HETEROCYCLES, Vol. 57, No. 7, 2002, pp. 1257 - 1264, Received, 15th April, 2002

A NEW SYNTHESIS OF 1,2-DIAZETINES *VIA* SIMPLE CYCLOACYLATION REACTIONS

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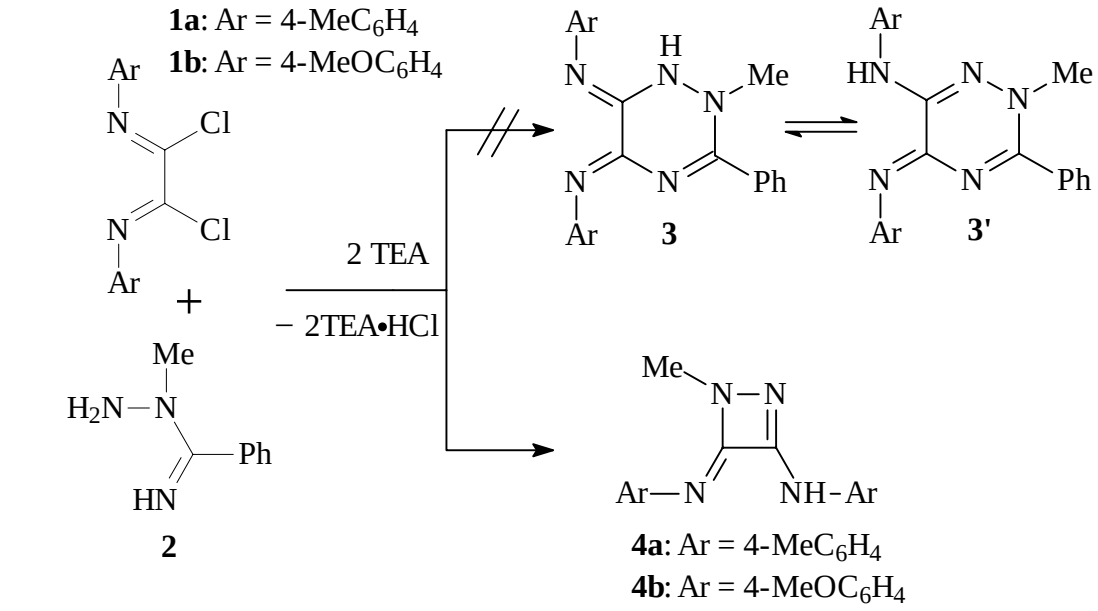
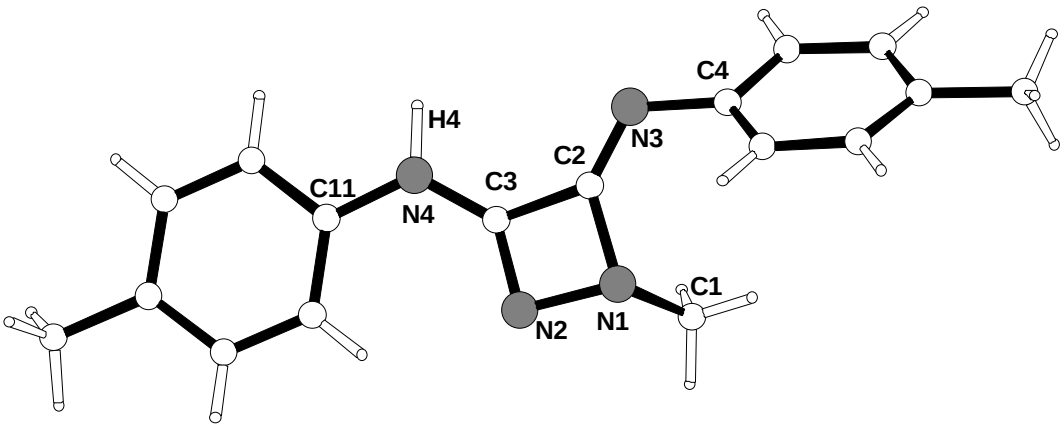
Abstract – Several new 1,2-diazetines (**4a-e)** were synthesized *via* simple cycloacylation reactions of various monoalkylhydrazines (**5a-c**) with *bis*-imidoyl chlorides of oxalic acid (**1**). An X-Ray crystal structure analysis obtained from single crystals of **4a** reveals an additional double bond in the 4-membered ring system. Treatment of these heterocycles with strong bases formed delocalized anions (**6**) which can be methylated giving 1,2-disubstituted diazetidines (**7a,b**). Alternatively, the latter derivatives can be synthesized *via* a cycloacylation employing 1,2-dimethylhydrazine and bis-electrophiles (**1**).

