Highly diastereoselective synthesis of octahydroacridines by domino imine condensation–intramolecular polar [4π⁺ + 2π]-cycloaddition of anilines and ω-unsaturated aldehydes

Uwe Beifuss,* Andreas Herde and Sabine Ledderhose

Institut für Organische Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany

Substituted 1,2,3,4,4a,9,9a,10-octahydroacridines with five stereogenic centres are formed highly diastereoselectively by the domino imine condensation–intramolecular polar [4π⁺ + 2π]-cycloaddition of anilines and ω-unsaturated aldehydes.

The stereoselective synthesis of partially unsaturated *N*-heterocycles such as tetrahydroquinolines[1] and tetra- or octahydroacridines,[2] important for pharmacological research and the synthesis of natural products, is much more difficult to achieve than the preparation of the corresponding aromatic systems. One way to gain access to partially unsaturated *N*-heterocycles is based on the cycloaddition of electron-poor neutral and cationic 2-azabutadienes with electron rich dienophiles, and numerous methods of generating cationic 2-azabutadienes *in situ* have been developed.[3,4] Recently we have shown that 1,2,3,4-tetrahydroquinolines can be prepared regio- and diastereo-selectively by intermolecular polar [4π⁺ + 2π]-cycloaddition of cationic 2-azabutadienes generated by cleavage of *N,S*-acetals, α-aminosulfones and α-aminonitriles.[5] Octahydroacridines have been obtained by intramolecular cyclization of cationic 2-azabutadienes derived from oxime sulfonates by Beckmann rearrangement[6a] and by Lewis acid-catalysed cyclizations of *N*-arylimines.[6b] So far little is known of the mechanism of such processes in general, and on the influence of the configuration of diene and dienophile on the stereochemical outcome of such cyclizations in particular.

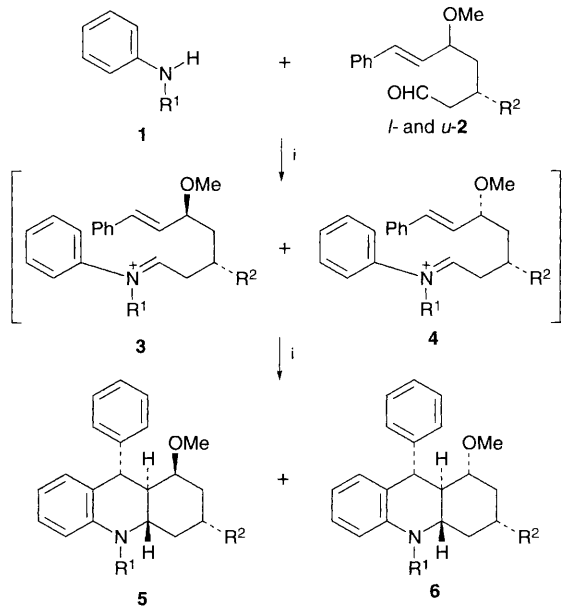
Here we report on the intramolecular polar [4π⁺ + 2π]-cycloaddition of di- and tri-substituted α-aryliminium ions **3** and **4**, generated *in situ* by imine condensation of anilines **1** and ω-unsaturated aldehydes **2**. This domino process[7] leads to the highly diastereoselective formation of octahydroacridines **5** and **6**† with five stereogenic centres (Scheme 1, Table 1).

The ω-unsaturated aldehydes **2a–c** were obtained in yields between 55 and 90% as mixtures of their *l*- and *u*-diastereoisomers by 1,4-addition of nucleophiles **8a–c** to the α,β-unsaturated aldehyde 7 (Scheme 2).[8]

The Lewis acid-catalysed domino reaction of aniline **1a** with aldehydes **2a** and **2b** exclusively gave the *trans*-annulated diastereoisomeric octahydroacridines **5a/6a** and **5b/6b** in 76 and 73% yield, respectively (Table 1, entries 1,2). Compounds **5** and **6** differ only with respect to the arrangement of the methoxy group at C-1: with type **5** the methoxy group occupies the *axial*, with type **6** the *equatorial* position. The same holds true for the transformations of *N*-methylaniline **1b** with **2a** and **2b**. Here also, only *trans*-annulated octahydroacridines are obtained; **5d/6d** and **5e/6e** were isolated in 71 and 70% yield (Table 1, entries 4, 5). Similar results were produced in the reactions of **1a** and **1b** with the phenylsulfanyl-substituted aldehyde **2c**. With **2c**, however, just **5c** and **5f**, respectively, with an *axial* methoxy group at C-1, could be isolated without decomposition (Table 1, entries 3, 6). Best yields were observed when the transformations were performed with BF_3·Et_2O (0.3 equiv.) as Lewis acid in CH_2Cl_2.

