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SYNTHESIS OF 2,5-DIAMINOPYRAZINE DERIVATIVES *VIA* DIMERIZATION OF 2*H*-AZIRIN-3-AMINES

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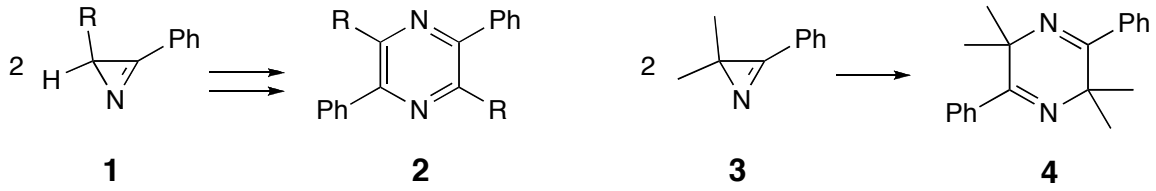
Dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – The 2-monosubstituted 2*H*-azirin-3-amine (**5c**) was prepared conveniently by subsequent treatment of *N*-methyl-*N*-phenylpropanamide in THF with LDA, diphenyl phosphorochloridate (DPPCl), and sodium azide in DMF. In the absence of nucleophiles, the reaction of **5c** in THF with $BF_3.OEt_2$ at –78°C yields 2,5-dihydro-2,5-dimethyl-3,6-bis(*N*-methyl-*N*-phenylamino)pyrazinium tetrafluoroborate (**11**). Treatment of the latter with NaOH yields the corresponding 2,5-dihydropyrazine derivative (**12**), whereas dehydrogenation with DDQ leads to 2,5-dimethyl-3,6-bis(*N*-methyl-*N*-phenylamino)pyrazine (**13**). The structures of **12** and **13** were established by X-ray crystallography.

INTRODUCTION

Pyrazines are of broad interest because of the physical properties and biological activities of some representatives, which make them attractive compounds in materials science and pharmaceutical chemistry. A recent review summarizes the syntheses and reactions of this heterocyclic system.[2] In the context of the present article, the dimerization and dehydrogenation of 3-phenyl-2*H*-azirines (**1**) to give 2,5-diphenylpyrazines (**2**) is especially worth mentioning (*Scheme 1*). This transformation can be achieved photochemically,[3] under acidic catalysis,[4,5] and via metal-catalyzed reactions.[6] In the case of 2,2-dimethyl-3-phenyl-2*H*-azirine (**3**), acid-catalyzed,[5] metal-catalyzed,[7] and base-catalyzed reactions[8] yield the 2,5-dihydropyrazine derivative (**4**).

Scheme 1



1 **2** **3** **4**

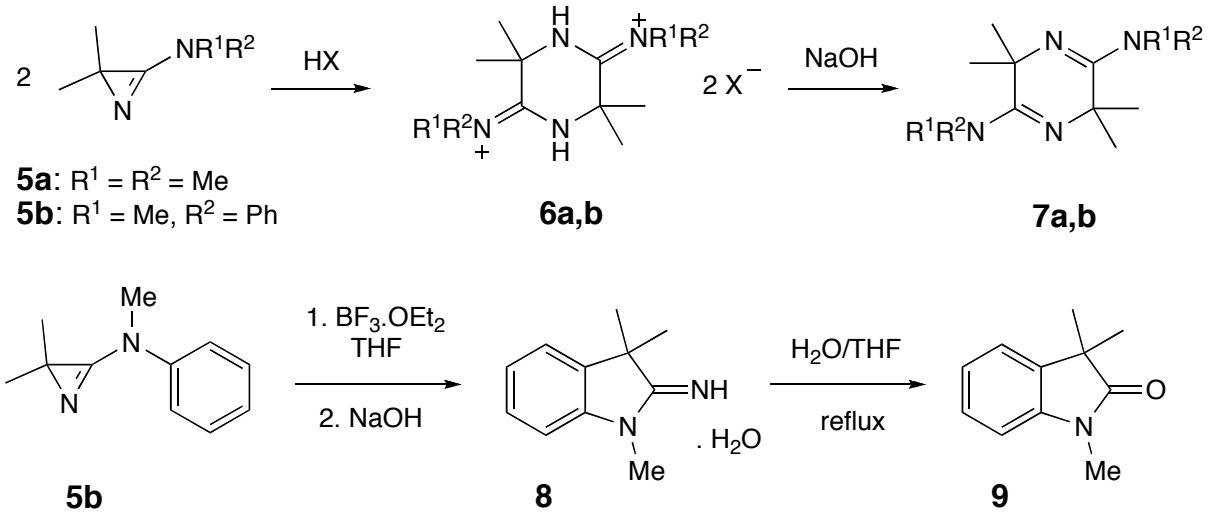
Amino-substituted pyrazines represent a relatively small group within the class of pyrazines. A pharmaceutically active example is 2-(dimethylamino)pyrazine ('Ampyzine').[9] The major routes for their preparation are various condensation reactions, *e.g.*, of 1,2-diamines with 1,2-diketones, benzoylcyanide, 1,2-bisimidates, etc., as well as the hetero-Diels-Alder reaction of ynamines with diiminosuccinonitrile, cyclization of 1-amino-2-[(cyanomethylidene)amino]maleonitrile, and the direct introduction of the amino group by substitution reactions with halopyrazines or via Hofmann and Curtius rearrangements (see ref. 2). The 2,5-diaminopyrazines have been studied only scarcely: the parent compound was obtained via the Curtius rearrangement of dimethyl pyrazine-2,5-dicarboxylate[10] and by decarboxylation of 2,5-diaminopyrazine-3,6-dicarboxylic acid.[11] Nucleophilic substitution by treatment of 2-amino-5-iodo-3,6-dimethylpyrazine with ammonium hydroxide led to the 2,5-diamino-3,6-dimethyl derivative.[12]

