Mannich Bases as Synthetic Intermediates: Synthesis of 3- and 4-Functionalized 2-Pyrazolines

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Z. Naturforsch. **2007**, *62b,* 540 – 548; received September 15, 2006

The reaction of styryl ketonic Mannich bases **2a** – **c** with phenylhydrazine leads to 3-functionalized 2-pyrazolines **4** or **6** depending on the reaction conditions. 3-[β-(Arylamino)ethyl]-2-pyrazolines **8a**,**b** were obtained *via* transamination between the methiodide salt **7** and primary arylamines. Treatment of 1-(*p*-anisyl)-1,2,5-tri(*N*-piperidino)pentan-3-one (**11**) with phenylhydrazine affords the 3,4-difunctionalized 2-pyrazoline **12**. The reactions of the keto bases **19** or **21** with hydrazines lead to 4-functionalized 2-pyrazolines **20** and **22**, the *N*-Mannich bases **23** and **24** are obtained from **22a**. The synthesis of 3-[β-(phenylthio)ethyl]-2-pyrazolines **28a**,**b** has been achieved by treating **26** or **27** with phenylhydrazine.

Key words: Styryl Ketonic Mannich Bases, 3- and 4-Functionalized 2-Pyrazolines

Introduction

Ketonic Mannich bases are of considerable importance as intermediates in the synthesis of condensed heterocyclic systems [1 – 5] and of heterocycles carrying a potential basic side chain of alkaloidal nature [6 – 10]. It has been reported earlier that Mannich bases derived from methyl styryl ketones, react with phenylhydrazine to give 3-[β-(substituted-amino)ethyl]-2-pyrazolines [11 – 13], which possess local anaesthetic activity comparable with cocaine [12]. However, the literature of C-3 functionalized 2-pyrazolines prepared from unsaturated ketonic Mannich bases is relatively limited.

In view of this, and in connection with our studies in this area [14 – 16], the reaction of phenylhydrazine with styryl ketonic Mannich bases of the type **2**, having a morpholine or piperazine group as a structural unit, and related compounds, was further investigated as a route to C-3 and C-4 functionalized 2-pyrazolines of pharmaceutical interest.

Results and Discussion

In the present study, we prepared 1-(*p*-anisyl)-5-(morpholin-4-yl)-1-penten-3-one hydrochloride (**2a**) and the 1-(3,4-methylenedioxyphenyl) analog (**2b**) by the reaction of *p*-anisalacetone (**1a**) [17] or piperonalacetone (**1b**) [18] with formaldehyde and morpholine hydrochloride. The keto base **2c** was obtained by transamination reaction between **2b** and *N*-phenylpiperazine. It was found that cyclization of the phenylhydrazones **3a**–**c**, derived from the styryl keto bases **2a**–**c**, can be directed selectively according to the conditions. Thus, **3a**–**c** were readily isomerized to 5-aryl-3-[β-(morpholin-4-yl)ethyl]- and 3-[β-(4-phenyl-piperazin-1-yl)ethyl]-1-phenyl-2-pyrazolines **4a** – **c**, respectively, under mild conditions (warming for a short time, Scheme 1).

On the other hand, treatment of **3a**,**b** with acetic acid under more drastic conditions (refluxing for 1 h), offers a facile method for the synthesis of 3-(*p*-methoxystyryl)- and 3-(3,4-methylenedioxystyryl)-1-phenyl-2-pyrazolines **6a**,**b**. It is believed that hydrazones **3** undergo deamination on prolonged heating to give **5**, followed by cyclization. The formation of **6** is in line with an earlier report [19] on the reaction of β-dimethylaminoethyl styryl ketone with phenylhydrazine, and with the observation of Andrisano *et al.* [20], who found that the styryl double bond is less reactive than that formed by deamination of the Mannich base.

