Synthesis of 2,3,6,7-Tetrahydro- and 2,3,4,5,6,7-Hexahydro-1*H*-1,4-diazepines *via* a Tandem Michael-type Addition–Intramolecular Aza-Wittig Sequence

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Intramolecular aza-Wittig reaction of azides derived from 1,2-amino azides and α,β-unsaturated ketones leads to 2,3,6,7-tetrahydro-1*H*-1,4-diazepines. Reduction of these compounds with lithium aluminium hydride affords the corresponding saturated heterocycles.

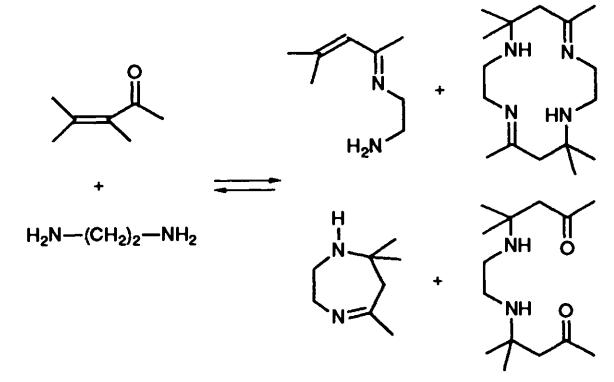
2,3,6,7-Tetrahydro-1*H*-1,4-diazepines have most commonly been prepared by the addition of 1,2-diamines to conjugated enones.[1] As has been shown by monitoring the reactions by ^{13}C NMR spectroscopy, complex mixtures are frequently formed (Scheme 1) and the isolated product often depends on the reaction conditions, the identity of the enone and the work-up techniques.[2]

Another limitation of this approach is that a mixture of regioisomers results in the case of an unsymmetrical 1,2-diamine[1c,1f]† (Scheme 2).

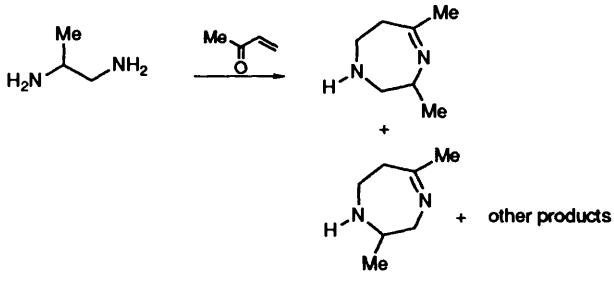
We have recently demonstrated the utility of 1,*n*-amino azides as synthetic equivalents of 1,*n*-diamines.[4] The simultaneous presence of a free and a potential amino group prevents the formation of the polyalkylation products usually observed, for example, in the reaction of amines with alkyl halides. Furthermore, it enables complete control of the regioselectivity[4a] (Scheme 3).

In addition to this, it is also possible to perform reactions chemioselectively on the free amino moiety. For example, Michael-type addition of 4-azido-1,*N*-dimethylbutylamine to acrylonitrile gave a single product which was converted into the corresponding spermidine analogue[4b] (Scheme 4).

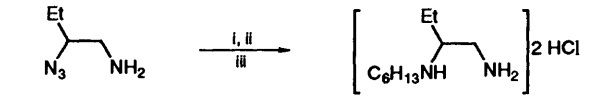
In continuation of this work, we now report a new route to 2,3,6,7-tetrahydro- and 2,3,4,5,6,7-hexahydro-1*H*-1,4-diazepines.