The structure elucidation of **5** and **6** was mainly based on NMR studies. For example, ^{1}H NMR and 2D COSY-experiments allowed an unambiguous configurational assignment of the diastereoisomers **5d**‡ and **6d**.§ In addition, An X-ray crystal structure analysis could be obtained for **5a**.¶

We assume that the reactions proceed as domino imine condensation–intramolecular polar [4π⁺ + 2π]-cycloaddition. In the first step the condensation of **1** with *l*- or *u*-**2** yields the corresponding iminium ions **3** and **4**, respectively. From PM3 calculations‖ on model compounds it is clear that not only di- but also tri-substituted iminium ions with an (*E*)-C=N⁺ bond are considerably more stable than the corresponding (*Z*)-isomers.

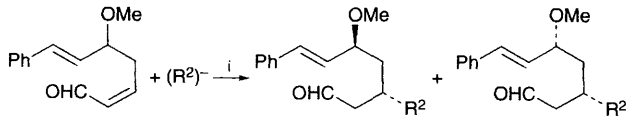


Scheme 1 *Reagents and conditions*: i, **2** (1.0 equiv.), CH_2Cl_2, −60 °C, **1** (1.0 equiv.), −60 °C, 10 min, BF_3·Et_2O (0.3 equiv.), then room temp., 12–15 h. The diastereomeric purity of **5** and **6** was determined by ^{1}H NMR and ^{13}C NMR.

Table 1 Diastereoselective formation of octahydroacridines **5** and **6** by domino imine condensation–intramolecular polar [4π⁺ + 2π]-cycloaddition

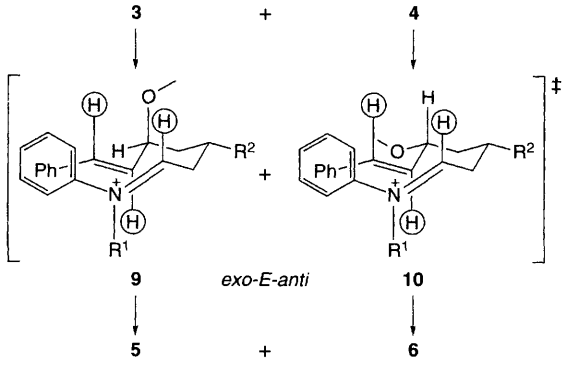
						Yield[b] (%)		
Entry	**1**	R¹	**2**	*l*-**2**:*u*-**2**[a]	**5**, **6**	**5** + **6**	**5**	**6**
1	**a**	H	**a**	1.3:1.0	**a**	76	38	29
2	**a**	H	**b**	1.1:1.0	**b**	73	35	29
3	**a**	H	**c**	1.3:1.0	**c**	63	30	23[c]
4	**b**	Me	**a**	1.3:1.0	**d**	71	31	25
5	**b**	Me	**b**	1.1:1.0	**e**	70	38	29
6	**b**	Me	**c**	1.3:1.0	**f**	67	31	23[c]

[a] *l*:*u* Ratios were determined by ^{1}H and/or ^{13}C NMR spectroscopy. [b] After column chromatography. [c] **6c** and **6f** could not be obtained pure due to decomposition upon purification.



7 **8** *l*-**2a** R^2 = $CH(CO_2Me)_2$ *u*-**2a** R^2 = $CH(CO_2Me)_2$; *l*-**2b** R^2 = $CH(CO_2Et)_2$ *u*-**2b** R^2 = $CH(CO_2Et)_2$; *l*-**2c** R^2 = SPh *u*-**2c** R^2 = SPh

Scheme 2 *Reagents and conditions*: i, for **2a** and **2b**: **8** (2.0 equiv.), THF, KOBu^t (0.3 equiv.), room temp., 30 min, **7** (1.0 equiv.), reflux, 2 h, 55% (with **2a**), 61% (with **2b**); for **2c**: **8** (10.0 equiv.), THF, 0 °C, BuLi (0.1 equiv.), 0 °C, 2 h, then room temp., 16 h, 90%



9 *exo-E-anti* **10**

5 + **6**

Scheme 3

This is why we assume the (*E*)-configuration for the C=N$^+$ bond in all iminium ions **3** and **4**.