In analogy to the reactions shown in *Scheme 1*, treatment of 2,2,*N*,*N*-tetramethyl-2*H*-azirin-3-amine (**5a**) in acetonitrile at –20°C with sulfonic acids gave the piperazine-2,5-bis(dimethyliminium) salts (**6a**)[13] (*Scheme 2*). Deprotonation with sodium hydroxide yielded the 3,6-diamino-2,5-dihydropyrazine (**7a**). It has been shown that this dimerization of 'aminoazirines' (**5**) can be achieved with various Brønsted acids.[14–17]

Within our research program aiming at the use of 'aminoazirines' (**5**) in heterocyclic synthesis,[18] we also investigated BF_3-catalyzed reactions, in which **5** was activated by complexation with the Lewis acid. The reaction with the sodium salt of carboxamides leads to 5-amino-4*H*-imidazoles,[19] whereas the reaction with lithium enolates of esters and amides yields 1,5-dihydro-2*H*-pyrrol-2-ones.[16] Furthermore, Brønsted acid or BF_3 catalysis of the reaction of **5** with α-amino acid esters gives 3,6-dihydropyrazin-2(1*H*)-ones.[20] Recently, we have shown that 2,2-disubstituted *N*-methly-*N*-phenyl-2*H*-azirin-3-amines (**5b**) in THF, in the absence of nucleophilic reagents, by treatment with BF_3 undergo a cyclization reaction to give 2-iminoindolines (**8**), which can smoothly be transformed into indolin-2-ones (**9**)[21,22] (*Scheme 2*). This reaction has successfully been used for the preparation of (±)-desoxynoreseroline.[23]

In the present paper, we describe the BF_3-catalyzed reaction of the 2-monosubstituted 2,*N*-dimethyl-*N*-phenyl-2*H*-azirine-3-amine (**5c**) in the absence of nucleophilic reagents.