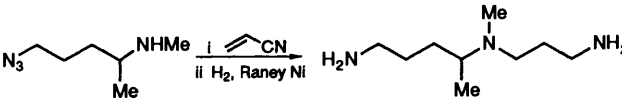
Scheme 1



Scheme 2



Scheme 3 *Reagents:* i, HCl; ii, $C_6H_{13}BCl_2$; iii, MeOH



Scheme 4

Results and Discussion

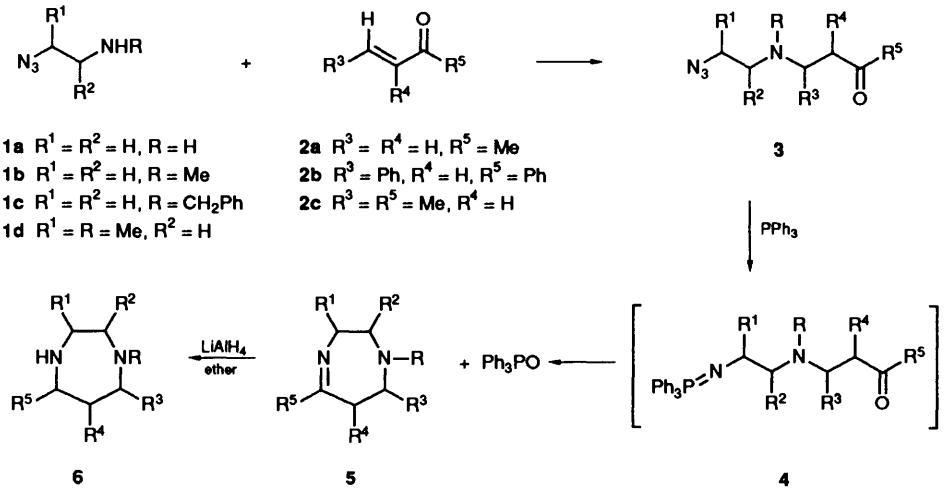
This approach is based on the following tandem sequence: Michael-type addition of the 1,2-amino azide **1** to the α,β-unsaturated ketone **2**, then intramolecular aza-Wittig cyclisation of the adduct **3**. Reduction of **5** with lithium aluminium hydride affords the corresponding saturated heterocycle **6** (Scheme 5).

Synthesis of 2,3,6,7-*Tetrahydro*-1H-1,4-*diazepines*.—The starting 1,2-amino azides were prepared according to reported procedures.[4a,4b] They can be obtained bearing a wide variety of substituents R^1, R^2 and R. For this study, azides **1a–d** and ketones **2a–c** were chosen as model substrates. Michael-type additions[5] were carried out in diethyl ether at room temperature, except for **2c**, where no solvent was used. The adducts **3** were isolated in good yields by distillation for **3a** and **3c–f**, and by recrystallization of the hydrochloride for **3b** (Table 1).

Treatment of azides **3** with an equimolar amount of triphenylphosphine in anhydrous diethyl ether led to the corresponding 2,3,6,7-tetrahydro-1*H*-1,4-diazepines **5**. The formation of these cyclization products can be assumed to proceed *via* the expected iminophosphorane intermediates **4** which were not isolated. This is an additional example of the use of the intramolecular aza-Wittig reaction for the synthesis of nitrogen heterocycles.[6] Compounds **5** were isolated by bulb-to-bulb distillation in good to moderate yields (Table 2).

Although the presence of **5a** and **5b** (R = H) was detected in

† The reaction of propane-1,2-diamine and methyl vinyl ketone gave a complex mixture of products. Distillation afforded the two regioisomeric 2,3,6,7-tetrahydro-1*H*-1,4-diazepines in a 20% yield.[3]



Scheme 5

Table 1 Synthesis of the azides 3

Compound	R^1	R^2	R	R^3	R^4	R^5	Yield (%)[a]
3a	H	H	H	H	H	Me	70
3b	H	H	H	Ph	H	Ph	68[b]
3c	H	H	Me	H	H	Me	83
3d	H	H	Me	Me	H	Me	79
3e	H	H	CH_2Ph	H	H	Me	70
3f	Me	H	Me	H	H	Me	80

[a] Isolated yields. [b] Isolated as its hydrochloride.

Table 2 Synthesis of the 2,3,6,7-tetrahydro-1*H*-1,4-diazepines 5

Compound	R^1	R^2	R	R^3	R^4	R^5	Yield (%)[a]
5c	H	H	Me	H	H	Me	84
5d	H	H	Me	Me	H	Me	62
5e	H	H	$PhCH_2$	H	H	Me	72
5f	Me	H	Me	H	H	Me	70

[a] Isolated yields.