A practical advantage of the reactions leading to compounds **4** and **6** is that it is often unnecessary to isolate the intermediate phenylhydrazones **3**. The structure proposed for compounds **4a** – **c** and **6a**,**b** was supported by analytical and spectral data. The mass spectra of **4a** – **c** showed very similar cleavage patterns. Cleavage of the side chain of **4a** and **b** at the β bond

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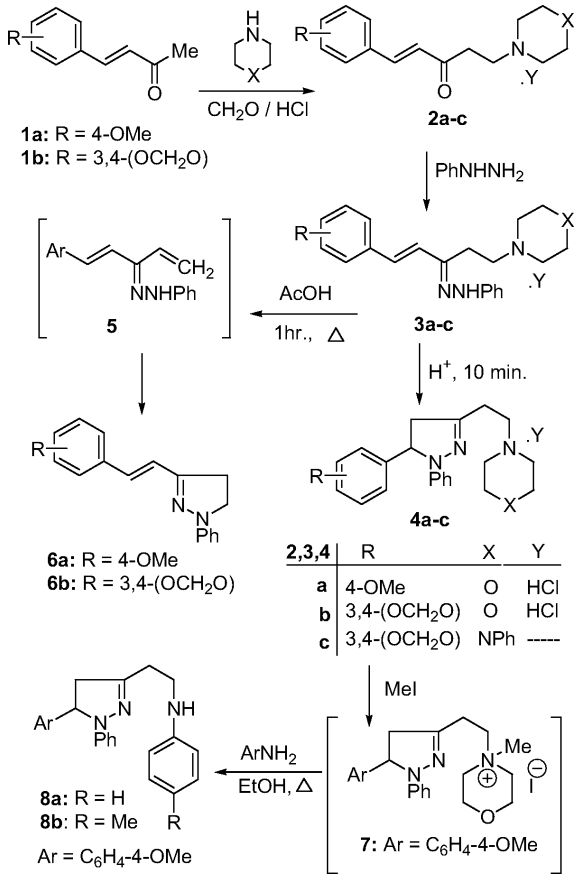
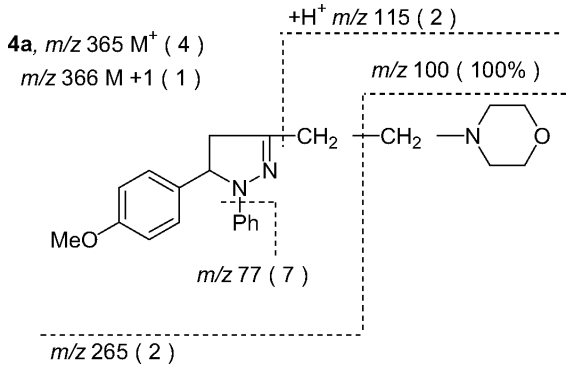


Scheme 1.

leads to the base peak at *m/z* = 100 (100 %), due to the *N*-morpholinomethyl ion [CH_2–$N(CH_2CH_2)_2O$], which undergoes further fragmentation to give a characteristic peak at *m/z* = 56 in the spectrum of **4a** (14.4 %) and **4b** (30 %). The basic side chain of **4c** can be identified by two peaks at *m/z* = 175 (100 %) [CH_2–$N(CH_2CH_2)_2NPh$] and 189 (23 %) [CH_2CH_2–$N(CH_2CH_2)_2NPh$]. The fragmentation pattern of **4a** is depicted in Scheme 2.

