An α-aminomethyl carbanion equivalent via a novel Barbier reaction: (1H-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; α-aminomethyl carbanion; Barbier reaction; mescaline; naphthotriazine; phenylethylamine; ultrasound.

We report herein a novel, ultrasound-promoted Barbier reaction1–3 and demonstrate its synthetic utility. The reaction results in the formal addition of a masked α-(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 α-aminocarbanion is a topic of current interest,4 and that the above sequence defines a novel route to the phenylethylamine group of alkaloids.5

In the course of other studies with 1H-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 α-substituted amines: 3 would therefore serve as an α-aminomethyl carbanion equivalent.

In fact, early work by Perkins6a had not only established that methylation of 1 yields substantial amounts of 2a (alongside the N1-isomer), but also that 2a condenses with benzaldehyde in the presence of ethanolic sodium ethoxide: although the resulting N2-styryl derivative was obtained in
low yields, the acidity of the N-methyl group in 2a had been proven. (The above results on the methylation of 1 were extended to include a variety of alkylating agents by Tavs and co-workers, but since then no major development in the above chemistry of 1 has apparently been reported.) 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 becomes apparent. (Indeed, the Henry reaction—followed by the reduction of the nitro group—defined one of the earliest known aminomethyl carbanion equivalents.) Clearly then, further elaboration of the above results of Perkins, 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 N1-isomer was observed, although a bis-N2-alkylation product—derived from 4 and 1—was isolated in 7% yield.) However, 4 was
unreactive towards \( n \)-butyllithium under a variety of conditions (\(-78–0^\circ\mathrm{C}/\mathrm{THF}\)). Although 4 was also reluctant to form the corresponding Grignard reagent, it was found possible to effect the Barbier reaction\(^1\)\(^–\)\(^3\) with it under the influence of ultrasound.\(^8\) 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.\(^6a\) 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\(^5\) as 'mescaline'.

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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\(^3\) 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$_2$SO$_4$) 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 ($^1$H and $^{13}$C) and mass spectra, and physical constants or elemental analyses as appropriate.

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**References**