A Simple Stereoselective Synthesis of Primary Allylic Amines from 4-Amino-1-azadienes

José Barluenga,* Enrique Aguilar, Jesús Joglar, Bernardo Olano, and Santos Fustero

Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071 Oviedo, Spain

A new and efficient synthesis of primary allylic amines (**2**) from 4-amino-1-azadienes (**1**) *via* 1-azadienes (**5**) by reduction processes is described; the process is very simple, highly stereoselective, and takes place with very high chemical yields.

Allylic amines, especially primary allylic amines, are an important class of compounds not only for their utility as intermediates in organic synthesis but also because of their physiological properties[1] and their presence in several natural products.[2] Despite the growing interest in these types of compounds, only a relatively small number of procedures are available for their synthesis.[2,3]

Oxidative rearrangement of allylic selenides in the presence of amines,[3b] allylic amination of alkenes or allylic derivatives *via* transition metal catalysed reactions,[3c] and mainly allylic amination of alkenes *via* pericyclic reactions[3d] are some of the more recent and successful procedures described in the literature. However, long reaction times, relatively low chemical yields and, most important of all, the necessity for previous protection of the amine function (which often implies either difficulties in their later elimination or at least multi-step transformations[3b—d]), are some of the apparent limitations on these procedures.

We have recently demonstrated that the easily available 4-amino-1-azadienes (**1**)[4] (which can be prepared in multigram quantities) are suitable synthons not only in the preparation of a wide range of heterocycles[5] but also in the regio- and stereo-selective preparation of different types of monofunctionalised and β- and γ-difunctionalised[6] compounds by single reduction processes. In connection with these studies, we report a direct and simple method for the conversion of

Table 1. Allylic amines (**2**) obtained by 'AlH_3' reduction from (**1**).

Entry	Compd.	R^2	R^3	Yield (%)	Ratio (**2**)/(**3**)[a]	B.p. /°C 10^{-3} torr
1	(**2a**)	H	Et	95 (R^1 = *p*-MeC_6H_4) (68)[c]	88/5[b]	50—53
2	(**2b**)	Me	*p*-MeC_6H_4	98 (R^1 = *p*-C_6H_4) (88)[c]	>99/—	102—105
3				93 (R^1 = cyclo-C_6H_{11}) (80)[c]	>99/—	102—105
4	(**2c**)	Me	cyclo-C_6H_{11}	93 (R^1 = Ph) (77)[c]	>99/—	88—91
5	(**2d**)	Me	Ph	97 (R^1 = Ph) (80)[c]	>99/—	91—94
6	(**2e**)	Et	Ph	94 (R^1 = Ph) (89) (50)[c]	58/42 (70/26)[b]	oil[e]
7	(**2f**)	CH_2=$CHCH_2$	Ph	90 (R^1 = Ph) (92) (50)[c]	15/85 (66/31)[b]	oil[e]
8	(**2g**)	$PhCH_2$	Ph	99 (R^1 = Ph) (94) (61)[c]	—/>99 (74/26)	oil[e]
9	(**2h**)	HC≡CCH_2	Ph	90 (R^1 = *p*-C_6H_4) (99) (70)[c]	—[d] (88/8)[b]	oil[e]

[a] Values of method A determined from the crude mixture by g.c.m.s. and/or ^{1}H n.m.r. (300 MHz) (values for Method B in parentheses). [b] Small amounts (≤4%) of the corresponding saturated amines[6a] were also identified by g.c.m.s. [c] Yield of isolated product (**2**), based on (**1**). [d] A mixture of compounds including that corresponding to the partial [compound (**2f**)] or total reduction of the triple bond is obtained. [e] Purified by flash chromatography.

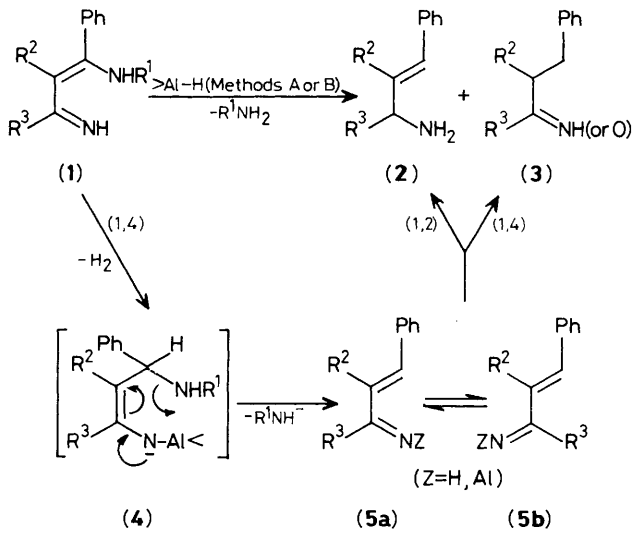
systems (**1**) into the corresponding primary allylic amines (**2**), avoiding the multistep sequences involved in most of the procedures previously reported.[3]