In connection with the present study, the synthesis of 2-pyrazolines of the type **8**, having a secondary arylamino group on the side chain, has been achieved by converting **4a** into the methiodide salt **7**, which was treated with aniline or *p*-toluidine to give 5-(*p*-anisyl)-3-[β-(phenylamino)ethyl]-1-phenyl-2-pyrazoline (**8a**) and the 3-[β-(*p*-tolylamino)ethyl] analog **8b**. The advantage of using **7** in this reaction lies in the fact that transamination occurs readily between quaternary salts and primary or secondary amines [21, 22]. The IR spectrum of **8a** showed strong bands at 3399 (NH)



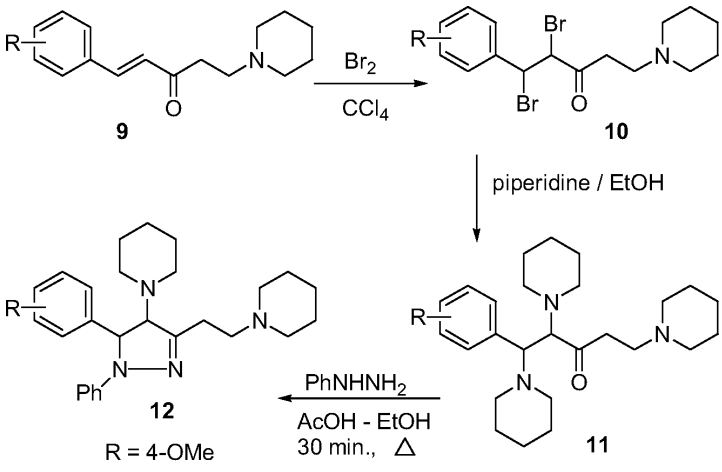
Scheme 2.

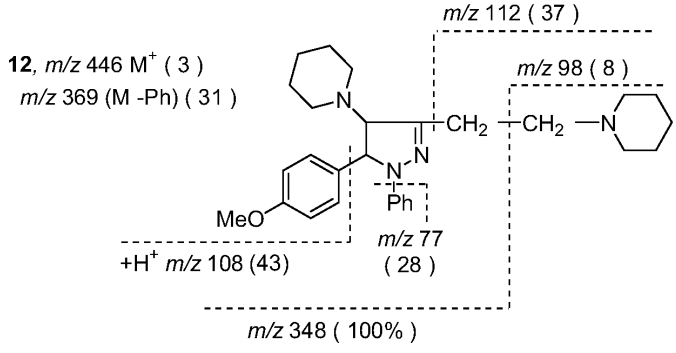
and 1325 cm^{-1} (C–N stretch of *sec.* aryl amine). Its ^1H NMR spectrum revealed the presence of a singlet for (N*H*) at δ = 9.0 and multiplets at 5.2 (5-H), 3.3 (4-H_2) and 2.8 [(CH_2)$_2$NHAr]. Similar signals appeared in the spectrum of **8b**.

In an interesting extension of this study, it has been found that a convenient route to the 3,4-difunctionalized 2-pyrazoline **12** starts with the *p*-methoxystyryl keto base **9** [23], which undergoes bromination to give the corresponding dibromo derivative **10** in a good yield (Scheme 3).

Treatment of dibromide **10** with piperidine afforded 1-(*p*-anisyl)-1,2,3-tri(piperidin-1-yl)pentan-3-one (**11**), the phenylhydrazone of which was readily converted into the target molecule 5-(*p*-anisyl)-1-phenyl-3-[β-(piperidin-1-yl)ethyl]-4-(piperidin-1-yl)-2-pyrazoline (**12**). Supporting evidence for structure **12** was provided by analytical and spectral data, and its mass fragmentation pattern agreed with the proposed structure (Scheme 3). The conversion of the phenylhydrazone of **11** into **12** is an intramolecular amine exchange reaction, which occurs by the elimination-addition sequence, that is operative with β-aminoketones [1, 2, 24], and their phenylhydrazones [1, 25, 26]. The formation of **12** as a sole product suggests the intermediacy of the styryl intermediate **15** (Scheme 4). Therefore, of the two possible intermediates **15** and **16** only **15** is expected, because the aryl group at C-1 increases the extent of the E1 elimination, since it stabilizes the carbonium character of the transition state **14′**, and also stabilizes the incipient double bond of **15**, which undergoes cyclization to afford **12**.

