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STAR-SHAPED THREEFOLD DIHYDROPYRIDINE AND XANTHENE DERIVATIVES

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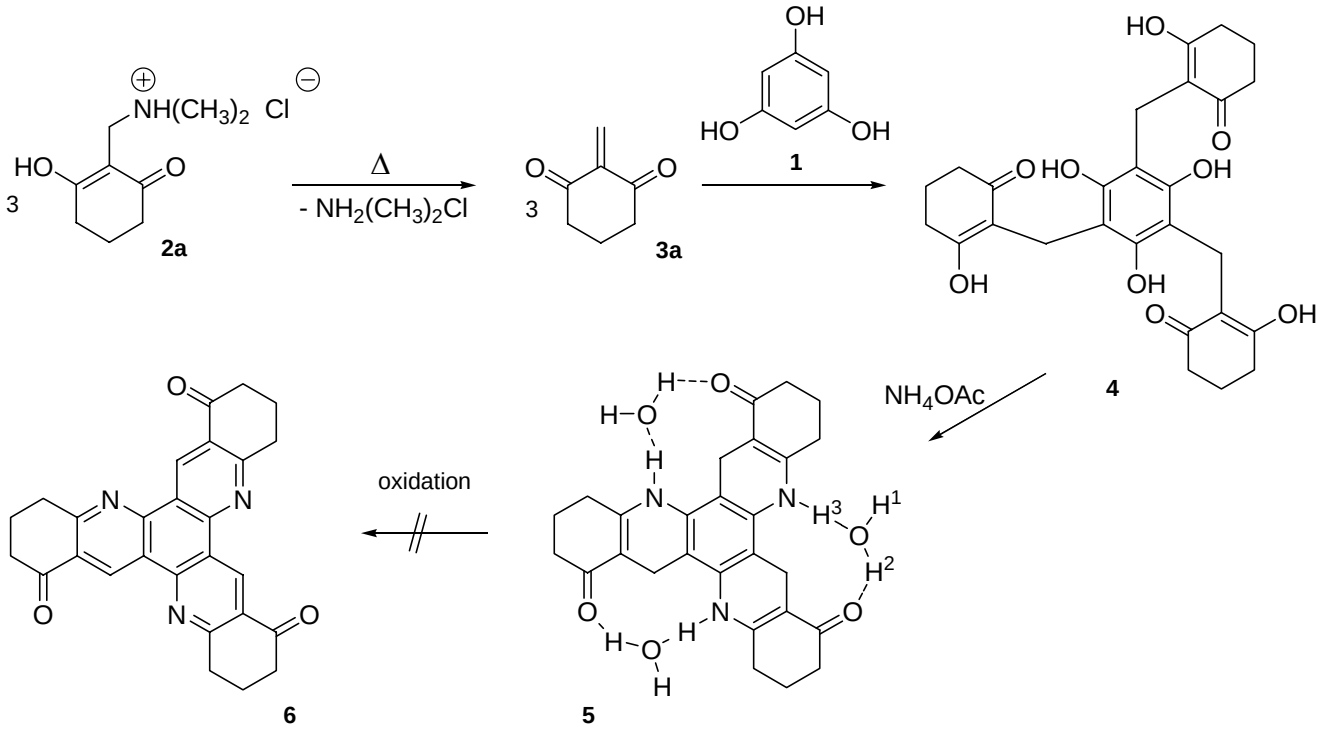
Abstract – Novel star-shaped threefold dihydropyridine (**5**) and xanthene derivatives (**8**) have been synthesized using a highly efficient one-pot procedure. Phloroglucinol (**1**) and Mannich bases (**2**) have been used as readily available starting materials. The hydrogen bonding in dihydropyridine derivative (**5**) is characterized by an uncommon high kinetic stability.

Not only since the Nobel Prize for Chemistry was rewarded to C. J. Pedersen, J.-M. Lehn and D. J. Cram in 1987, supramolecular chemistry has become an expanding field of research and the design of novel structures as ligands for supramolecular ensembles still remains an important goal for synthetic chemists.[1] In recent years, numerous methods for the synthesis of oligopyridine derivatives, such as bipyridines or terpyridines with one or two coordination sites, have been developed.[2] However, oligopyridine structures bearing three coordination sites have hardly been described in the literature.[3]

In previous works we have shown, that iminium salts and Mannich bases are also versatile building blocks for highly efficient one-pot syntheses of a huge variety of mono-, bi- and terpyridine derivatives.[4] It was our goal to synthesize star-shaped tritope ligands in one-pot procedures applying the strategies developed in our group in the synthesis of novel oligotope ligands.[5] These structures are of increasing interest due to their potential applications as core molecules in dendritic structures.[6]