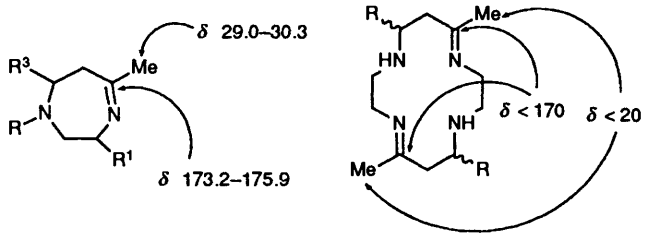
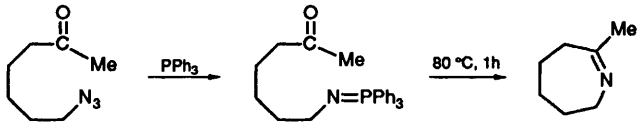


Fig. 1

the ^1H and ^{13}C NMR spectra of the crude mixtures, we were unable to isolate them in reasonable yields. The 2,3,6,7-tetrahydro-1*H*-1,4-diazepine structure of **5** was supported by spectroscopic data. The observation of the molecular ion in the mass spectra and the presence of signals at δ 29.0–30.3 (C–CH_3) and 173.2–175.9 (*C*=N–) in the ^{13}C NMR spectra, which correspond closely to those given in the literature for related compounds,[2,7] allows the exclusion of a dimeric structure (Fig. 1).

It is also worth noting that the reaction of ω-keto azide **7** with triphenylphosphine actually gives an iminophosphorane at room temperature, but that it is necessary to increase the reaction temperature to 80 °C in order to observe an intramolecular cyclisation [8] (Scheme 6).



Scheme 6

Synthesis of 2,3,4,5,6,7-*Hexahydro*-1H-1,4-*diazepines* **6**.—Various reagents ($NaBH_4$, H_2 in the presence of PtO_2) have been used to reduce 2,3,6,7-tetrahydro-1*H*-1,4-diazepines.[9] In our experience, low and irreproducible yields were obtained. The reduction with a solution of $LiAlH_4$ in diethyl ether gave the best results and the saturated heterocycles **6** were isolated by distillation (after hydrolysis) (Table 3). For **6d** a mixture of two diastereoisomers (60:40) was obtained. Compounds **6** were characterized by mass spectroscopy, elemental analysis, ^1H and ^{13}C NMR spectroscopy.

To conclude, we have reported an efficient new route to 2,3,6,7-tetrahydro- and 2,3,4,5,6,7-hexahydro-1*H*-1,4-diazepines **5** and **6** that complements those existing in the literature. This approach involves a Michael-type addition followed by an intramolecular aza-Wittig cyclisation. Compounds **5** and **6** are, in general, isolated in good yields and, in the case of an unsymmetrical derivative, the use of a 1,2-amino azide facilitates the production of a single regioisomer. 1,2-Amino azides are therefore valuable synthetic equivalents of the corresponding alkane-1,2-diamines and should prove to be useful building blocks in the construction of other heterocyclic structures.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker WP 80 CW and a Bruker AM 300 spectrometer (75.5 MHz for ^{13}C). Chemical shifts are reported in δ (ppm) and coupling constants (*J*) are given in Hz. Mass spectra were measured at 70 eV on a Varian MAT 311 Spectrometer (Centre Régional de Mesures Physiques de l'Ouest). Elemental analyses were performed by the Laboratoire Central d'Analyses du CNRS, Lyon. M.p.s were determined with a Kofler apparatus and are uncorrected. Reagent grade reagents and solvents were used as received from chemical suppliers. The starting 1,2-amino azides were prepared according to reported procedures.[4a,4b]

CAUTION: Because of their potentially explosive properties, all experiments (especially distillations) involving azides were

Table 3 Synthesis of the 2,3,4,5,6,7-hexahydro-1*H*-1,4-diazepines **6**

Compound	R^1	R^2	R	R^3	R^4	R^5	Yield (%)[a]
6c	H	H	Me	H	H	Me	63
6d	H	H	Me	Me	H	Me	88[b]
6e	H	H	$PhCH_2$	H	H	Me	91

[a] Isolated yield. [b] Mixture of diastereoisomers.

carried out with the appropriate protection under a well ventilated hood.