However, this reaction is often complicated by a competing nucleophilic attack of the phenylhydrazone moiety on the incipient carbonium ion **14** to give **17**,





Scheme 3.

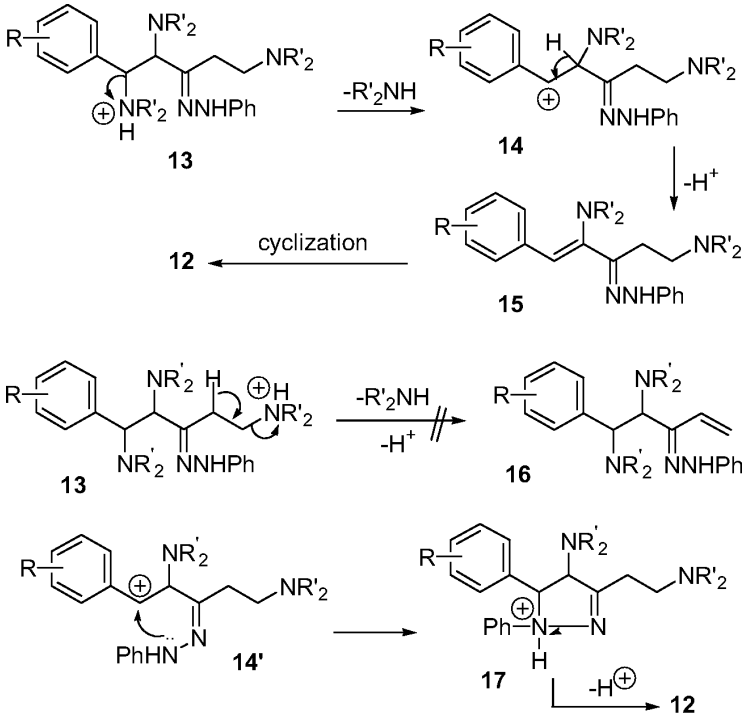
followed by deprotonation to **12** (*i. e.* SN1 type mechanism).

In addition, we have found that compounds **19a** – **c**, which are structurally related to **11**, could be used as intermediates for the synthesis of C-4 functionalized 2-pyrazolines of the type **20**. Thus, 2,3-di(morpholin-4-yl)-1,3-diphenylpropan-1-one (**19a**) was obtained from the dibromoketone **18a** and morpholine as reported earlier [27]. Analogously, treating **18a** or **b** with the appropriate amine gave **19b**,**c**. Reaction of **19a** and **b** with phenylhydrazine afforded 4-(1,3,5-triaryl-4,5-dihydro-1H-pyrazol-4-yl)morpholines **20a**,**b**. The same reaction with **19c**, obtainable *in situ* from **18a** and *N*-methylpiperazine, proceeded equally well, providing **20c**. Compounds **20a**–**c** are formed by a reaction sequence identical to that depicted in Scheme 5. The mass and ^{1}H NMR spectra are consistent with the proposed structures.

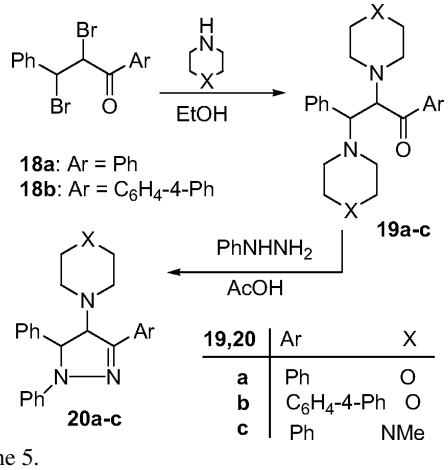
In line with this, the synthesis of 4-hydroxy-2-pyrazolines **22a**,**b** has been achieved by treating 2-hydroxy-3-(morpholin-4-yl)-1,3-diphenylpropan-1-one (**21**) with hydrazines. Mannich reaction of **22a** with formaldehyde and piperidine or piperazine afforded **23** and **24**, respectively. The structures of compounds **22** – **24** were supported by analytical and spectral data (Scheme 6).