Phloroglucinol (**1**) was chosen as the nucleophilic starting material to react in a threefold Michael-type reaction. On heating a suspension of **1** and **2a** (3 eq.) in the presence of ammonium acetate (6 eq.), selectively the threefold dihydropyridine (**5**) was obtained in 60% yield (**Scheme 1**). It is well known, that Mannich bases (**2**)[7] easily undergo thermal elimination of amine to form α,β-unsaturated ketones (**3**). We suppose that the highly reactive Michael acceptor (**3a**) will react with phloroglucinol (**1**) to give intermediate (**4**). In presence of ammonium acetate as source for ammonia, cyclization leads to the novel tris(1,4-dihydropyridine) derivative (**5**).[8] Interestingly, the reaction sequence is stopped at this stage and the spontaneous oxidation to form the pyridine derivative did not occur.[4] So far, all attempts failed to

aromatize the 1,4-dihydropyridine derivative. In many cases ($RuCl_3/O_2$, chloranil, DDQ, H_2O_2) the starting material was recovered. Other methods (CAN, $KMnO_4$, MnO_2, $Cu(OAc)_2$, HNO_3, $NaNO_2$) only led to the decomposition of **5**.

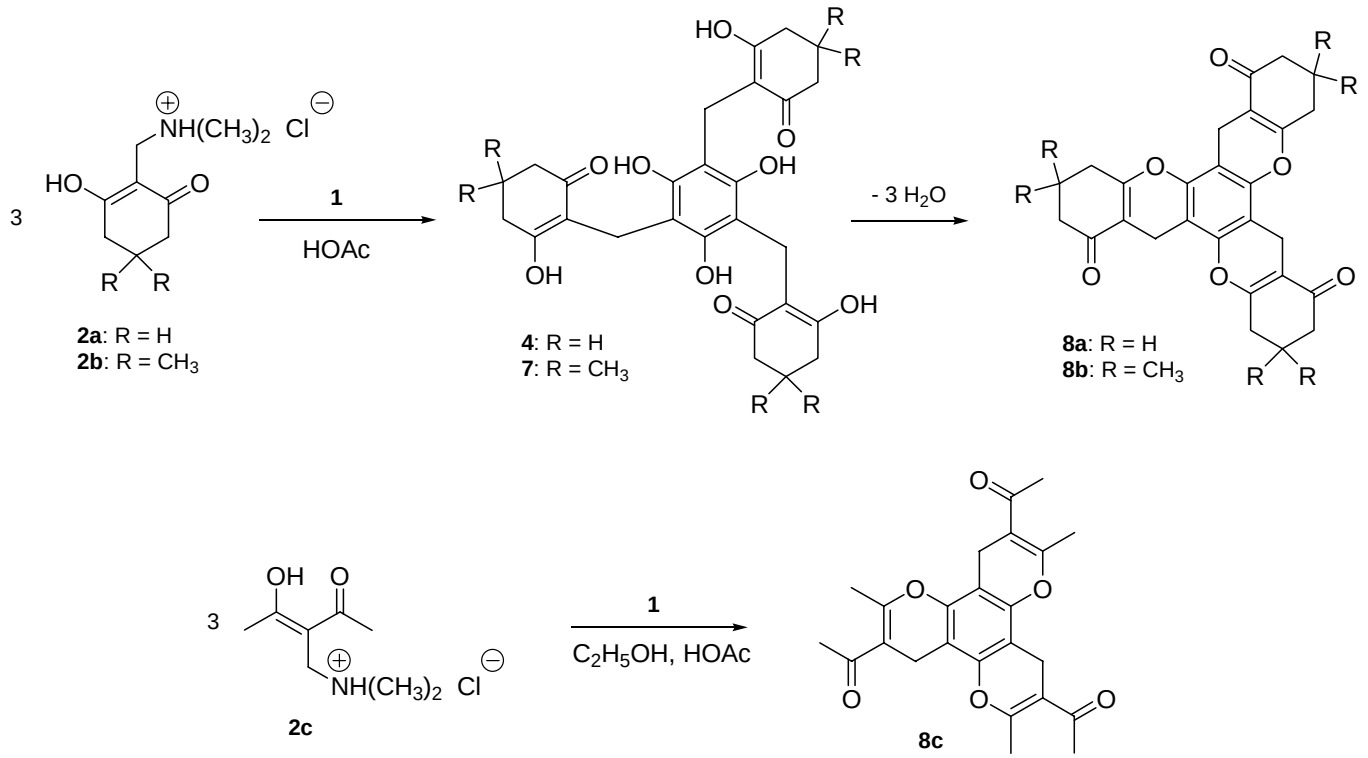


Scheme 1

The surprising stability of **5** obviously results from the three molecules of water each fixed by hydrogen bonding between the carbonyl groups and the protons attached to nitrogen. MS spectrometry (FAB^+) gave further evidence for the remarkable stability of **5** as on ionization the M^+-peak at 495 *m/z* ($441+3H_2O$) could be observed. Simple *ab initio* calculation methods[9] gave average bond energies of 7.2 kcal/mol for each H_2O-molecule (3.6 kcal/mol per hydrogen). In comparison to literature values for similar structures,[10] this bond strength can be ranked as medium.

The signals for both of the water protons and the proton attached to nitrogen can clearly be separated and assigned by ^1H NMR spectroscopy of **5** in DMSO-d_6. The uncommon high kinetic stability of the hydrogen bonding of **5** in respect of host-guest-systems[11] was studied in detail by ^1H NMR spectroscopy. Exchange experiments in D_2O showed that the signal at 11.95 ppm can be assigned to the proton H^1 not involved in hydrogen bonding. This proton was exchanged by deuterium within 10 min whereas H^2 and H^3 (7.64 ppm and 7.87 ppm) were hardly exchanged in hours. The broad signals observed in the ^1H NMR spectra using other solvents ($CDCl_3$, acetone-d_6, methanol-d_4) might be explained by aggregation processes and will be subject of further investigations.