Scheme 2



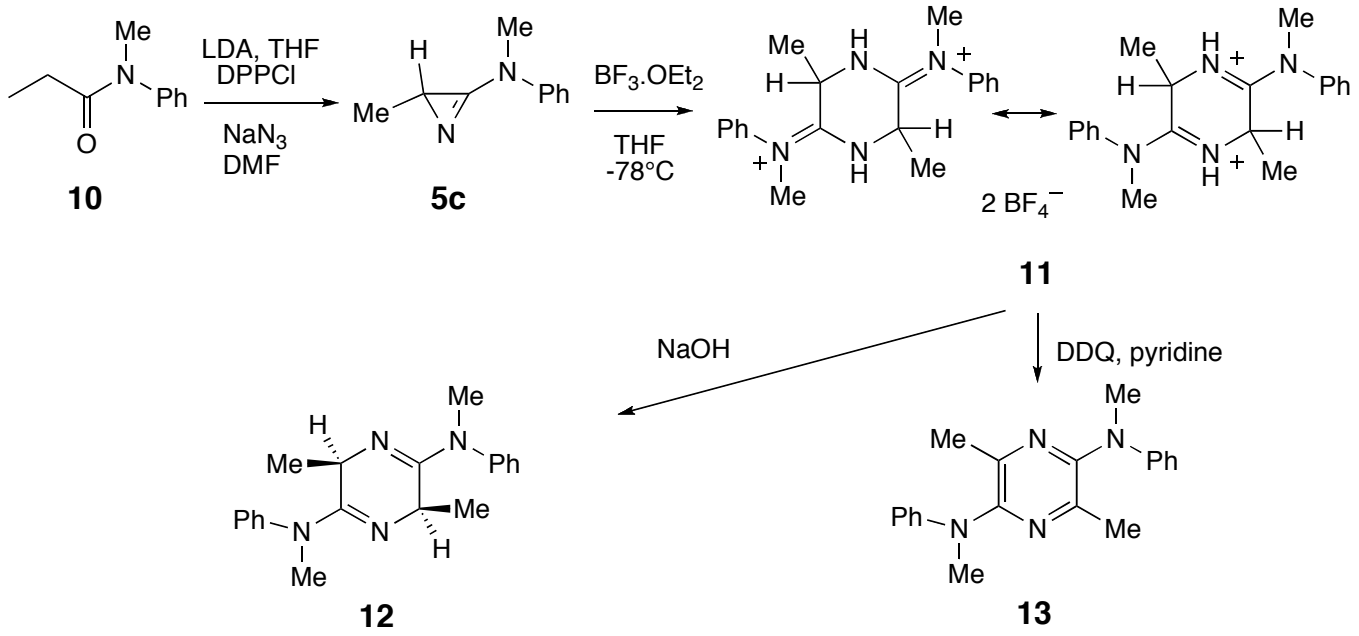
RESULTS AND DISCUSSION

The 2-monosubstituted 'aminoazirine' (**5c**) was prepared according to a protocol described earlier.[24] Thus, subsequent reaction of *N*-methyl-*N*-phenylpropanamide (**10**) in THF with LDA, diphenyl phosphorochloridate (DPPCl), and sodium azide in DMF yielded **5c** (*Scheme 3*).[25] Treatment of a solution of **5c** in THF at –78°C with an approximately equimolar amount of BF_3 in diethyl ether and warm-up to room temperature gave 2,5-dihydro-2,5-dimethyl-3,6-bis(*N*-methyl-*N*-phenylamino)piperazinium tetrafluoroborate (**11**) in 52% yield as a white powder.

The structure of **11** was elucidated on the basis of its analytical and spectroscopic data and its chemical behavior (see later). Characteristic are the IR absorptions (KBr) at 3429 (N–H) and 1658 cm^{-1} (C=N), the ^{1}H-NMR spectrum (d_6-DMSO) with signals at 4.62 (*q*, CH), 3.47 (*s*, MeN), and 1.48 ppm (*d*, Me), and the ^{13}C-NMR spectrum with the corresponding signals at 47.0 (*d*), 40.7 (*q*), and 20.2 ppm (*q*) together with the singlet for C=N at 161.1 ppm. It is worth mentioning that only one set of signals appears, indicating that only one isomer of **11** has been formed.

The formation of **11** could be explained by the BF_3-catalyzed ring opening of **5c** to give a 1-azaallyl cation, which reacts with a second molecule of **5c**.[17] The formed adduct then undergoes the cyclization to give the six-membered ring as a BF_3 complex. Decomplexation by fluoride ion and protonation leads to **11**. On the other hand, there are some doubts about the ring opening of azirinium ions to give 1-azaallyl cations.[27] Therefore, a direct attack of **5c** onto the BF_3 complex of **5c** under ring opening may be more likely as the first reaction step.

Scheme 3



Treatment of the salt **11** with 30% aqueous NaOH afforded the free base, *i.e.*, the 2,5-dihydropyrazine derivative **12** in 97% yield as colorless crystals (*Scheme 3*). As expected, the spectroscopic data are very similar to those of **11**: in the IR spectrum (KBr), the C=N absorption appears at 1639 cm^{-1} but no N–H band is present. The characteristic signals in the ^{1}H-NMR spectrum (d_6-DMSO) are at 4.22 (*q*, CH), 3.10 (*s*, MeN), and 1.04 ppm (*d*, Me), *i.e.*, all are shifted to higher field. Finally, the structure of **12** was established by X-ray crystallography (*Figure 1*).