General Procedure for the Preparation of Azides **3**.—A solution of 1,2-amino azide **1** (0.01 mol) in dry diethyl ether (10 cm^3) was added dropwise to a solution of the α,β-unsaturated ketone **2** (0.01 mol) in the same solvent (10 cm^3) at 0 °C. For **1a** and **2a**, the addition was done very slowly with a syringe pump.

The reaction mixture was stirred at room temperature for 8 h. Diethyl ether was removed under reduced pressure. The residual material was filtered on a short column of silica gel, eluting with diethyl ether–pentane (1:1) to give an oil which was purified by bulb-to-bulb distillation. For **3b**, slow addition of a 1 mol dm^{-3} HCl solution in diethyl ether (10 cm^3) to the crude mixture gave the corresponding hydrochloride which was collected by filtration and recrystallised from ethanol.

4-[N-(2-*Azidoethyl*)*amino*]*butan*-2-*one* **3a**. 70%; b.p. 80–85 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 1.79 (1 H, s), 2.17 (3 H, s), 2.65 (t, *J* 6.3, 2 H), 2.80 (t, *J* 5.7, 2 H), 2.85 (t, *J* 6.3, 2 H) and 3.40 (t, *J* 5.7, 2 H); δ_C(75 MHz, $CDCl_3$) 30.1, 43.6, 43.9, 48.5, 51.2 and 208.1; *m/z* $M^{\cdot+}$ was not observed (Found: $[M - CH_2N_3^{\cdot}]^+$, 100.0766. $C_5H_{10}NO$ requires 100.0762).

3-[N-(2-*Azidoethyl*)*amino*]-1,3-*diphenylpropan*-1-*one hydrochloride* **3b**·HCl. 68%; m.p. 160–162 °C (ethanol); δ_H(300 MHz; $CDCl_3$) 2.86–2.97 (2 H, m), 3.70–3.80 (1 H, m), 3.82–3.92 (1 H, m), 4.03 (dd, *J* 7.8 and 17.8, 1 H), 4.24 (dd, *J* 5.7 and 17.8, 1 H), 4.86 (dd, *J* 5.7 and 7.8, 1 H), 7.37–7.50 (8 H, m), 7.72–7.76 (1 H, m), 7.82–7.88 (1 H, m) and 9.60–10.80 (2 H, br s); δ_C(75 MHz; $CDCl_3$) 42.7, 44.4, 47.0, 59.7, 128.3, 128.8, 128.9, 129.6, 129.9, 133.6, 134.0, 135.7 and 196.2 (Found: C, 61.8, H, 5.8; N, 16.4. $C_{17}H_{19}ClN_4O$ requires C, 61.7; H, 5.7; N, 16.9%).

4-[N-(2-*Azidoethyl*)-N-*methylamino*]*butan*-2-*one* **3c**. 83%; b.p. 44–60 °C (0.03 mmHg); δ_H(300 MHz; $CDCl_3$) 2.18 (s, 3 H), 2.26 (s, 3 H), 2.55–2.64 (m, 4 H), 2.68–2.74 (m, 2 H) and 3.82 (t, *J* 6.0, 2 H); δ_C(75 MHz; $CDCl_3$) 30.2, 41.6, 42.0, 48.7, 52.0, 56.5 and 207.8 [Found: C, 39.3; H, 4.3; N, 24.4. $C_7H_{14}N_4O$, $C_6H_3N_3O_7$ (picrate) requires C, 39.1; H, 4.3; N, 24.6%].