In the course of this study, the styryl keto bases **9** and **25** [23] were converted into the corresponding β-phenylthioethyl styryl ketones **26a**,**b** through their reaction with thiophenol according to a previous report [20]. The potential of compounds **26a**,**b** as precursors to 2-pyrazolines having a β-phenylthioethyl side chain at C-3, was illustrated by treating their phenylhydrazones with ethanolic HCl to afford 1,5-diaryl-3-(β-phenylthioethyl)-2-pyrazolines **28a**,**b** (Scheme 7).

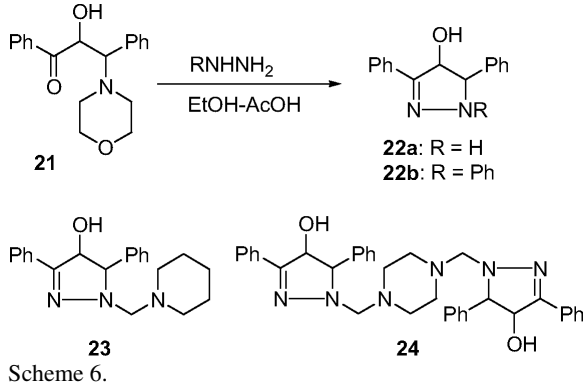
Compound **28a** was also obtained as a sole product from the phenylhydrazone of **27**, indicating that the reaction involves the preferential elimination of the thiophenyl group at C-1 of **27**. The ^{1}H NMR spectrum of **28a** showed multiplets at δ = 2.64 – 2.76 [(C*H*$_2$)$_2$SPh],



Scheme 4.



Scheme 5.

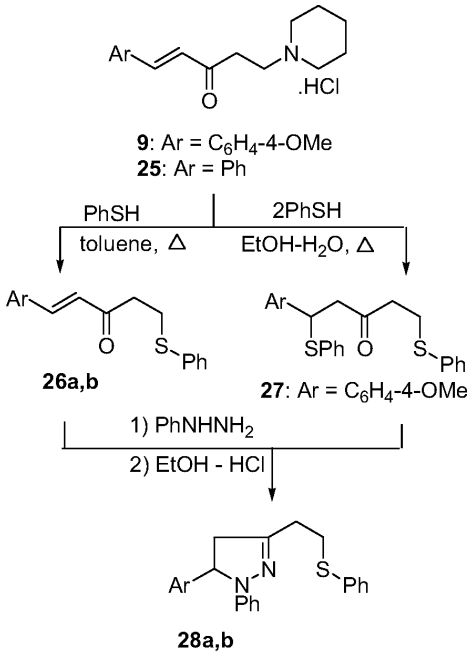


Scheme 6.

3.21 – 3.46 (4-H_2) and 4.91 – 5.02 (5-H). Similar signals appeared in the spectrum of **28b**. The formation of **28a** from **27** is in harmony with the formation of **12** from **11**.

Experimental Section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer. ^{1}H NMR data were obtained in $CDCl_3$solution on a Varian XL 200 MHz instrument using TMS as internal standard. Chemical shifts δ are reported in ppm downfield from internal TMS. Mass spectra were recorded on a GC-MS QP-1000 EX Shimadzu instrument. The course of the reaction and the purity of the synthesized compounds was monitored by TLC using EM science silica gel coated plates with visualization by irradiation with an ultraviolet lamp. Compounds **1a** [17], **1b** [18], **9** [23], **18a**,**b**,



Scheme 7.

19a [27], **25** [23], and **26b** [20] were prepared as previously described.