Four-membered nitrogen heterocycles are wide spread in synthetic organic chemistry and in nature in the form of biological active compounds such as ß-lactams. However, four-ring heterocycles that bear two nitrogen atoms in 1,2-position are quite rare and only a few examples have been reported in the literature. [1] To our knowledge, there are few derivatives which possess an additional double bond between nitrogen and carbon ring atoms. [2] In this article, we describe a new and efficient synthesis of 1-substituted 4-imino-1,2-diazetines (**4a-e**) and discuss their alkylation which leads to the 1,2-disubstituted diazetidine-3,4-diimines (**7a,b**).

Our aim was originally to synthesize triazines (**3**) by cyclization of amidrazones (**2**) [3] with bis-imidoyl chlorides of oxalic acid (**1**). Derivatives (**3**) should preferably exist in the prototropic form (**3'**) as compared to corresponding five-membered heterocycles. [4] This cyclic arrangement of the amidine substructure should be able to efficiently complex various metal ions. [5]

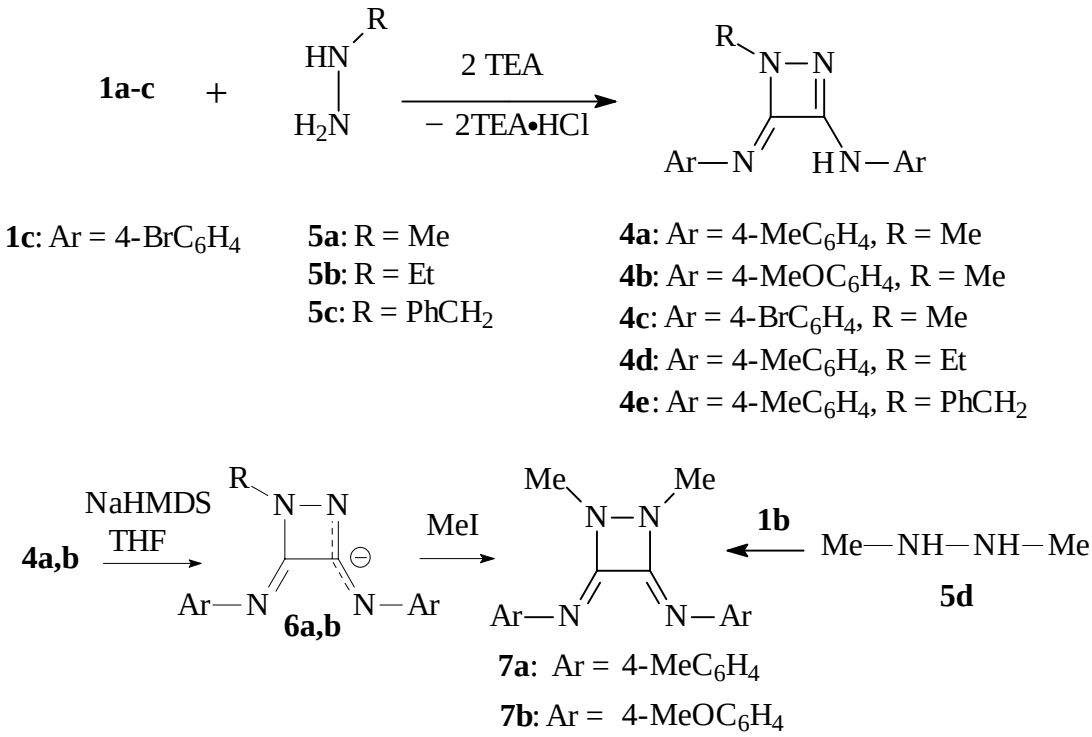




Scheme 1 and Figure 1: Perspective drawing of **4a**; the numbering corresponds to that used for the X-Ray analysis. Selected distances [Å] and angles [°]: N1-C2 1.463(2), N1-C1 1.4746(19), N1-N2 1.5241(17), N2-C3 1.314(2), N3-C2 1.254(2), N3-C4 1.4288(19), N4-C3 1.3419(19), N4-C11 1.4188(19), C2-C3 1.467(2), N4-H4 0.9886, C2-N1-C1 114.79(13), C2-N1-N2 86.66(11), C3-N2-N1 90.77(12), N1-C2-C3 87.46(13), N2-C3-C2 94.84(13).

Reaction of the bis-imidoyl chloride (**1a)** with the amidrazone (**2**) in THF in the presence of triethylamine at room temperature afforded a yellow colored solution in which a new main product was detected by TLC. Isolation of this product was complicated because a fast decomposition of the compound to tarry materials took place particularly at temperatures higher than room temperature. Therefore, the solvent was concentrated at low temperatures *in vacuo* to give the new crystalline