The crystal structure of **12** proves that the molecule has the *cis*-configuration. Since the space group is centrosymmetric, the crystals are racemic. The molecule has local, but not crystallographic C_2 symmetry. The central six-membered ring has a shallow boat conformation with the methyl-substituted C-atoms (C(3) and C(6)) forming the ends of the boat. These atoms are 0.194(1) and 0.200(1) Å, respectively, from the plane defined by N(1), C(2), N(4), and C(5). The *cis*-oriented methyl groups at C(3) and C(6) are in axial positions with respect to the boat conformation. Whereas the methyl groups at the exocyclic N-atoms lie in the 'amidine planes' (N(1)–C(2)–N(2) and N(4)–C(5)–N(5)), the phenyl groups are not coplanar with these planes but are twisted by almost 90°. The difference of the bond lengths N(1)–C(2)/N(4)–C(5) (1.280(1) Å) and N(2)–C(2)/N(5)–C(5) (1.390(1)/1.383(1) Å) indicates the lack of extensive conjugation.

The dehydrogenation of **11** to give the aromatic pyrazine **13** (*Scheme 3*) could be achieved by the reaction of **11** in pyridine with 2,3-dichloro-5,6-dicyano-4-benzoquinone (DDQ). Crystallization in hexane gave the product as pale yellow crystals in 72% yield. The ^{1}H- as well as the ^{13}C-NMR spectrum shows the

absence of the CH group present in **11** and **12**, and only the singlets for MeN (3.41/39.2 ppm) and MeC (2.10/20.9 ppm) are present besides the absorptions of aromatic residues. Again, the crystal structure of **13** was determined by X-ray crystallography (*Figure 1*).

a) b)

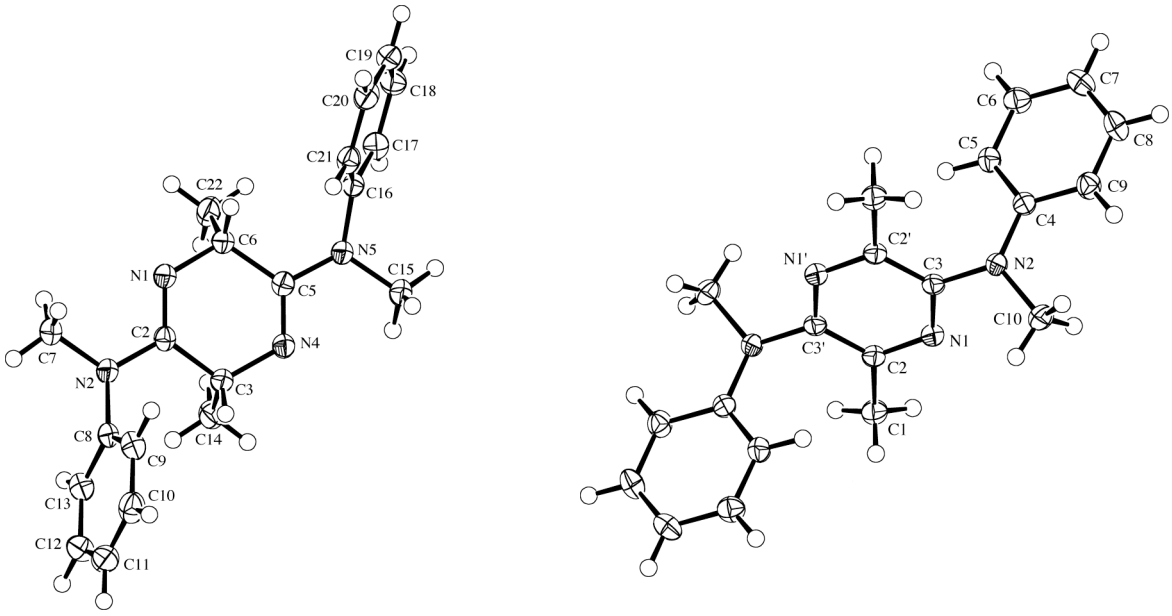


Figure 1. ORTEP plots[28] of the molecular structures of a) **12** and b) **13** (arbitrary numbering of the atoms; 50% probability ellipsoids)

The molecule of **13** possesses a crystallographic centre of inversion. The pyrazine ring is planar with the the C-atoms of the methyl groups at C(2) and C(2') and the exocyclic N-atoms being also in this plane. The methyl and phenyl groups at the exocyclic N-atoms are twisted out of the plane of the heterocycle. Furthermore, the exocyclic N(2)–C(3) bond (1.421(2) Å) of the amidine system is almost as long as a normal C,N single bond, *i.e.*, there is no extensive conjugation within the amidine moiety.