4-[N-(2-*Azidoethyl*)-N-*methylamino*]*pentan*-2-*one* **3d**. 79%; b.p. 60–65 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 0.99 (d, *J* 6.6, 3 H), 2.17 (s, 3 H), 2.28 (s, 3 H), 2.36 (dd, *J* 7.5 and 15.5, 1 H), 2.60 (t, *J* 6.3, 2 H), 2.65 (dd, *J* 6.5 and 15.5, 1 H), 3.23–3.53 (m, 1 H) and 3.26 (t, *J* 6.3, 2 H); δ_C(75 MHz; $CDCl_3$) 14.0, 30.3, 36.6, 47.9, 49.3, 52.8, 55.2 and 207.9; *m/z* $M^{\cdot+}$ was not observed (Found: $M - CH_2N_3^{\cdot}]^+$, 128.1070. $C_7H_{14}NO$ requires 128.1075).

4-[N-(2-*Azidoethyl*)-N-*benzylamino*]*butan*-2-*one* **3e**. 70%; b.p. 105–110 °C (0.1 mmHg); δ_H(300 MHz; $CDCl_3$) 1.91 (3 H, s), 2.50 (t, *J* 7.0, 2 H), 2.57 (t, *J* 6.0, 2 H), 2.73 (t, *J* 7.0, 2 H), 3.15 (t, *J* 6.0, 2 H), 3.52 (2 H, s) and 7.15–7.26 (5 H, m); δ_C(75 MHz; $CDCl_3$) 30.2, 41.7, 48.9, 49.1, 53.4, 59.2, 127.2, 128.4, 128.8, 138.8 and 208.0; *m/z* $M^{\cdot+}$ was not observed (Found: $[M - CH_2N_3^{\cdot}]^+$, 218.1414. $C_{13}H_{18}N_2O$ requires 218.1419).

4-([N-(2-*Azidopropyl*)-N-*methylamino*]*butan*-2-*one* **3f**. 80%; b.p. 50–55 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 1.17 (d, *J* 6.6, 3 H), 2.17 (3 H, s), 2.26 (3 H, s), 2.31 (dd, *J* 4.7 and 13.1, 1 H), 2.46 (dd, *J* 8.6 and 13.1, 1 H), 2.58–2.80 (4 H, m) and 3.56–3.67 (1 H, m); [Found: C, 40.9; H, 4.7; N, 23.6. $C_8H_{16}N_4O$, $C_6H_3N_3O_7$ (picrate) requires C, 40.7; H, 4.6; N, 23.7%].

General Procedure for the Cyclisation of Azides **3**.—Triphenylphosphine (1.315 g; 5 mmol) was added in small portions under nitrogen to a stirred solution of the azide **3** (5 mmol) in dry diethyl ether (10 cm^3). The mixture was stirred at room temperature for 8 h. After addition of dry pentane (20 cm^3), triphenylphosphine oxide was filtered off. The solvents were removed under reduced pressure and the residual material was triturated with diethyl ether–pentane (5 cm^3–15 cm^3). Filtration and evaporation afforded a colourless oil which was purified by bulb-to-bulb distillation.

2,3,6,7-*Tetrahydro*-1,5-*dimethyl*-1H-1,4-*diazepine* **5c**. B.p. 20–25 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 1.85 (3 H, s), 2.11 (3 H, s), 2.09–2.18 (2 H, m), 2.20–2.27 (2 H, m), 2.28–2.36 (2 H, m) and 3.40–83.48 (2 H, m); δ_C(75 MHz; $CDCl_3$) 29.1, 35.0, 47.0, 51.7, 52.6, 56.1 and 175.4; (Found: $M^{\cdot+}$, 126.1164. $C_7H_{14}N_2$ requires 126.1157).

2,3,6,7-*Tetrahydro*-1,5,7-*trimethyl*-1H-1,4-*diazepine* **5d**. B.p. 35–40 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 1.04 (d, *J* 6.7, 3 H), 2.06 (3 H, s), 2.35 (3 H, s), 2.36–2.52 (2 H, m), 2.55–2.72 (2 H, m), 2.74–2.83 (1 H, m) and 3.56–3.76 (2 H, m); δ_C(75 MHz; $CDCl_3$) 14.8, 30.3, 41.7, 43.4, 51.4 (2 C), 54.1 and 174.5 (Found: $M^{\cdot+}$, 140.1319. $C_8H_{16}N_2$ requires 140.1313).