derivative (**4a**) in a 38% yield. Under the same reaction conditions, **2** could be reacted with the bis-imidoyl chloride (**1b**) giving **4b** in a 48% yield. The X-Ray analysis of the pale yellow crystals of **4a** succeeded and the result is shown in Figure 1. Instead of a six-membered heterocycle (**3**), the diazetine (**4a**) was unexpectedly formed. Figure 1 reveals some characteristic structural details of this compound: Whereas the bond lenghth between N1-C2 amounts to 1.463 (2) Å, the bond between N2 and C3 is shortened 1.314(2) Å . The hydrogen atom is fixed in the exocyclic position at N4. The bond C2-N3 has a clear double bond character (1.254 Å) and can therefore be regarded as being part of a semicyclic amidine system. The four-membered ring system is almost planar with a torsion angle of only 3.6°. In the crystal lattice, two molecules of **4a** are connected by weak H-bond bridges between N1 and N4‘-H.



Scheme 2

Since the starting material was clearly the amidrazone (**2**), the initial acylation is presumably followed by a fragmentation to benzonitrile which could be detected by GC-MS. Alternatively, the methyl-hydrazine (**5a**) could be cycloacylated with the bielectrophilic derivative (**1a**) smoothly yielding the diazetine (**4a**) (56%). In an analogous manner, the new four-membered heterocycles (**4b-e**) could be synthesized starting from other monosubstituted alkylhydrazines (**5b,c**). Under the same conditions, employment of monoarylhydrazines produced a wide spectrum of products which have not been further characterized.