*1-Aryl-5-(morpholin-4-yl)-1-penten-3-one hydrochlorides **2a, b***

To a solution of *p*-anisalacetone (**1a**) (1.76 g, 10 mmol) or piperonalacetone (**1b**) (1.9 g, 10 mmol) and morpholine hydrochloride (1.23 g, 10 mmol) in absolute ethanol (20 mL), paraformaldehyde (0.45 g, 15 mmol) was added, and the mixture was refluxed for 1 h. Paraformaldehyde (0.15 g, 5 mmol) was added and the reaction mixture was refluxed for another 1 h. On cooling, yellow crystals of **2a**,**b** were separated, and were recrystallized from ethanol.

*1-(p-Anisyl)-5-(morpholin-4-yl)-1-penten-3-one hydrochloride (**2a**)*

M. p. 178 °C (ethanol). Yield 60 % (yellow crystals). – IR (KBr): ν = 1683 (α,β-unsaturated CO), 1601, 1497, 1445, 1250, 1150 cm^{-1}. – $C_{16}H_{22}ClNO_3$ (311.80): calcd. C 61.63, H 7.11, N 4.49; found C 61.55, H 7.08, N 4.33.

*1-(3,4-Methylenedioxyphenyl)-5-(morpholin-4-yl)-1-penten-3-one hydrochloride (**2b**)*

M. p. 164 °C (ethanol). Yield 67 % (yellow crystals). – IR (KBr): ν = 1678 (α,β-unsaturated CO), 1600, 1485, 1330, 1235, 1039 cm^{-1}. – $C_{16}H_{20}ClNO_4$ (325.79): calcd. C 58.99, H 6.19, N 4.30; found C 58.90, H 6.07, N 3.91.

*1-(3,4-Methylenedioxyphenyl)-5-(4-phenylpiperazin-1-yl)-1-penten-3-one (**2c**)*

A mixture of **2b** (0.3 g, 1 mmol) and N-phenylpiperazine (0.16 g, 1 mmol) in 50 % aqueous ethanol (20 mL) was refluxed for 90 min. The product that was obtained on cooling was filtered and crystallized from ethanol to give **2c**. – M. p. 110 °C. Yield 82 % (yellow crystals). – IR (KBr): ν = 1680 (α,β-unsaturated CO), 1610, 1480, 1350, 1115, 1040 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.31 (t, 2H, $COCH_2CH_2N$), 2.44 (m, 4H, $N(CH_2CH_2)_2NPh$), 2.62 (t, 2H, $COCH_2CH_2N$), 3.11 (m, 4H, $N(CH_2CH_2)_2NPh$), 5.88 (s, 2H, O–CH_2–O), 6.63 (d, 1H, CH=C*H*–CO), 7.22 – 7.53 (m, 8H, aromatic), 7.64 (d, 1H, C*H*=CH–CO). – $C_{22}H_{24}N_2O_3$ (364.44): calcd. C 72.50, H 6.64, N 7.69; found C 72.38, H 6.51, N 7.54.

*1-Aryl-5-(morpholin-4-yl)-1-penten-3-one phenylhydrazone hydrochlorides **3a, b***

To a solution of **2a** (0.62 g), or **2b** (0.65 g, 2 mmol) in ethanol (20 mL), phenylhydrazine (0.22 g, 2 mmol) and acetic acid (0.2 mL) were added. After standing at r. t. for 30 min, yellow crystals of the phenylhydrazines were separated. The products were recrystallized from ethanol to give **3a**,**b**.

*1-(p-Anisyl)-5-(morpholin-4-yl)-1-penten-3-one phenylhydrazone hydrochloride (**3a**)*

M. p. 181 °C (ethanol). Yield 84 % (yellow crystals). – IR (KBr): ν = 3289 (NH), 1605 (C=N), 1495, 1390, 1108, 1025 cm^{-1}. – $C_{22}H_{28}ClN_3O_2$ (401.93): calcd. C 65.74, H 7.02, N 10.45; found C 65.66, H 6.92, N 10.30.