Thus, the treatment of (**1**) (15 mmol) with an excess of 'AlH_3' ($3LiAlH_4$ + $AlCl_3$)† [ratio (**1**) AlH_3 ≥ 1 : 5] in ether at room temperature for several hours (4—12 h) leads to the corresponding primary allylic amines (**2**) in very high yields‡ (see Scheme 1 and Table 1). The process is highly stereoselective, affording exclusively the stereoisomer *E* indicated (**2**) (nuclear Overhauser enhancement experiments).

The formation of the allylamines (**2**) can be understood by assuming a three-step mechanism (Scheme 1), in which the initial 1,4-reduction of (**1**) is followed by amine elimination and 1,2-imine reduction of the intermediate 1-azadiene (**5**).§

The reduction of the 1-azadiene intermediate (**5**) might also lead to the corresponding imine or carbonyl compounds (**3**), owing to competing 1,2- *vs.* 1,4-attack.[7] The ratio of allylamine (**2**) to imine compound (**3**)¶ was found to be strongly dependent on the bulk of R^2, which would have a significant influence on the (**5a**) ⟷ (**5b**) equilibrium. For example, in the series methyl, ethyl, allyl, and benzyl (entries 5—8, Table 1) the proportion of (**2**) observed [determined by ^{1}H n.m.r. (300 MHz) and g.c.–m.s.] was >99, 58, 15, and 0% respectively.

This apparent limitation can be circumvented by using method B (see Scheme 1); that is, reducing the system (**1**) (15



Scheme 1. *Reagents and conditions:* Method A: AlH_3 (excess)/ether/room temp., or Bu^i_2AlH (≥3 equiv.)/toluene/room temp. Method B: (i) Bu^i_2AlH (2 equiv.)/toluene/room temp.; (ii) anhydrous MeOH; (iii) $NaBH_4$/MeOH/room temp. [ratio (**1**): $NaBH_4$ ~1 : 2].

† In some instances (entry 1, Table 1) Bu^i_2AlH [ratio (**1**): Bu^i_2AlH ≥1 : 3] was used instead of AlH_3 as reducing agent.

‡ All products were obtained as oils, and were unequivocally characterised on the basis of their spectroscopic and mass spectral data and showed satisfactory microanalyses; *e.g.*, (**2a**): ^{1}H n.m.r. ($CDCl_3$) δ 0.91 (t, 3H), 1.52 (m, 2H), 1.59 (br. s, 2H, NH_2), 3.32 (q, 1H), 6.10 (dd, 1H, *J* 7.2 and 15.9 Hz), 6.43 (d, 1H, *J* 15.9 Hz), 7.15—7.36 (m, 5H); ^{13}C n.m.r. ($CDCl_3$) δ 136.8, 134.4, 128.7, 128.1, 126.9, 125.9, 52.2, 30.3, 10.2; *m/z* 161 (M^+), 132, 77. (**2d**): ^{1}H n.m.r. ($CDCl_3$) δ 1.65 (br. s, 2H, NH_2), 1.66 (s, 3H), 4.56 (s, 1H), 6.70 (s, 1H), 7.01—7.32 (m, 10H); ^{13}C n.m.r. ($CDCl_3$) δ 145.2, 142.8, 139.2, 130.8, 130.2, 129.4, 128.1, 127.3, 126.0, 64.3, 15.9; *m/z* 223 (M^+), 208, 106. (**2f**): ^{1}H n.m.r. ($CDCl_3$) δ 1.56 (br. s, 2H, NH_2), 2.52 (dd, 1H), 3.00 (dd, 1H), 4.60 (s, 1H), 4.96 (m, 2H), 5.72 (m, 1H), 6.84 (s, 1H), 6.92—7.30 (m, 10H); ^{13}C n.m.r. ($CDCl_3$) δ 144.1, 142.8, 137.7, 136.4, 129.7—126.1, 116.1, 60.4, 33.9; *m/z* 249 (M^+), 208, 106.

§ The azadiene (**5**) (Z = H) could be identified from the crude mixture (*e.g.*, entries 2 and 5, Table 1), by ^{1}H n.m.r. and g.c.–m.s. (70% yield), when a 2 : 1 molar ratio of Bu^i_2AlH (**1**) was used (see method B). This interesting type of compound is not easily available by other procedures. Their reactivity in other synthetic transformations is now being studied.