In the second step of the domino process **3** and **4** undergo an intramolecular cyclization with the formation of three new stereogenic centres in sequence to yield the cycloadducts **5** and **6**, respectively. These cyclizations may either proceed as a one step intramolecular [4π$^+$ + 2π]-cycloaddition[3] or as a two step intramolecular 1,2-C=N$^+$ addition[9a]–intramolecular cationic cyclization[9b] sequence (Scheme 3).

In all cases studied so far only **5** and **6**, two out of 16 possible diastereoisomers, are formed, which can best be explained by assuming that both (*E*)-iminium ions **3** and **4** undergo kinetically controlled intramolecular polar [4π$^+$ + 2π]-cycloadditions. Passing the decalin-like *exo-E-anti*-transition state structures **9** and **10** the cycloadducts **5** and **6**, respectively, are obtained highly diastereoselectively. The conformation of **9** and **10** is governed by the bulky substituents R^2 preferring a *pseudoequatorial* arrangement. This view is strongly supported by the fact that the *l*:*u* ratio as well as the (*E*)-stereochemistry of the dienophilic double bond of **2** is retained during the whole process (Table 1). Furthermore, it was shown that **5** and **6** do not isomerize under reaction conditions. Additionally, AM1 calculations‖ suggest that the diastereoisomers obtained are not the most thermodynamically stable of the 16 possible diastereoisomers, which is consistent with a kinetically controlled process.

This work was supported by the Fonds der Chemischen Industrie. S. L. thanks the Cusanuswerk for a doctoral fellowship. We are grateful to Professor L. F. Tietze for his generous support and his interest in our work.

Footnotes

† Satisfactory analytical and spectral data were obtained for all compounds.

‡ *Selected data for* **5d**: δ_H (300 MHz; C_6D_6; Me_4Si; *J* in Hz) 0.74 (1 H, dt, *J* 2 and 14, 2-H_{ax}), 1.12 (1 H, dt, *J* 11 and 12, 4-H_{ax}), 1.77 (1 H, dt, *J* 2.5 and 11, 9a-H), 1.94 (1 H, ddd, *J* 2, 4 and 14, 2-H_{eq}), 2.36 (1 H, ddd, *J* 2.5, 3.5 and 12, 4-H_{eq}), 2.60–2.70 (1 H, m, 3-H_{ax}), 2.70 (3 H, s, NCH_3), 2.90–2.98 (1 H, m, 1-H), 2.95 (3 H, s, OCH_3), 3.22 (1 H, d, *J* 7.5, 3-CH), 3.28 (3 H, s, CO_2CH_3), 3.31 (3 H, s, CO_2CH_3), 3.43 (1 H, dt *J* 3.5 and 11, 4a-H), 4.24 (1 H, d, *J* 11, 9-H), 6.60 (1 H, dt, *J* 1 and 8, 7-H), 6.64 (1 H, dd, *J* 1 and 8, 5-H), 6.73 (1 H, dt, *J* 1.5 and 8, 6-H), 7.04–7.24 (6 H, m, 8-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H).

§ *Selected data for* **6d**: δ_H (500 MHz; C_6D_6; Me_4Si; *J* in Hz) 1.02 (1 H, dt, *J* 10.5 and 12, 4-H_{ax}), 1.12 (1 H, q, *J* 11.5, 2-H_{ax}), 2.10 (1 H, m_c, 4-H_{eq}), 2.18 (1 H, dt, *J* 8.5 and 10.5, 9a-H), 2.16–2.25 (2 H, m, 2-H_{eq}, 3-H), 2.43 (1 H, ddd, *J* 3.5, 10.5 and 11.5, 1-H), 2.60 (3 H, s, OCH_3), 2.80 (3 H, s, NCH_3), 2.80 (1 H, dt, *J* 4 and 10.5, 4a-H), 3.23 (1 H, d, *J* 7, 3-CH), 3.30 (3 H, s,CO_2CH_3), 3.32 (3 H, s, CO_2CH_3), 3.85 (1 H, d, *J* 8.5, 9-H), 6.66–6.70 (2 H, m, 5-H, 7-H), 6.95 (1 H, ddd, *J* 1, 1.5 and 8, 8-H), 6.99–7.08 (2 H, m, 6-H, 4′-H), 7.10–7.15 (2 H, m, 3′-H, 5′-H), 7.23–7.26 (2 H, m, 2′-H, 6′-H).