*1-(3,4-Methylenedioxyphenyl)-5-(morpholin-4-yl)-1-penten-3-one phenylhydrazone hydrochloride (**3b**)*

M. p. 179 °C (ethanol). Yield 77 % (yellow crystals). – IR (KBr): ν = 3275 (NH), 1615 (C=N), 1449, 1380, 1120, 1010 cm^{-1}. – $C_{22}H_{26}ClN_3O_3$ (415.91): calcd. C 63.53, H 6.30, N 10.10; found C 63.33, H 6.10, N 9.85.

*5-Aryl-3-[β-(morpholin-4-yl)ethyl]-1-phenyl-2-pyrazoline hydrochlorides **4a, b***

A solution of **3a** or **3b** (1 g, 2.5 mmol) in 1N HCl (20 mL) was heated on a water bath for 10 min. The products obtained on cooling were filtered and crystallized from water to give **4a**,**b**.

*5-(p-Anisyl)-3-[β-(morpholin-4-yl)ethyl]-1-phenyl-2-pyrazoline hydrochloride (**4a**)*

M. p. 192 °C (water). Yield 87 % (white crystals). – IR (KBr): ν = 1610 (C=N), 1520, 1450, 1345, 1250,

1130 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 365 (4) $[M-HCl]^+$, 115 (2) $[CH_2–CH_2–N(CH_2CH_2)_2O + H]^+$, 100 (100) $[CH_2–N(CH_2CH_2)_2O]^+$, 77 (7) $[Ph]^+$, 56 (14) $[C_3H_6N]^+$. – $C_{22}H_{28}ClN_3O_2$ (401.93): calcd. C 65.74, H 7.02, N 10.45; found C 65.72, H 6.87, N 10.13.

*5-(3,4-Methylenedioxyphenyl)-3-[β-(morpholin-4-yl)ethyl]-1-phenyl-2-pyrazoline hydrochloride (**4b**)*

M. p. 188 °C (water). Yield 70 % (white crystals). – IR (KBr): ν = 1605 (C=N), 1512, 1435, 1325, 1210, 1066 cm^{-1}. – MS (EI, 70 eV): *m/z* (%) = 379 (12) $[M-HCl]^+$, 100 (100) $[CH_2–N(CH_2CH_2)_2O]^+$, 77 (13) $[Ph]^+$, 56 (30) $[C_3H_6N]^+$. – $C_{22}H_{26}ClN_3O_3$ (415.91): calcd. C 63.53, H 6.30, N 10.10; found C 63.44, H 5.90, N 9.96.

*5-(3,4-Methylenedioxyphenyl)-3-[β-(4-phenylpiperazin-1-yl)ethyl]-1-phenyl-2-pyrazoline (**4c**)*

A solution of **2c** (0.73 g, 2 mmol) and phenylhydrazine (0.22 g, 2 mmol) in ethanol (20 mL) containing (0.1 mL) of acetic acid, was heated on a water bath for 15 min. The product obtained on cooling was filtered and crystallized from ethanol to give **4c**. M. p. 148 °C. Yield 65 % (yellow crystals). – IR (KBr): ν = 1605 (C=N), 1496, 1339, 1260, 1120 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.41 (m, 4H, $N(CH_2CH_2)_2NPh$), 2.56 (t, 2H, CH_2CH_2N), 2.71 (t, 2H, CH_2CH_2N), 2.95 [m, 4H, $N(CH_2CH_2)_2NPh$], 3.27 (d, 2H, 4-H_2), 5.23 (m, 1H, 5-*H*), 5.88 (s, 2H, O–CH_2–O), 7.24 – 7.63 (m, 8H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 332 (17) $[M-C_6H_3{:}O_2CH_2\text{-}3,4]^+$, 300 (35) $[M-2Ph]^+$, 189 (23) $[CH_2CH_2–N(CH_2CH_2)_2NPh]$, 175 (100) $[CH_2–N(CH_2CH_2)_2NPh]^+$, 77 (28) $[Ph]^+$. – $C_{28}H_{30}N_4O_2$ (454.56): calcd. C 73.98, H 6.65, N 12.33; found C 73.78, H 6.52, N 12.10.