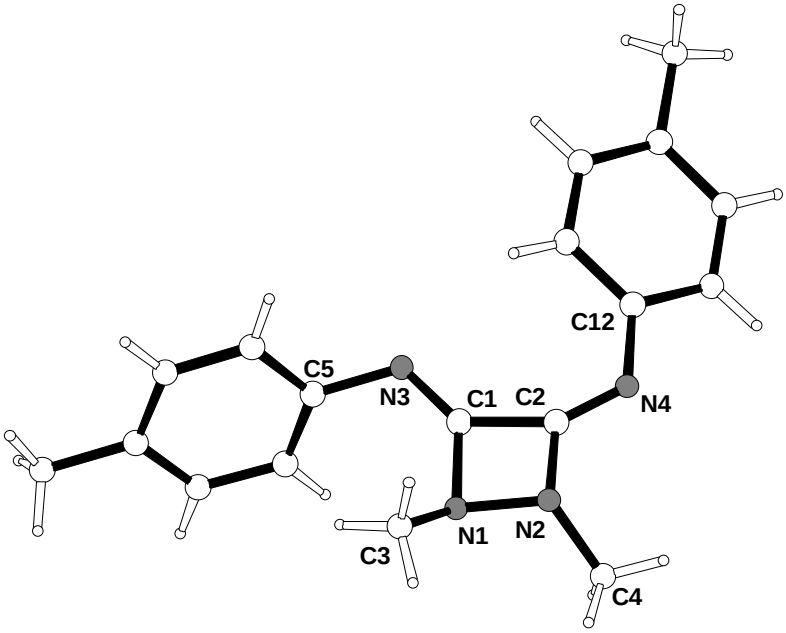


Figure 2: Perspective drawing of **7b**; the numbering corresponds to that used for the X-Ray analysis. Selected distances [Å] and angles [^{o}]: N1-C1 1.428(2), N1-C3 1.468(2), N1-N2 1.4883(19), N2-C2 1.410(2), N2-C4 1.458(2), N3-C1 1.264(2), N3-C5 1.427(2), N4-C2 1.268(2), N4-C12 1.417(2), C1-C2 1.507(2), C1-N1-C3 118.71(14), C1-N1-N2 89.06(11), C2-N2-C4 121.23(14), C2-N2-N1 90.64(11), N1-C1-C2 89.21(12), N2-C2-C1 88.98(12).

The diazetines (**4**) could be deprotonated upon treatment with strong bases such as sodium hexamethyldisilazide to give the deep red anions (**6**). These species are stable at room temperature and can be alkylated by simple electrophiles such as methyl iodide. The attack of methyl iodide takes place with a remarkable regioselectivity at the ring nitrogen atom to form the symmetric 1,2-dimethyldiazetidine (**7a**). The latter can be alternatively synthesized by a cycloacylation of 1,2-dimethylhydrazine (**5d**) with the bis-imidoyl chloride (**1a**). In an analogous fashion, the 1,2-disubstituted diazetidine (**7b**) was obtained either by cyclization of **5d** with **1b** or *via* the deprotonation-alkylation sequence starting from **4b**. Final and unambigous proof for the regioselectivity of this alkylation was obtained by X-Ray structural analysis of the derivative **7b** (Figure 2). In contrast to the monomethylated heterocycle (**4a**), the ring system is slightly puckered with a torsion angle of 10.8^{o}. Both methyl groups are arranged in a *trans* position with angles of 121.2 ^{o} and 118.7 ^{o}.

EXPERIMENTAL

General: All reagents were of commercial quality (Aldrich, Lancaster, Fluka, Merk). Reactions were monitored by TLC, on aluminium plates coated with silica (type 60 from Fluka). Column

chromatography was carried out on silica (Fluka, silica 60, particle size 0.063- 0.2 mm). Melting points were measured with a B-545 (Boetius system) from Büchi, and are uncorrected. The ^{1}H- and ^{13}C NMR spectra were obtained with a Bruker AC 250 (250 MHz) spectrometer. MS spectra were taken from measurements with a Hewlett Packard LD/MSD 1100 mass spectrometer. Elemental analyses were carried out with an automatic analyzer Varion EL III from Elementar Analysensysteme GmbH.

Crystal Structure Determination:

Data collection: The data for the compounds (**4a**) and (**7b**) were collected at 200 K on a Siemens SMART 1000 CCD-diffractometer fitted with a molybdenum tube (K_α, λ = 0.71073 Å) and a graphite-monochromator.

Structure Solution and Refinement: The structure was solved by direct methods and refined anisotropically with the SHELX programme [6] (refinement by least-squares against F2).

Crystal Data for **4a** [7]: $C_{17}H_{18}N_4$, M = 278.4, monoclinic, a = 12.516(2), b = 12.951(3), c = 10.230(2) Å, α = 90.00, β = 111.565(3), γ = 90.00, V = 1542.1(5) $Å^3$, space group $P2_1/c$, Z = 4, D_c = 1.199 g cm^{-3}, F(000) = 592, Absorp. coeff. = 0.074 mm^{-1}, Crystal size = 0.25 × 0.25 × 0.15 mm, No. of reflections: unique = 3781, observed [I > 2σ(I)] = 15861, R1 [I > 2σ(I)] = 0.0461, wR2 = 0.1104.

