method (a).

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