CONCLUSIONS

The BF_3-catalyzed dimerization of 2-monosubstituted 2*H*-azirin-3-amines of type (**5c**) offers a convenient access to 2,5-dimethylaminopyrazine derivatives. It is worth mentioning that there is a remarkable difference in the behavior of **5c** and the corresponding 2,2-disubstituted derivative (**5b**) when treated with BF_3: whereas in the case of **5b** the intramolecular cyclization to an indoline derivative occurs exclusively (*Scheme 2*), the 2-monosubstituted **5c** undergoes only the dimerization reaction (*Scheme 3*). It is not easy to find a convincing explanation for this difference. On the one hand, the ring opening to give an azaallyl cation should be more favored in the case of the 2,2-disubstituted **5b**, which leads to a 'tertiary'

carbenium ion. On the other hand, the 'secondary' carbenium ion in the case of **5c** should be more reactive, in intra- as well as in intermolecular reactions. Obviously different is the steric situation. It is conceivable that an intermolecular attack of a second azirine molecule – especially at C(2) of the azirine/BF_3 complex – is more sensitive to steric hindrance than the intramolecular reaction.

EXPERIMENTAL

General remarks. TLC: silica gel 60 F_{254} aluminium sheets (0.25 mm, Merck). Melting points: Büchi B-510 apparatus, uncorrected. IR spectra: Perkin-Elmer-1600-FT-IR spectrophotometer, in KBr; in cm^{-1}. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra: Bruker ARX-300 instrument, at 330 K, in d_6-DMSO or $CDCl_3$; chemical shifts in ppm, coupling constants *J* in Hz; multiplicity of C atoms from DEPT spectra. CI-MS: Finnigan SSQ-700 or MAT-90 instrument; NH_3 as carrier gas.

*Synthesis of 2,*N*-dimethyl-*N*-phenyl-2*H*-azirin-3-amine* (**5c**). See ref.[24] To a stirred solution of diisopropylamine (1.1 equiv.) in THF at –20°C, butyllithium (2 M solution in pentane, 1.1 equiv.) was added under argon, and the mixture was allowed to warm to 0°C. A solution of *N*-methly-*N*-phenylpropanamide (**10**) (1 equiv.) in THF was added dropwise and the mixture was stirred at 0°C for 1 h. Then, diphenyl phosphorochloridate (DPPCl) (1.03 equiv.) was added dropwise. After 30 min, the ice bath was removed and the mixture was stirred for 24 h. The formed precipitate was filtered off under argon. The filtrate was dropped into a suspension of NaN_3 (3 equiv.) in dry DMF, and the mixture was stirred for 4 days at rt. Then, Et_2O was added and the mixture filtered over a Celite pad, the solvent was evaporated, and the residue was dissolved in Et_2O. The solution was washed twice with 5% aqueous $NaHCO_3$ and the aqueous layer was washed again with Et_2O. The combined organic layers were dried over $MgSO_4$, the solvent was evaporated under reduced pressure, and the crude product was purified by bulb-to-bulb distillation. Yield: 50%.

*Preparation of 2,5-dihydro-2,5-dimethyl-3,6-bis(*N*-methyl-*N*-phenylamino)piperazinium tetrafluoroborate* (**11**). To a stirred solution of **5c** (326 mg, 2.0 mmol) in THF (30 mL), $BF_3.OEt_2$ (approx. 48% BF_3 in Et_2O); 0.53 mL, 2.0 mmol) was –78°C, the solution was allowed to warm up slowly to *ca.* 23°C and was stirred for 12 h at this temperature. After addition of Et_2O and filtration, the crude product was washed with Et_2O yielding 264 mg (52%) of **11**. White powder, mp 298.5–300.5°C. IR (KBr): 3429*m*, 3260*m*, 3009*w*, 1658*s*, 1593*m*, 1490*m*, 1456*w*, 1436*w*, 1412*w*, 1391*w*, 1338*m*, 1284*w*, 1244*w*, 1070*s*, 778*m*, 705*m*. ^{1}H-NMR (d_6-DMSO, 330 K): 7.65–7.48 (*m*, 10 arom. H); 4.62 (*q*, *J* = 7, 2 CH); 3.47 (*s*, 2 MeN); 1.48 (*d*, *J* = 7, 2 Me). ^{13}C-NMR (d_6-DMSO, 330 K): 161.1 (*s*, 2 C=N); 140.7 (*s*, 2 arom. C); 129.9, 129.0, 126.0 (3*d*, 10 arom. CH); 47.0 (*d*, 2 CH); 40.7 (*q*, 2 MeN); 20.2 (*q*, 2 Me). CI-MS: 322 (23), 321