¶ Compounds (**2**) and (**3**) were readily separated by simple acid–base extraction, and purified by distillation or flash-chromatography (n-hexane : ether 7 : 3 and then ether). Compounds (**3**) were isolated and identified as their carbonyl derivatives (see ref. 6).

mmol) with Bu^i_2AlH (2 equiv.) in toluene at room temperature, and later treatment '*in situ*' of the azadiene (**5**) initially formed with an excess of $NaBH_4$ (2 equiv.) in methanol as solvent, at the same temperature. In this way, the chemoselectivity of the method is significantly improved (see entries 6—8, values in parentheses, Table 1).

In summary, we have reported an efficient and simple 'one pot' stereoselective synthesis of the synthetically important primary allylic amines by reduction of 4-amino-1-azadienes (**1**). The simplicity, high chemical yields, and stereoselectivity make the described method, in our opinion, the optimum route for synthesising primary allylic amines (**2**), some of which [*e.g.*, (**2f**) and (**2h**)] are either very difficult or impossible to obtain by other procedures. In this way, compounds (**2f**) and (**2h**) can be highly versatile synthons as intermediates in synthetic organic chemistry.

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References

1 (a) W. Bartmann and J. Kaiser, Ger. Offen., 2 103 119, 1972 (*Chem. Abstr.*, 1972, **77**, 140141m); (b) P. B. Berntson and P. A. Carlson, Ger. Offen., 2 220 333, 1974; (*Chem. Abstr.*, 1974, **80**, 108383t); (c) H. Kato, Ger. Offen., 2 350 125 (*Chem. Abstr.*, 1974; 1974, **80**, 37401e); (d) R. R. Rando, *Acc. Chem. Res.*, 1975, **8**, 281; (e) A. Stütz, *Angew. Chem.*, 1987, **93**, 323; *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 320; (f) T. N. Chase and D. B. Towers, 'GABA in Nervous System Function,' Raven Press, New York, 1976; (g) C. Walsh, *Tetrahedron*, 1982, **38**, 871; (h) A. Kawazoe, *Jpn. Kokai Tokkyo Koho* JP 7358,146, 1973 (*Chem. Abstr.*, 1974, **80**, 815w); (i) L. R. Morris, U.S. Pat. US3, 539,632, 1970; (*Chem. Abstr.*, 1971, **74**, 42123a).

2 R. B. Cheikh, R. Chaabouni, A. Laurent, P. Misson, and A. Nafti, *Synthesis*, 1983, 685.

3 (a) A. Laurent, P. Mison, A. Nafti, R. B. Cheikh, and R. Chaabouni, *J. Chem. Res.*, 1984, (*S*), 354; (*M*), 3164; T. M. Bargar, J. R. McCowan, J. R. MacCarthy, and E. R. Wagner, *J. Org. Chem.*, 1987, **52**, 678; G. Deleris, J. Dunogues, and A. Gadras, *Tetrahedron*, 1988, **44**, 4243; (b) R. G. Shea, J. N. Fitzner, J. E. Fankhauser, and P. B. Hopkins, *J. Org. Chem.*, 1984, **49**, 3647; R. G. Shea, J. N. Fitzner, J. E. Fankhauser, A. Spaltenstein, P. A. Carpino, R. M. Peevey, D. V. Pratt, B. J. Tenge, and P. B. Hopkins, *J. Org. Chem.*, 1986, **51**, 5243; (c) R. D. Connell, T. Rein, B. Åkermark, and P. Helquist, *ibid.*, 1988, **53**, 3845; (d) G. Kresze and H. Münsterer, *ibid.*, 1983, **48**, 3561.

4 (a) H. Hoberg and J. Barluenga, *Synthesis*, 1970, 142; (b) J. Barluenga, J. Jardón, and V. Gotor, *J. Org. Chem.*, 1985, **50**, 802.

5 J. Barluenga, M. Tomás, A. Ballesteros, V. Gotor, C. Krüger, and Y.-H. Tsay, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 181, and references cited therein.

6 (a) J. Barluenga, E. Aguilar, B. Olano, and S. Fustero, *J. Org. Chem.*, 1988, **53**, 1741; (b) J. Barluenga, B. Olano, S. Fustero, M. C. Foces-Foces, and F. Hernández, *J. Chem. Soc., Chem. Commun.*, 1988, 410, and references cited therein.

7 The competition 1,2- *vs.* 1,4-addition is well documented for the reduction of α,β-unsaturated carbonyl compounds. See, *e.g.*, (a) H. C. Brown and H. M. Hess, *J. Org. Chem.*, 1969, **34**, 2206; (b) R. O. Hutchins and D. Kandasamy, *ibid.*, 1975, **40**, 2530; (c) E. J. Corey, K. B. Becker, and R. K. Varma, *J. Am. Chem. Soc.*, 1972, **94**, 8616.