The unusual structure of **5** has not been described in the literature before. Yet, only some examples of similar disk-shaped molecules have been reported.[1] Further research focused on mechanistic studies to isolate and identify intermediates in the reaction cascade described above. Therefore, phloroglucinol (**1**) and a Mannich base (**2**) (3 eq.) were reacted without any source of ammonia to give threefold xanthene derivatives (**8**) in moderate yields (**Scheme 2**). The proposed mechanism for the formation of **4**/**7** is consistent with the one discussed above (**Scheme 1**). In absence of ammonia, these intermediates cyclized to give O-analogues (**8**) of dihydropyridine derivatives (**5**).



Scheme 2

It is well known, that xanthene derivatives can be converted into the corresponding pyridine derivatives reacting them with a source of ammonia.[13] However, in the present case this transformation failed on refluxing **8** with NH_4OAc in acetic acid or NH_3/ethanol. This observation could be explained by the stabilizing effect caused by the central aromatic ring.

To the best of our knowledge, xanthene derivatives of this special structure have not been described before (no compounds with this substructure were found in the Beilstein Crossfire database). Very few papers cope with the synthesis of pyrane derivatives derived from Mannich bases, though the procedure is different from the one presented here (Hetero-Diels-Alder reactions with dienophiles).[13] Some xyloketals of similar structure have also been isolated from mangrove fungus.[14]

Though we did not yet succeed in the synthesis of tritope ligands using the methodologies developed in our group,[4] novel star-shaped threefold dihydropyridine (**5**) and xanthene derivatives (**8**) displaying interesting properties were synthesized. Furthermore, we could obtain useful information about the reactivity and application potential of Mannich bases in respect of future investigations.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. All solvents were dried and distilled according to standard procedures and stored under argon. Chromatographic separation was performed on aluminum oxide (neutral, Macherey & Nagel, 0.063-0.200 mm). Melting points were obtained on a Büchi SMP-20 mp apparatus and are uncorrected. IR spectra were measured on a Nicolet 510 P FT-IR spectrometer. All NMR spectra were recorded on a Bruker ARX 200 instrument (200 MHz for ^{1}H and 50 MHz for ^{13}C) with TMS as an internal standard. FAB^{+}-MS spectra were recorded using a Finigan MAT 8230 apparatus, GC-MS spectra were recorded on a Finigan MAT Magnum TM spectrometer. Elemental analyses were obtained on a Perkin-Elmer M 240 analyzer.