1-*Benzyl*-2,3,6,7-*tetrahydro*-5-*methyl*-1H-1,4-*diazepine* **5e**. B.p. 65–70 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 2.00 (3 H, s), 2.32–2.36 (2 H, m), 2.41–2.47 (4 H, m), 3.49 (2 H, s), 3.57–3.60 (2 H, m) and 7.19–7.22 (5 H, m): δ_C(75 MHz; $CDCl_3$) 29.4, 35.5, 50.8, 52.1, 54.4, 63.4, 126.9, 128.3, 129.2, 138.3 and 176.0 (Found: $M^{\cdot+}$, 202.1466. $C_{13}H_{18}N_2$ requires 202.1470).

2,3,6,7-*Tetrahydro*-1,3,5-*trimethyl*-1H-1,4-*diazepine* **5f**. B.p. 40–45 °C (0.1 mmHg); δ_H(80 MHz; $CDCl_3$) 1.30 (d, *J* 6.9, 3 H), 1.75–2.95 (6 H, m), 2.08 (3 H, s), 2.30 (3 H, s) and 3.33–3.85 (1 H, m); δ_C(20 MHz; $CDCl_3$) 23.2, 29.3, 35.3, 47.2, 52.3, 55.9, 63.0 and 173.2.

General Procedure for the Reduction of **5**.—To a cooled and stirred solution of the compound **5** (2 mmol) in dry diethyl ether (10 cm^3) was added a 1 mol dm^{-3} diethyl ether solution (2 cm^3) of $LiAlH_4$ at a rate so as to maintain the temperature at 0–5 °C. The mixture was then stirred at room temperature for 4 h. After the successive addition of water (75 mm^3), 20% aq. NaOH (60 mm^3) and water (190 mm^3),[10] the reaction mixture was filtered and the residue washed with diethyl ether (2 × 10 cm^3). The filtrate was dried over K_2CO_3. Evaporation of the solvent left a colourless oil which was purified by bulb-to-bulb distillation.

2,3,4,5,6,7-*Hexahydro*-1,5-*dimethyl*-1H-1,4-*diazepine* **6c**. B.p. 20–25 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 1.08 (d, *J* 6.4, 3 H), 1.44 (dddd, *J* 3.4, 8.4, 8.4 and 14.7, 1 H), 1.86 (dddd, *J* 3.4, 4.4, 7.9 and 14.8, 1 H), 1.83 (1 H, br s), 2.37 (3 H, s), 2.48–2.69 (4 H, m), 2.85 (ddd, *J* 4.7, 5.7 and 6.7, 1 H) and 2.95–3.10 (2 H, m), δ_H(75 MHz; $CDCl_3$) 23.9, 37.1, 46.7, 47.3, 52.8, 55.2 and 61.6 [Found: C, 38.8; H, 3.9; N, 19.1. $C_7H_{16}N_2$, $C_{12}H_6N_6O_{14}$ (dipicrate) requires C, 38.9; H, 3.8; N, 19.1%] (Found: $M^{\cdot+}$, 128.1308. $C_7H_{16}N_2$ requires 128.1313).

2,3,4,5,6,7-*Hexahydro*-1,5,7-*trimethyl*-1H-1,4-*diazepine* **6d**. B.p. 35–40 °C (0.01 mmHg); mixture of two diastereoisomers A and B (60:40), δ_H(300 MHz; $CDCl_3$) 1.03–1.13 (6 H, m), 1.47–1.72 (2 H, m), 2.17 (1 H, br s), 2.38 (3 H, s) and 2.60–3.12 (6 H, m); δ_C(75 MHz; $CDCl_3$); isomer A (major) 20.7, 24.3, 41.8, 45.0, 45.5, 52.7, 56.7 and 58.9. Isomer B (minor) 19.5, 24.3, 40.6, 41.2, 48.1, 50.4, 56.3 and 58.3 [Found: C, 40.0; H, 4.0; N, 18.3. $C_8H_{18}N_2$, $C_{12}H_6N_6O_4$ (dipicrate) requires C, 40.0; H, 4.0; N, 18.6%].