¶ *Crystal structure solution and refinement*: diffraction data were collected on a Siemens-Stoe AED four-circle diffractometer at 293 K with Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods with SHELX-86 and refined by full-matrix least-squares on F^2 (SHELX-93). Non-hydrogen atoms were refined anisotropically and hydrogen atoms inserted in calculated positions. *Crystal data*: $C_{25}H_{29}NO_5$, *M* = 423.5, monoclinic, space group $P2_1/c$, *a* = 1011.40(10), *b* = 2917.3(8), *c* = 763.70(10) pm, α = 90, β = 94.300(10), γ = 90 °, *V* = 2.2470(7) nm^3, *Z* = 4, D_c = 1.252 Mg/m^3, μ_{calc} = 0.087 mm^{-1}, *F*(000) = 904, crystal size 0.4 × 0.4 × 0.3 mm, 11486 collected reflections, 2933 independent reflections, goodness of fit 1.087, refinement converged for all data with *R*1 = 0.0743 and *wR*2 = 0.1391. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/44. The X-ray analysis of **5a** was performed by Dr M. Noltemeyer and H.-G. Schmidt (Institut für Anorganische Chemie, Tammannstr. 4, D-37077 Göttingen, Germany).

‖ Calculations were performed using the VAMP and MOPAC 6.0 packages. VAMP (T. Clark, Universität Erlangen-Nünberg) is a vectorieed version of AMPAC and MOPAC.

References

1 J. P. Michael, *Nat. Prod. Rep.*, 1995, **12**, 465; P. Magnus, D. Parry, T. Iliadis, S. A. Eisenbeis and R. A. Fairhurst, *J. Chem. Soc., Chem. Commun.*, 1994, 1543; M. Isobe, T. Nishikawa, N. Yamamoto, T. Tsukiyana, A. Ino and T. Okita, *J. Heterocycl. Chem.*, 1992, **29**, 619.

2 G. M. Shutske, G. M. Bores, K. C. Bradshaw, F. P. Huger, K. J. Kapples, R. D. Larsen, D. K. Rush and J. D. Tomer, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 865; E. T. Michalson, S. D'Andrea, J. P. Freeman and J. Szmuszkovicz, *Heterocycles*, 1990, **30**, 415.

3 Reviews: H. Waldmann, *Synthesis*, 1994, 535; D. L. Boger and S. N. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987; R. R. Schmidt, *Angew. Chem.*, 1973, **85**, 235; *Angew. Chem. Int. Ed. Engl.*, 1973, **12**, 212.

4 J. M. Mellor and G. D. Merriman, *Tetrahedron*, 1995, **51**, 6115; A. R. Katritzky, B. Rachwal and S. Rachwal, *J. Org. Chem.*, 1995, **60**, 3993; H.-J. Ha, Y.-G. Ahn and J.-K. Chon, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2631; T. Fuchigami and S. Ichikawa, *J. Org. Chem.*, 1994, **59**, 607.

5 U. Beifuss, O. Kunz, S. Ledderhose, M. Taraschewski and C. Tonko, *Synlett*, 1996, 34; U. Beifuss and S. Ledderhose, *J. Chem. Soc., Chem. Commun.*, 1995, 2137.

6 (*a*) S. Sakane, Y. Matsumura, Y. Yamamura, Y. Ishida, K. Maruoka and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 672; (*b*) O. Temme and S. Laschat, *J. Chem. Soc., Perkin Trans. 1*, 1995, 125.

7 Review: L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115.

8 A. Ishida and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 161.

9 (*a*) Review: M. Tramontini and L. Angiolini, *Tetrahedron*, 1990, **46**, 1791; (*b*) review: G. A. Olah, R. Krishnamurti and G. K. S. Prakash, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 3, p. 293.

Received, 28th December 1995; Com. 5/08399K