(2-Hydroxy-6-oxocyclohex-1-enylmethyl)dimethylammonium chloride (2a)

A solution of 1,3-cyclohexandione (3.00 g, 26.8 mmol) in dry CH_2Cl_2 (10 mL) was cooled to -40°C. N,N-Dimethylmethyleneammonium chloride[16] (2.40 g, 26.8 mmol) was added, the reaction mixture was stirred at this temperature for 3 h and then kept in the fridge for 12 h. During this time, the hydrochloride of the Mannich base crystallized. The product was isolated, recrystalized from CH_2Cl_2 dried in vacuo to give 4.12 g (76%) of a white solid, mp 134 °C (lit.,[17] 72%, mp 134.7 °C). ^{1}H NMR ($CDCl_3$/methanol-d_4 (5:1)): 1.92 (m_c, 2H, CH_2), 2.49 (t, ^{3}J = 6.3 Hz, 4H, CH_2), 2.69 (s, 6H, CH_3), 3.85 (s, 2H, CH_2).

(2-Hydroxy-6-oxo-4,4-dimethylcyclohex-1-enylmethyl)dimethylammonium chloride (2b)

N,N-Dimethylmethyleneammonium chloride[16] (0.66 g, 7.14 mmol) was added to a solution of dimedone (1.00 g, 7.10 mmol) in dry acetonitrile (7 mL). The reaction mixture was stirred at rt for 2 h, during this time, the hydrochloride of the Mannich base crystallized. The product was isolated, recrystalized from CH_2Cl_2 and dried in vacuo to give 1.41 g (85%) of a white solid, mp 134 °C (lit.,[17] 87%, mp 134 °C). ^{1}H NMR ($CDCl_3$): 1.02 (s, 6H, CH_3), 2.43 (m_c, 4H, CH_2), 2.71 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 3.94 (s, 1H, N*H*), 9.85 (bs, 1H, O*H*).

3-Dimethylaminomethyl-4-hydroxypent-3-en-2-one hydrochloride (2c)

N,N-Dimethylmethyleneammonium chloride[16] (0.94 g, 10 mmol) was added to a solution of acetylacetone (1.00 g, 10.0 mmol) in acetonitrile (7 mL). The reaction mixture was stirred at rt for 30

min; during this time, the hydrochloride of the Mannich base crystallized. The product was isolated, recrystallized and dried in vacuo to give 1.54 g (80%) of a white solid, mp 139 °C (lit.,[18] 93%, mp 139 °C). ^{1}H NMR (methanol-d_4): 2.40 (s, 6H, C*H*$_3$), 2.92 (s, 6H, NC*H*$_3$), 4.18 (s, 2H, C*H*$_2$).

3,4,6,9,10,11,12,14,15,16,17,18-Dodecahydro-2*H*,5*H*,8*H*-5,11,17-triazatrinaphthylene-1,7,13-trione (5)

A suspension of **2a** (1.92 g, 9.4 mmol), phloroglucinol (**1**) (0.51 g, 3.1 mmol) and ammonium acetate (6.5 g, 84.3 mmol) in ethanol (40 mL) was heated at reflux for 4 h under an atmosphere of Ar. The solvent was evaporated after cooling. The solid residue was resolved in CH_2Cl_2 (50 mL) and water (50 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (5 x 50 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The crude product was purified by flash column chromatography on neutral Al_2O_3 (eluent: CH_2Cl_2/MeOH 75:1) to give 0.93 g (60%) of a pale yellow solid, mp 253 °C (decomp). IR (KBr): ν = 3343, 3203, 2935, 2888, 2629, 1656, 1615, 1512, 1450, 1408, 1181, 1103, 994. ^{1}H NMR (DMSO-d_6): 1.77 (m, 2H, C*H*$_2$), 2.23 (m, 2H, C*H*$_2$), 2.40 (m, 2H, C*H*$_2$), 3.26 (s, 2H, C*H*$_2$), 7.64 (s, 1H), 7.87 (s, 1H), 11.95 (s, 1H). ^{13}C NMR (DMSO-d_6): 19.0, 21.7, 29.7, 35.7, 106.7, 108.2, 152.4, 168.7, 196.8. FAB$^+$-MS (matrix: 2-nitrobenzyl alcohol); *m/z* (%): 495 (31) [M^+], 477 (4) [M^+-H_2O], 460 (3) [M^++H-2H_2O]$^+$, 385 (4), 307 (20), 289 (13), 154 (100). Anal. Calcd for $C_{27}H_{33}N_3O_6$: C 65.44 H 6.71 N 8.48. Found C 65.37 H 6.68 N 8.53.