(100, [*M*–2 BF_4–1]$^+$), 320 (7), 319 (19). Anal. Calcd for $C_{20}H_{26}B_2F_8N_4$: C, 48.42; H, 5.28; N, 11.29. Found: C, 48.19; H, 5.45; N, 11.19.

*Preparation of 2,5-dihydro-2,5-dimethyl-3,6-bis(*N-*methyl*-N-*phenylamino)pyrazine* (**12**). A solution of **11** (90 mg, 0.18 mmol) in the least amount of water was cooled to 0°C, and 30% aqueous NaOH (9 mL) was added. The cooled mixture (ice bath) was stirred for 7 h. After extraction with CH_2Cl_2, the organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and recrystallisation from Et_2O yielded 56.3 mg (97%) of **12**. Colorless crystals, mp 120–121°C. Crystals suitable for an X-ray crystal-structure determination were obtained from Et_2O. IR (KBr): 3057*w*, 2982*m*, 2965*m*, 2926*m*, 2896*m*, 1639*s*, 1594*s*, 1494*s*, 1454*m*, 1413*m*, 1376*s*, 1362*m*, 1318*m*, 1289*m*, 1274*s*, 1143*s*, 1130*s*, 1072*m*, 1042*m*, 1022*w*, 1000*w*, 935*m*, 774*m*, 705*s*. ^{1}H-NMR (d_6-DMSO): 7.45–7.38, 7.30–7.20 (2*m*, 10 arom. H); 4.22 (*q*, *J* = 7, 2 CH); 3.10 (*s*, 2 MeN); 1.04 (*d*, *J* = 7, 2 Me). ^{1}H-NMR ($CDCl_3$): 7.40–7.32, 7.28–7.20 (2*m*, 10 arom. H); 4.40 (*q*, *J* = 7, 2 CH); 3.21 (*s*, 2 MeN); 1.17 (*d*, *J* = 7, 2 Me). ^{13}C-NMR (d_6-DMSO): 162.2 (*s*, 2 C=N); 146.0 (*s*, 2 arom. C); 129.3, 127.5, 126.1 (3*d*, 10 arom. CH); 48.7 (*d*, 2 CH); 39.0 (*q*, 2 MeN); 22.5 (*q*, 2 Me). ^{13}C-NMR ($CDCl_3$): 163.5 (*s*, 2 C=N); 145.9 (*s*, 2 arom. C); 129.2, 127.8, 126.3 (3*d*, 10 arom. CH); 49.5 (*d*, 2 CH); 39.5 (*q*, 2 MeN); 22.7 (*q*, 2 Me). CI-MS: 322 (23), 321 (100, [*M*+1]$^+$), 320 (16), 319 (71).

*Preparation of 2,5-dimethyl-3,6-bis(*N-*methyl*-N-*phenylamino)pyrazine* (**13**). To a solution of **11** (50 mg, 0.10 mmol) in 2 mL of pyridine, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ; 30 mg, 0.13 mmol) was added, and the mixture was stirred at rt for 24 h. Column chromatography (SiO_2, AcOEt/hexane 1:5) followed by crystallization from hexane yielded 23 mg (72%) of **13**. Pale yellow blocks, mp 106.4–107.3°. Crystals suitable for an X-ray crystal-structure determination were grown from hexane. IR (KBr): 3090*w*, 3066*w*, 3027*w*, 3003*w*, 2943*m*, 1598*s*, 1576*w*, 1524*w*, 1500*s*, 1476*s*, 1238*m*, 1188*w*, 1176*m*, 1143*s*, 1118*m*, 1090*w*, 1029*w*, 1000*w*, 993*m*, 981*m*, 880*w*, 806*w*, 764*w*, 749*s*, 692*m*. ^{1}H-NMR ($CDCl_3$): 7.29–7.21, 6.94–6.86, 6.80–6.74 (3*m*, 10 arom. H); 3.41 (*s*, 2 MeN); 2.10 (*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 149.1, 148.3, 144.3 (3*s*, 6 arom. C); 129.1, 120.5, 117.9 (3*d*, 10 arom. CH); 39.2 (*q*, 2 MeN); 20.9 (*q*, 2 Me). CI-MS: 320 (23), 319 (100, [*M*+1]$^+$), 241 (7). Anal. Calcd for $C_{20}H_{22}N_4$: C, 75.44; H, 6.96; N, 17.60. Found: C, 75.07; H, 7.02; N, 17.68.