Crystal Data for **7b** [7]: $C_{18}H_{20}N_4$, M = 293.4, monoclinic, a = 17.3396(12), b = 6.2497(4), c = 15.3469(11) Å, α = 90.00, β = 101.3110(10), γ = 90.00, V = 1630.8(19) $Å^3$, space group $P2_1/c$, Z = 4, D_c = 1.191 g cm^{-3}, F(000) = 624, Absorp. coeff. = 0.073 mm^{-1}, Crystal size = 0.25 × 0.25 × 0.15 mm, No. of reflections: unique = 3977, observed [I > 2σ(I)] = 16688, R1 [I > 2σ(I)] = 0.0476, wR2 = 0.1305.

*General procedure for the synthesis of 1,2-diazetines (**4**):*

*a) by cycloacylation of amidrazone (**2**) with bis-imidoyl chlorides (**1**):* To a mixture of **2** (0.93 g, 5 mmol) and the corresponding **1** (5 mmol) in 30 mL of THF was added dropwise triethylamine (2.10 mL, 15 mmol). The mixture was stirred at rt for 90 min, filtered and the filtrate evaporated. Column chromatography (silica gel, toluene/acetone 10:1) of the crude product and crystallization from methanol gives the compounds (**4**).

*b) by cyclization of alkylhydrazines (**5**) with bis-imidoyl chlorides (**1**)*: The corresponding bis-imidoyl chloride (**1**) (5 mmol) was solved in 30 mL of THF at –15°C. A mixture of alkylhydrazine (**5**) (5 mmol) and triethylamine (1.39 mL, 10 mmol) in 5 mL of THF was added dropwise under stirring. The

formed suspension was stirred for 60 min at rt and then the triethylamine hydrochloride was removed by filtration. The solvent was evaporated and the residue crystallized from methanol to give the title compounds.

For compound (**4d**) a slightly modified procedure was used: To a mixture of the bis-imidoyl chloride (**1a**) (1.53g, 5 mmol) and ethylhydrazine oxalate (0.77 g, 5 mmol) suspended in 30 mL of THF was added dropwise triethylamine (2.80 mL, 20 mmol). After stirring for 45 min at 45°C, the triethylamine salts were removed by filtration. The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel, toluene/ acetone 20:1) to give compound (**4d**) as yellow crystals.

Derivative (**4e**): Benzylhydrazine dihydrochloride (0.97 g, 5 mmol) was treated with bis-imidoyl chloride (**1a**) under the conditions described for compound (**4a**). Purification by column chromatography (silica gel, toluene/ acetone 20:1) gives the pure product.

*Methylation of 1,2-diazetines (**4a,b**) to 1,2-Dialkylderivatives (**7a,b**):* A solution of the corresponding derivative (**4**) (2 mmol) in 15 mL of THF was treated at –30°C with sodium hexamethyl disilazide (1 mL of a 2 M THF-solution). The color of the solution turned from yellow to red. The solution of the formed anion (**6**) was stirred for 10 min and then methyl iodide (0.13 mL, 2 mmol) was added dropwise. After completion of the addition, the mixture was allowed to warm to rt and stirring was continued for 30 min. After filtration, the solvent was evaporated *in vacuo* and the crude product was recrystallized from hexane to give derivatives (**7a,b**).

*Synthesis of **7b** by cyclization of **5d** with **1b***: 1,2-Dimethylhydrazine dihydrochloride (**5d**) (0.53 g, 4 mmol) and the bis-imidoyl chloride (**1b**) (1.35 g, 4 mmol) were suspended in 25 mL of THF at –10° C. Triethylamine (2.3 mL, 16 mmol) was added, and then the solution was stirred for 12 h at 40°C. After filtration and evaporation of the filtrate the crude product (**7b**) was purified by column chromatography (silica gel, toluene/ acetone 20:1).