2,3,4,6,8,9,10,12,14,15,16,18-Dodecahydro-5,11,17-trioxatrinaphthylene-1,7,13-trione (8a)

A stirred suspension of **2a** (1.0 g, 4.9 mmol) and phloroglucinol (**1**) (0.26 g, 1.6 mmol) in acetic acid (10 mL) was heated at 120 °C for 16 h under an atmosphere of Ar. The white precipitate was filtered off and washed with water (3 x 25 mL). The crude product was purified by flash column chromatography on neutral Al_2O_3 (eluent: CH_2Cl_2/MeOH, 100:1) to give 0.26 g (37%) of a white solid, mp >270 °C. IR (KBr): ν = 2950, 2903, 2841, 1657, 1626, 1264, 1383, 1222, 1106, 1026. ^{1}H NMR (DMSO-d_6): 1.99 (t, ^3J = 5.9 Hz, 2H, C*H*$_2$), 2.38 (m$_c$, 2H, C*H*$_2$), 2.49 (m$_c$, 2H, C*H*$_2$), 3.22 (s, 2H, C*H*$_2$); ^{13}C NMR (DMSO-d_6): 20.8, 24.7, 31.8, 40.8, 109.2, 113.7, 150.3, 174.0, 203.2. GC-MS (70 eV); *m/z* (%): 444 (79) [M^+], 388 (12), 352 (21), 338 (100), 282 (31). Anal. Calcd for $C_{27}H_{24}O_6$: C 72.96 H 5.44. Found C 72.73 H 5.61.

3,3,9,9,16,16-Hexamethyl-2,3,4,6,8,9,10,12,14,15,16,18-dodecahydro-5,11,17-trioxatrinaphthylene-1,7,13-trione (8b)

A stirred suspension of **2b** (0.70 g, 3.0 mmol) and phloroglucinol (**1**) (0.17 g, 1.0 mmol) in acetic acid (5 mL) was heated at 120 °C for 16 h under an atmosphere of Ar. The reaction mixture was neutralized with sat. aq. Na_2CO_3 and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried

(Na_2SO_4) and the solvent evaporated. The residue was purified by flash column chromatography on neutral Al_2O_3 (eluent: CH_2Cl_2/MeOH, 100:1) to give 0.32 g (20%) of a white solid, mp >270 °C. IR (KBr): ν = 2960, 1657, 1616, 1435, 1383, 1217, 1166, 1036. ^{1}H NMR ($CDCl_3$): 1.16 (s, 18H, C*H*$_3$), 2.37 (s, 6H, C*H*$_2$), 2.48 (s, 6H, C*H*$_2$), 3.39 (s, 6H, C*H*$_2$). ^{13}C NMR ($CDCl_3$): 16.9, 28.8, 32.5, 41.7, 51.1, 105.4, 108.7, 146.7, 164.9, 198.5. Anal. Calcd for $C_{33}H_{36}O_6$: C 74.96 H 6.87. Found C 75.24 H 6.93.

1-(7,11-Diacetyl-2,6,10-trimethyl-4*H*,8*H*,12*H*-dipyrano[2,3-*f*;2',3'-*h*]chromene-3-yl)ethanone (8c)

A stirred suspension of **2c** (0.40 g, 2.07 mmol) and phloroglucinol (**1**) (0.11 g, 0.69 mmol) in ethanol (5 mL) was refluxed for 3 h under an atmosphere of Ar. The solvent was evaporated after cooling. The residue was resolved in acetic acid (5 mL) and heated at 120 °C for further 2 h. The reaction mixture was neutralized with sat. aq. Na_2CO_3 and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. The crude product was purified by flash column chromatography on neutral Al_2O_3 (eluent: CH_2Cl_2/MeOH, 100:1) to give 90 mg (35%) of a white solid, mp >250 °C (decomp). IR (KBr): ν = 2933, 2891, 2847, 1662, 1617, 1553, 1372, 1216, 1121, 1109, 1047. ^{1}H NMR ($CDCl_3$): 2.30 (s, 9H, C*H*$_3$), 2.30 (s, 9H, C*H*$_3$), 3.42 (s, 6H, C*H*$_2$). ^{13}C NMR ($CDCl_3$): 20.2, 20.9, 30.3, 103.7, 109.3, 146.3, 159.2, 199.6. GC-MS (70 eV); *m/z* (%): 408 (53) [M^+], 393 (65), 365 (22), 314 (40), 299 (53), 271 (21). Anal. Calcd for $C_{24}H_{24}O_6$: C 70.57 H 5.92. Found C 70.71 H 5.68.

