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# An $\alpha$ -aminomethyl carbanion equivalent via a novel Barbier reaction: (1*H*-naphtho[1,8-*de*]-1,2,3-triazin-2-yl)methyl anion

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## Abstract

A novel sonication-promoted Barbier reaction putatively generated the titled species from the corresponding naphthotriazinylmethyl chloride and magnesium in THF: its formal addition to a variety of carbonyl compounds in situ occurred in excellent yields. Subsequent catalytic hydrogenolysis of the triazine moiety demasked the amine, thus defining a route to various phenylethylamines (including the alkaloid ‘mescaline’), or ethanolamines (in two cases), in excellent overall yields. © 2000 Elsevier Science Ltd. All rights reserved.

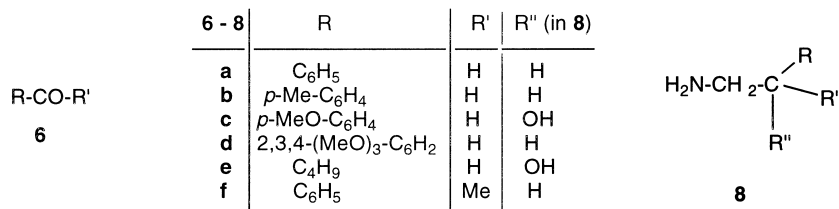
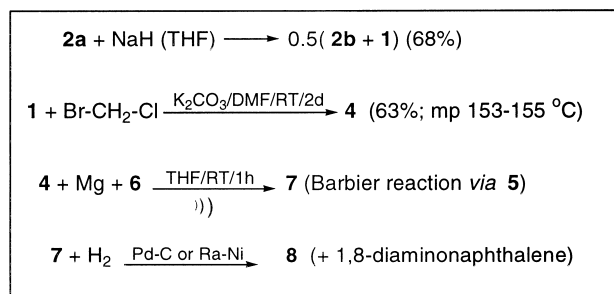
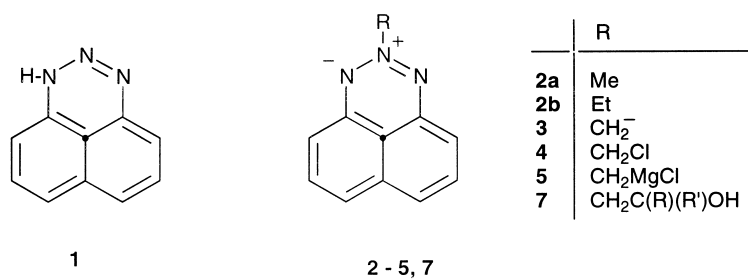
**Keywords:** alkaloids;  $\alpha$ -aminomethyl carbanion; Barbier reaction; mescaline; naphthotriazine; phenylethylamine; ultrasound.

We report herein a novel, ultrasound-promoted Barbier reaction<sup>1–3</sup> and demonstrate its synthetic utility. The reaction results in the formal addition of a masked  $\alpha$ -(*primary*-amino)-methyl carbanion to a variety of carbonyl compounds, the amine function then being released hydrogenolytically. The two-step sequence is relatively facile and occurs in excellent overall yields. The synthetic potential of the process derives from the fact that the generation of an  $\alpha$ -amino carbanion is a topic of current interest,<sup>4</sup> and that the above sequence defines a novel route to the phenylethylamine group of alkaloids.<sup>5</sup>

In the course of other studies with 1*H*-naphtho[1,8-*de*]-1,2,3-triazine **1**, we were drawn to the possibility of generating the ylidic species **3** via the deprotonation of the 2-methyl derivative **2a** (Scheme 1). Interest in **3** derives from the fact that its alkylation—and the subsequent reductive cleavage of the triazine moiety—would define a novel synthetic route to  $\alpha$ -substituted amines: **3** would therefore serve as an  $\alpha$ -aminomethyl carbanion equivalent.

In fact, early work by Perkins<sup>6a</sup> had not only established that methylation of **1** yields substantial amounts of **2a** (alongside the *N*<sub>1</sub>-isomer), but also that **2a** condenses with benzaldehyde in the presence of ethanolic sodium ethoxide: although the resulting *N*<sub>2</sub>-styryl derivative was obtained in

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Scheme 1.

low yields, the acidity of the *N*-methyl group in **2a** had been proven. (The above results<sup>6a</sup> on the methylation of **1** were extended to include a variety of alkylating agents by Tavs and co-workers,<sup>6b</sup> but since then no major development in the above chemistry of **1** has apparently been reported.<sup>6c</sup>)

In fact, the triaza-ylidic moiety in **3** is isoelectronic with the nitromethane anion; thus, the analogy between the above reaction and the classical Henry 'nitroaldol' reaction<sup>7</sup> becomes apparent. (Indeed, the Henry reaction—followed by the reduction of the nitro group—defined one of the earliest known aminomethyl carbanion equivalents.<sup>4b</sup>) Clearly then, further elaboration of the above results of Perkins,<sup>6a</sup> particularly in aprotic media, was of interest. However, sodium hydride-mediated deprotonation of **2a** in THF led to the ethyl derivative **2b**, apparently via methyl transfer from unreacted **2a** to **3** (which is apparently faster than the deprotonation); similar results were obtained with lithium diisopropylamide in THF.