*1-Methyl-3-(4-tolylamino)-4-(4-tolylimino)-Δ^2-1,2-diazetine (**4a**):* Yield a) 0.53 g (38 %), b) 0.78 g (56 %) , yellow crystals, mp 116 °C (decomp). – ^{1}H-NMR (250 MHz, THF-d_8): δ = 9.07 (s, 1H, NH); 7.40-7.37 (m, 2H, $CH_{arom.}$); 7.16-7.06 (m, 6H, $CH_{arom.}$); 2.59 (s, 3H, CH_3-N); 2.32 (s, 3H, CH_3); 2.27 (s, 3H, CH_3). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 158.2 ($C_{4\text{-ring.}}$); 157.1 ($C_{4\text{-ring}}$); 138.4, 136.6, 132.1, 130.4, 124.8, 118.7 (C_{arom}); 40.8 (CH_3-N); 21.2 (CH_3); 21.0 (CH_3). - MS *m/z* (%): 557 [2M+H$^+$] (85); 279 [M+H$^+$] (100); 50 (39). Anal. Calcd for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.15; H, 6.19; N, 19.98.

*1-Methyl-3-(4-methoxyphenylamino)-4-(4-methoxyphenylimino)-Δ^2-1,2-diazetine (**4b**):* Yield a) 0.73 g (47 %), b) 0.98 g (63 %) , orange crystals, mp 121 °C (decomp). – ^{1}H-NMR (250 MHz, THF-d_8): δ = 8.91 (s, 1H, NH); 7.45-7.40 (m, 2H, CH_{arom}); 7.19-7.14 (m, 2H, CH_{arom}); 6.92-6.83 (m, 4H, CH_{arom}); 3.78 (s, 3H, CH_3O); 3.73 (s, 3H, CH_3O); 2.63 (s, 3H, CH_3-N). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 159.0 ($C_{4\text{-ring}}$); 155.8 ($C_{4\text{-ring}}$); 137.2, 134.0, 126.4, 119.4, 114.7 (C_{arom}); 55.4 (CH_3O); 55.4 (CH_3O); 40.2 (CH_3-N). - MS *m/z* (%): 621 [2M+H$^+$] (68); 311 [M+H$^+$] (100); 50 (41). Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.68; H, 5.59; N, 18.00.

*1-Methyl-3-(4-bromophenylamino)-4-(4-bromophenylimino)-Δ^2-1,2-diazetine (**4c**):* Yield b) 1.12 g (55 %) , yellow crystals, mp 108 °C (decomp). – ^{1}H-NMR (250 MHz, THF-d_8): δ = 9.37 (s, 1H, NH); 7.53-7.43 (m, 6H, CH_{arom}); 7.12-7.08 (m, 2H, CH_{arom}); 2.61 (s, 3H, CH_3-N). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 157.4 ($C_{4\text{-ring}}$); 157.3 ($C_{4\text{-ring}}$); 143.1, 139.3, 132.3, 132.5, 131.7, 125.8, 120.0, 114.7 (C_{arom}); 40.2 (CH_3-N). - MS *m/z* (%): 816 [2M+H$^+$] (21); 676 (22); 409 [M+H$^+$](91); 102 (100). Anal. Calcd for $C_{15}H_{12}N_4Br_2$: C, 44.15; H, 2.96; N, 13.73. Found: C, 44.20; H, 2.70; N, 13.62.

*1-Ethyl-3-(4-tolylamino)-4-(4-tolylimino)-Δ^2-1,2-diazetine (**4d**)*: Yield b) 0.57 g (39 %), yellow crystals, mp 96 °C (decomp). – ^{1}H-NMR (250 MHz, THF-d_8): δ = 8.93 (s, 1H, NH); 7.41-7.38 (m, 2H, CH_{arom}); 7.14-7.03 (m, 6H, CH_{arom}); 2.83 (q, ^3J = 7.0 Hz, 2H, CH_2-N); 2.30 (s, 3H, CH_3); 2.26 (s, 3H, CH_3); 1.02 (t, ^3J = 7.0 Hz, 3H, CH_3). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 158.4 ($C_{4\text{-ring}}$); 155.5 ($C_{4\text{-ring}}$); 142.6, 138.2, 136.1, 131.8, 130.1, 130.0, 124.1, 118.4 ($C_{arom.}$); 47.4 (CH_2-N); 20.9 (CH_3); 20.7 (CH_3); 11.5 (CH_3). - MS *m/z* (%): 585 [2M+H$^+$] (100); 400 (80); 293 [M+H$^+$] (99); 90 (47).