1-*Benzyl*-2,3,4,5,6,7-*hexahydro*-5-*methyl*-1H-1,4-*diazepine* **6e**. B.p. 70–75 °C (0.01 mmHg); δ_H(300 MHz; $CDCl_3$) 1.08 (d, *J* 6.5, 3 H), 1.50 (dddd, *J* 3.7, 8.6, 8.6 and 14.5, 1 H), 1.63 (1 H, bs), 1.80 (dddd, *J* 3.8, 3.8, 7.8 and 14.4, 1 H), 2.52–2.64 (4 H, m), 2.68–2.84 (1 H, m), 2.92–3.07 (2 H, m), 3.62 (2 H, s) and 7.18–7.36 (5 H, m); δ_C(75 MHz; $CDCl_3$) 23.9, 37.7, 47.3, 52.8, 53.1, 58.9,

63.0, 126.8, 128.1, 128.8 and 139.6 (Found: $M^{\bullet+}$, 204.1620. $C_{13}H_{20}N_2$ requires 204.1626).

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References

1 (*a*) J. Elguero, E. Gonzalez and R. Jacquier, *Bull. Soc. Chim. Fr.*, 1969, 2054; (*b*) K. Hideg and D. Lloyd, *J. Chem. Soc. C*, 1971, 3441; (*c*) A. Bonvicini and G. Cantatore, *Chim. Ind. (Milan)*, 1972, **54**, 974; (*d*) K. Samula and E. Jurkowka-Kowalczyk, *Rocz. Chem.*, 1974, **48**, 2287; (*e*) S. P. Kasprzyk and S. Szymanski, *Pol. J. Chem.*, 1979, **53**, 525; (*f*) S. P. Kasprzyk and R. A. Kolinski, *Pol. J. Chem.*, 1984, **58**, 721.

2 D. Lloyd, W. Scheibelein and K. Hideg, *J. Chem. Res.* 1981, (*S*), 61; (*M*), 838 and references therein.

3 A. Benalil, unpublished results.

4 (*a*) A. Benalil, B. Carboni and M. Vaultier, *Tetrahedron*, 1991, **47**, 8177; (*b*) B. Carboni, A. Benalil and M. Vaultier, *J. Org. Chem.*, in the press.

5 M. S. Gibson, in *The Chemistry of the Amino Group*, ed. S. Patai, Interscience Publishers, London, 1968, pp. 61–65.

6 Y. Gololobov and L. F. Kasukhin, *Tetrahedron*, 1992, **48**, 1353; S. Eguchi, Y. Matsushita and K. Yamashita, *Org. Prep. Proced. Int.*, 1992, **24**, 209. For recent results, see also: J. Kurita, T. Iwata, S. Yasuike and T. Tsuchiya, *J. Chem. Soc., Chem. Commun.*, 1992, 81; G. A. McCort and J. C. Pascal, *Tetrahedron Lett.*, 1992, **33**, 4443; P. Molina, A. Arques, A. Alias, M. V. Vinader, M. C. Fores-Fores and F. H. Cano, *Tetrahedron*, 1992, **48**, 3091; S. Eguchi, K. Yamashita and Y. Matsushita, *Synlett.*, 1992, 295.

7 O. H. Hankovsky, K. Hideg, D. Lloyd and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1345.

8 M. Vaultier, P. H. Lambert and R. Carrié, *Bull. Soc. Chim. Fr.*, 1986, 83.

9 G. Cantatore and A. Bonvinici, *Chim. Ind. (Milan)*, 1972, **54**, 980; S. P. Kasprzyk and R. A. Kolinski, *Bull. Pol. Acad. Sci. Chem.*, 1984, **32**, 151; W. Heinrich and W. Heigel, *Ger. Pat.*, 1,047,785/1958 (*Chem. Abstr.*, 1961, **55**, 4552e).

10 N. G. Gaylord, *Reduction with complex metal hydrides*, Interscience Publishers, New York, 1956, p. 1011.

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