We then explored the possibility of preparing the 2-chloromethyl derivative **4** in the hope of effecting a chlorine–lithium exchange with *n*-butyllithium. Treatment of the triazine **1** with bromochloromethane in dimethylformamide in the presence of potassium carbonate over 2 days at 25°C afforded **4** in 63% yield. (Interestingly, none of the *N*<sub>1</sub>-isomer was observed, although a bis-*N*<sub>2</sub>-alkylation product—derived from **4** and **1**—was isolated in 7% yield.) However, **4** was

unreactive towards *n*-butyllithium under a variety of conditions ( $-78$ – $0^{\circ}\text{C}/\text{THF}$ ). Although **4** was also reluctant to form the corresponding Grignard reagent, it was found possible to effect the Barbier reaction<sup>1–3</sup> with it under the influence of ultrasound.<sup>8</sup> Thus, when a mixture of **4**, magnesium and benzaldehyde **6a** in THF was sonicated for 1 h, the naphthotriazinylbenzyl alcohol **7a** was isolated in 87% yield. The wide extent of the reaction was demonstrated with a number of aromatic aldehydes **6a–6d** bearing electron-donating substituents, with valeraldehyde **6e** and with acetophenone **6f**, to afford the corresponding alcohols **7** in excellent yields (Table 1). The reaction—which occurs via the putative Grignard reagent **5**—failed, however, with 3-methoxy- and 3,4-dimethoxybenzaldehyde—as it also generally did in the absence of the sonication.

The catalytic hydrogenolyses of the alcohols **7** were then investigated, and found to be facile at normal temperature and pressure, generally in the presence of 10% Pd–C. Both the triazine and the benzylic alcohol moieties (in the aromatic cases) were found to be cleaved to afford the corresponding arylethylamine products **8** in excellent yields (Table 1), together with the expected 1,8-diaminonaphthalene by-product.<sup>6a</sup> However, the triazine moiety could be selectively cleaved in two cases, **7c** (with Raney nickel) and **7e**, to furnish the corresponding amino alcohols **8c** and **8e**, also in high yields (Table 1). The amines **8** possess the skeleton of the phenylethylamine group of alkaloids, **8d** being well known<sup>5</sup> as ‘mescaline’.

Table 1  
Percent yields for the formation of the benzyl alcohols **7** and the phenylethylamines **8**

<b>7/8</b>	<b>7</b>	<b>8</b>
<b>a</b>	87	76
<b>b</b>	97	88
<b>c</b>	82	94
<b>d</b>	88	82
<b>e</b>	91	92
<b>f</b>	72	79

The reasons for the above lack of reactivity of the 3-methoxy- and 3,4-dimethoxybenzaldehydes are not clear, particularly in view of the normal reactivity of 4-methoxy- and 3,4,5-trimethoxybenzaldehydes. The Barbier reaction is believed<sup>3</sup> to occur via a complex mechanism involving the radical anions of the reacting partners which are formed at the metal surface, and it is possible that the redox potential of the carbonyl compound exerts a subtle influence on its reactivity. It would appear that a 3-methoxy group destabilises—and hence suppresses the formation of—the ketyl radical anion derived from the aromatic aldehyde; however, in the case of 3,4,5-trimethoxybenzaldehyde, the relatively low concentration of the derived ketyl species may possibly be countered by a relatively large increase in its further reactivity—both being presumed consequences of the above destabilising effect.

In summary, a novel Barbier reaction has been effected, which defines a new  $\alpha$ -(primary-amino)-methyl carbanion equivalent, and leads efficiently to the naturally occurring phenylethylamine

skeleton: either the 2-arylethylamines or the 2-arylethanolamines may thus be selectively accessed. Further studies are planned.

**Typical procedures:** *Alcohols 7:* the chloromethyltriazine **4**, magnesium and the carbonyl compound **6** (0.5 mmol each) in dry THF (2 ml) were treated with a trace of iodine, and the mixture sonicated for 1 h (on a 'Julabo USR 3' instrument at 35 kHz). Water was added to the mixture and this was extracted with ether. The extracts were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated to obtain the crude product, which upon chromatography afforded the pure **7**. *Phenylethylamines 8:* the alcohols **7** (0.3 mmol) in ethanol (3 ml) were hydrogenated with 10% Pd-C (freshly prepared W-2 grade Raney-Ni in the case of **7c**) at NTP for 24 h. The catalyst was filtered off, the solvent evaporated, and the resulting crude material chromatographed to furnish the pure amines **8**. All products were characterised by IR, NMR (<sup>1</sup>H and <sup>13</sup>C) and mass spectra, and physical constants or elemental analyses as appropriate.

### Acknowledgements

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