*1-Benzyl-3-(4-tolylamino)-4-(4-tolylimino)-Δ^2-1,2-diazetine (**4e**)*: Yield b) 0.83 g (47 %), yellow crystals, mp 91 °C (decomp). – ^{1}H-NMR (250 MHz, THF-d_8): δ = 9.07 (s, 1H, NH); 7.41-7.38 (m, 2H, CH_{arom}); 7.19-7.06 (m, 11H, CH_{arom}); 4.04 (s, 2H, CH_2-N); 2.33 (s, 3H, CH_3); 2.26 (s, 3H, CH_3). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 158.9 ($C_{4\text{-ring}}$); 155.4 ($C_{4\text{-ring}}$); 142.5, 138.3, 137.8, 136.9, 132.1, 130.6, 129.7, 128.8, 127.8, 125.0, 118.4 (C_{arom}); 57.0 (CH_2-N); 21.3 (CH_3); 21.1 (CH_3). - MS *m/z* (%): 709 [2M+H$^+$] (76); 517 (80); 355 [M+H$^+$] (100).

*1,2-Dimethyl-3,4-bis-(4-tolylimino)-1,2-diazetidine (**7a**)*: Yield 0.42 g (72 %), yellow crystals, mp 88 °C. - ^{1}H-NMR (250 MHz, THF-d_8): δ = 7.55-7.52 (m, 1H, CH_{arom}); 7.13-6.96 (m, 5H, CH_{arom}); 6.49-6.17 (m, 2H, CH_{arom}); 2.97, (s, 3H, CH_3-N); 2.63, (s, 3H, CH_3-N); 2.30 (s, 6H, CH_3). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 155.1 ($C_{4\text{-ring}}$); 154.9 ($C_{4\text{-ring}}$); 143.1, 136.0, 135.2, 130.0, 129.6, 128.9, 125.0,

122.7, 121.2 (C_{arom}); 39.0 (CH_3-N); 38.7 (CH_3-N); 21.0 (CH_3); 20.9 (CH_3). - MS *m/z* (%): 293 [$M+H^+$] (100); 90 (25). Anal. Calcd for $C_{18}H_{20}N_4$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.82; H, 6.80; N 18.98.

*1,2-Dimethyl-3,4-bis-(4-methoxyphenylimino)-1,2-diazetidine (**7b**)*: Yield (by cyclization of **5d**) 0.79 g (61 %); (by methylation of **4b**) 0.56 g (78 %), yellow crystals, mp 103 °C . - ^{1}H-NMR (250 MHz, THF-d_8): δ = 7.72-6.20 (m, 8H, CH_{arom}); 3.77, 3.76 (2s, 6H, CH_3O); 2.96, (s, 3H, CH_3-N); 2.66, (s, 3H, CH_3-N). - ^{13}C-NMR (63 MHz, THF-d_8): δ = 158.3 ($C_{4\text{-ring}}$); 153.8 ($C_{4\text{-ring}}$); 138.5, 138.6, 126.9, 124.4, 122.3, 122.2, 114.7, 114.6, 114.1, 113.4 (C_{arom}); 55.4 (CH_3O); 55.3 (CH_3O); 38.9 (CH_3-N). - MS *m/z* (%): 325 [$M+H^+$] (100); 90 (43). Anal. Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.90; H, 6.50; N, 17.31.

ACKNOWLEDGEMENTS

The supports of the *Fonds der Chemischen Industrie* and *Deutsche Forschungsgemeinschaft (SFB 436)* are gratefully acknowledged.

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7. Further details of the crystal structure investigations are available on requests from CCDC, 12 Union Road, GB-Cambridge CB2 1EZ, on quoting the depository number CCDC 181295 (**4a**) and CCDC 181296 (**7b**), the name of the authors, and the journal citation.