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An α-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.

Keywords: alkaloids; α-aminomethyl carbanion; Barbier reaction; mescaline; naphthotriazine; phenylethylamine; ultrasound.

We report herein a novel, ultrasound-promoted Barbier reaction[1–3] 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-amino carbanion 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 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 α-substituted amines: **3** would therefore serve as an α-aminomethyl carbanion equivalent.

In fact, early work by Perkins[6a] had not only established that methylation of **1** yields substantial amounts of **2a** (alongside the N_1-isomer), but also that **2a** condenses with benzaldehyde in the presence of ethanolic sodium ethoxide: although the resulting N_2-styryl derivative was obtained in

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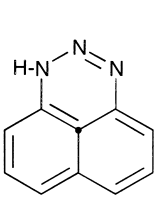

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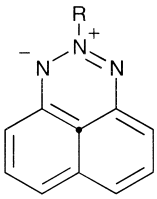


2 - 5, 7

	R
2a	Me
2b	Et
3	CH_2^-
4	CH_2Cl
5	CH_2MgCl
7	$CH_2C(R)(R')OH$

2a + NaH (THF) ⟶ 0.5(**2b** + **1**) (68%)

1 + $Br\text{-}CH_2\text{-}Cl$ $\xrightarrow{K_2CO_3/DMF/RT/2d}$ **4** (63%; mp 153-155 °C)

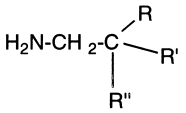
4 + Mg + **6** $\xrightarrow[)))}{THF/RT/1h}$ **7** (Barbier reaction *via* **5**)

7 + H_2 $\xrightarrow{Pd\text{-}C \text{ or } Ra\text{-}Ni}$ **8** (+ 1,8-diaminonaphthalene)

R-CO-R'

6

6 - 8	R	R'	R'' (in **8**)
a	C_6H_5	H	H
b	*p*-Me-C_6H_4	H	H
c	*p*-MeO-C_6H_4	H	OH
d	2,3,4-$(MeO)_3$-C_6H_2	H	H
e	C_4H_9	H	OH
f	C_6H_5	Me	H



8

Scheme 1.

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

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[7] becomes apparent. (Indeed, the Henry reaction—followed by the reduction of the nitro group—defined one of the earliest known aminomethyl carbanion equivalents.[4b]) Clearly then, further elaboration of the above results of Perkins,[6a] 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_1-isomer was observed, although a bis-N_2-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°C/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'.

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

7/8	7	8
a	87	76
b	97	88
c	82	94
d	88	82
e	91	92
f	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[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 α-(*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_2SO_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 (^1H and ^{13}C) and mass spectra, and physical constants or elemental analyses as appropriate.

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References

1. March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; p. 921.
2. Li, C.-J. *Tetrahedron* **1996**, *52*, 5643–5668, and references cited therein.
3. Molle, G.; Bauer, P. *J. Am. Chem. Soc.* **1982**, *104*, 3481–3487.
4. (a) Katritzky, A. R.; Qi, M. *Tetrahedron* **1998**, *54*, 2647–2668, and references cited therein. (b) Saavedra, J. E. In *Umpoled Synthons*; Hase, T. A., Ed.; John Wiley & Sons: New York, 1987; pp. 101–121, and references cited therein. (c) Saavedra, J. E. *J. Org. Chem.* **1983**, *48*, 2388–2392.
5. Finar, I. L. *Organic Chemistry*; Addison Wesley Longman: Harlow, UK, 1997; Vol. 2, pp. 702–708.
6. (a) Perkins, M. J. *J. Chem. Soc.* **1964**, 3005–3008. (b) Tavs, P.; Sieper, H.; Beecken, H. *Liebigs Ann. Chem.* **1967**, *704*, 150–160. (c) Neuenhoeffer, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Boulton, A. J.; McKillop, A., Eds.; Pergamon: Oxford, 1984; Vol. 3, pp. 369–384.
7. Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp. 321–340.
8. Ref. 1, pp. 364–365, and references cited therein.