X-Ray Crystal-Structure Determination of **12** *and* **13** (*Figure 1*).[29] All measurements for **12** were made on a *Nonius KappaCCD diffractometer*[30] fitted with an *Oxford Cryosystems Cryostream 700* cooler, while those for **13** were conducted on a *Rigaku AFC5R* diffractometer on a 12kW rotating anode generator. Graphite-monochromated MoK_α radiation (λ = 0.71073 Å) was employed in each case. In the case of **12**,

data reduction was performed with *HKL Denzo and Scalepack*.[31] The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections were merged. Data collection and refinement parameters are given below, and views of the molecules are shown in *Figure 1*. The structures of **12** and **13** were solved by direct methods using SIR92[32] and SHELXS97,[33] respectively, which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions and each was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom. The refinement of each structure was carried out on *F* using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. Corrections for secondary extinction were applied. In the case of **12**, three reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral atom scattering factors for non-H-atoms were taken from ref.[34], and the scattering factors for H-atoms were taken from ref.[35] Anomalous dispersion effects were included in F_c;[36] the values for f' and f'' were those of ref.[37] The values of the mass attenuation coefficients are those of ref.[38] All calculations were performed using the teXsan program.[39] Crystal data for **12**: Crystallized from Et_2O, $C_{20}H_{24}N_4$, M = 320.44, colorless, prism, crystal dimensions 0.17 × 0.20 × 0.30 mm, monoclinic, space group $P2_1/c$, Z = 4, reflections for cell determination 5546, a = 13.6542(2) Å, b = 7.0044(1) Å, c = 18.5864(3) Å, β = 96.3381(6)°, V = 1766.73(5) Å^3, D_X = 1.205 g·cm^{-3}, μ(MoK_α) = 0.0732 mm^{-1}, T = 160(1) K, ϕ and ω scans, $2\theta_{max}$ = 60°, total reflections measured 51896, symmetry independent reflections 5161, reflections used in refinement [$I > 2\sigma(I)$] 3699, parameters refined 218, final R (on F; $I > 2\sigma(I)$ reflections) = 0.0469, wR = 0.0466 ($w = [\sigma^2(F_o) + (0.01F_o)^2]^{-1}$, goodness of fit 2.223, secondary extinction coefficient 1.4(4)×10^{-6}, final Δ_{max}/σ = 0.001, $\Delta\rho$ (max; min) = 0.28; –0.23 e Å^{-3}. Crystal data for **13**: Crystallized from hexane, $C_{20}H_{22}N_4$, M = 318.42, pale yellow, block, crystal dimensions 0.35 × 0.40 × 0.45 mm, monoclinic, space group $P2_1/c$, Z = 2, reflections for cell determination 25, a = 10.632(2) Å, b = 7.743(2) Å, c = 10.880(3) Å, β = 110.12(2)°, V = 841.0(4) Å^3, D_X = 1.257 g·cm^{-3}, μ(MoK_α) = 0.0766 mm^{-1}, T = 173(1) K, $\omega/2\theta$ scans, $2\theta_{max}$ = 55°, total reflections measured 2180, symmetry independent reflections 1928, reflections used in refinement [$I > 2\sigma(I)$] 1529, parameters refined 110, final R (on F; $I > 2\sigma(I)$ reflections) = 0.0409, wR = 0.0417 ($w = [(\sigma^2(F_o) + (0.005F_o)^2]^{-1}$, goodness of fit 2.326, secondary extinction coefficient 2.1(3)×10^{-6}, final Δ_{max}/σ = 0.0003, $\Delta\rho$ (max; min) = 0.19; –0.16 e Å^{-3}.

ACKNOWLEDGEMENTS

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