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REFERENCES AND NOTES

1. J.-M. Lehn, 'Supramolecular Chemistry – Concepts and Perseptives', VCH, Weinheim, 1995.
2. U. S. Schubert and C. Eschbaumer, *Angew. Chem., Int. Ed.*, 2002, **41**, 2892; U. S. Schubert and M. Heller, *Eur. J. Org. Chem.*, 2003, 947.
3. P. N. W. Baxter, J.-M. Lehn, G. Baum, and D. Fenske, *Chem. Eur. J.*, 1999, **5**, 102; P. N. W. Baxter, J.-M. Lehn, B. O. Kneisel, G. Baum, and D. Fenske, *Chem. Eur. J.*, 1999, **5**, 113; F. Romero and R. Ziessel, *Tetrahedron Lett.*, 1994, **35**, 9203; D. Tzalis and Y. Tor, *J. Chem. Soc., Chem. Commun.*, 1996, 1043; E. C. Riesgo, X. Jin, and R. P. Thummel, *J. Org. Chem.*, 1996, **61**, 3017; E. C. Constable and M. W. Cargill Thompson, *J. Chem. Soc., Dalton Trans.*, 1992, 3467.
4. R. Keuper, N. Risch, U. Flörke, and H.-J. Haupt, *Liebigs Ann.*, 1996, **5**, 705; U. Westerwelle, A. Esser, and N. Risch, *Chem. Ber.*, 1991, **124**, 571; D. Sielemann, R. Keuper, and N. Risch, *J. Prakt. Chem.*, 1999, **341**, 487; D. Sielemann, R. Keuper, and N. Risch, *Eur.J. Org. Chem.*, 2000, 543; R.

Keuper and N. Risch, *Eur. J. Org. Chem.*, 1998, 2609; R. Keuper and N. Risch, *J. Prakt. Chem.*, 1998, **340**, 424; A. Winter and N. Risch, *Synthesis*, 2003, 2667; D. Sielemann, A. Winter, U. Flörke, and N. Risch, *Org. Biomol. Chem.*, 2004, **2**, 863.

5. A. Winter, 'Oligotope Ligands and Nicotinonitriles – Modern Applications of the Mannich Reaction in the Synthesis of Pyridine Derivatives', PhD thesis, Paderborn University, 2003.
6. E. C. Constable, *J. Chem. Soc., Chem. Commun.*, 1997, **12**, 1073; T. W. Bell, *Science*, 1996, **271**, 1077; S. Campagna, G. Denti, S. Serroni, A. Juris, M. Venturi, V. Ricevuto, and V. Balzani, *Chem. Eur. J.*, 1995, **1**, 211.
7. G. Kienast and L. F. Tietze, *Angew. Chem., Int. Ed.*, 1976, **15**, 239.
8. It is not yet clear, on which stage of the reaction sequence ammonia is involved. An alternative reaction pathway could be proposed assuming a prior formation of a threefold imine resp. enamine from **1** and ammonia.
9. DFTB-Method; M. Elstner, Physics Department, Faculty of Science, Paderborn University, Warburger Str. 100, 33098 Paderborn, Germany.
10. M. D. Joesten, *J. Chem. Edu.*, 1982, **79**, 362.
11. D. S. Lawrence, T. Jiang, and M. Levett, *Chem. Rev.*, 1995, **98**, 2229.
12. G. Ege and C. Freund, *Tetrahedron Lett.*, 1978, **39**, 3677; S. von Niementowski, *Chem. Ber.*, 1906, **39**, 319; C. M. Hall, J. B. Wright, G. Johnson, and A. J. Taylor, *J. Med. Chem.*, 1977, **20**, 1337.
13. K. Singh, H. Singh, and J. Singh, *Tetrahedron*, 1996, **52**, 14237; O. S. Wolfbeis and H. Junek, *Z. Naturforsch.*, 1975, **30**, 249.
14. M. Tramontini, *Synthesis*, 1973, 703.
15. Y. Lin, X. Wu, S. Feng, G. Jiang, J. Luo, S. Zhou, L. L. P. Vrijmoed, E. B. G. Jones, K. Krohn, K. Steingröver, and F. Zsila, *J. Org. Chem.*, 2001, **66**, 6252.
16. L. F. Tietze and T. Eicher, 'Reaktionen und Synthesen im organisch-chemischen Praktikum', Thieme Verlag, Stuttgart, 1981.
17. R. Keuper and N. Risch, *Eur. J. Org. Chem.*, 1998, 2609.
18. H. Möhrle and R. Schaltenbrand, *Pharmazie*, 1985, **40**, 697.