*3-(Substituted styryl)-1-phenyl-2-pyrazolines **6a, b***

A solution of **3a** or **3b** (1 g, 2.5 mmol) in glacial acetic acid (10 mL) was heated on a steam bath for 1 h, poured onto water (50 mL) and basified with NH_4OH. The products obtained were filtered and crystallized from ethanol – ethyl acetate (1 : 1) to give **6a**,**b**.

*3-(p-Methoxystyryl)-1-phenyl-2-pyrazoline (**6a**)*

M. p. 170 °C. Yield 65 % (yellow crystals). – IR (KBr): ν = 1597 (C=N), 1503, 1460, 1377, 1254, 1174, 1030 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.68 (m, 2H, 4-H_2), 3.31 (m, 2H, 5-H_2), 3.77 (s, 3H, $ArOCH_3$), 5.88 (d, 1H, Ar–CH=C*H*–), 6.95 (d, 1H, Ar–C*H*=CH–), 7.23 – 7.54 (m, 9H, aromatic). – $C_{18}H_{18}N_2O$ (278.35): calcd. C 77.67, H 6.52, N 10.06; found C 77.49, H 6.33, N 9.91.

*3-(3,4-Methylenedioxystyryl)-1-phenyl-2-pyrazoline (**6b**)*

M. p. 138 °C. Yield 72 % (pale brown crystals). – IR (KBr): ν = 1605 (C=N), 1505, 1442, 1352, 1250, 1127, 1034 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.66 (m, 2H, 4-H_2), 3.29 (m, 2H, 5-H_2), 5.91 (s, 2H, O–CH_2–O), 6.15 (d, 1H, Ar–CH=C*H*–), 6.92 (d, 1H, Ar–C*H*=CH–), 7.21 – 7.48 (m, 8H, aromatic). – $C_{18}H_{16}N_2O_2$ (292.33): calcd. C 73.95, H 5.52, N 9.58; found C 73.88, H 5.42, N 9.35.

*5-(p-Anisyl)-3-[β-(arylamino)ethyl]-1-phenyl-2-pyrazolines **8a, b***

The free base of **4a**, obtained by basification of 1.2 g (3 mmol) of **4a** with dilute NH_4OH, was treated in ethanol (20 mL) with methyl iodide (0.43 g, 3 mmol), and the mixture was heated on a water bath at 50 °C for 1 h. Then aniline (0.28 g, 3 mmol) or *p*-toluidine (0.32 g, 3 mmol) was added and the mixture was refluxed for 1 h. The products obtained on cooling were filtered and crystallized from ethanol – ethyl acetate (1 : 1) to give **8a**,**b**.

*5-(p-Anisyl)-3-[β-(phenylamino)ethyl]-1-phenyl-2-pyrazoline (**8a**)*

M. p. 110 °C. Yield 68 % (yellow crystals). – IR (KBr): ν = 3399 (NH), 1605 (C=N), 1325 (C–N stretch of *sec.* aryl amine), 1259, 1100 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.81 (m, 4H, $(CH_2)_2$–N), 3.34 (d, 2H, 4-H_2), 4.02 (s, 3H, $ArOCH_3$), 5.21 (m, 1H, 5-*H*), 7.12 – 7.60 (m, 14H, aromatic), 9.03 (s, 1H, PhN*H*). – $C_{24}H_{25}N_3O$ (371.47): calcd. C 77.60, H 6.78, N 11.31; found C 77.49, H 6.58, N 11.08.

*5-(p-Anisyl)-3-[β-(p-tolylamino)ethyl]-1-phenyl-2-pyrazoline (**8b**)*

M. p. 128 °C. Yield 73 % (yellow crystals). – IR (KBr): ν = 3375 (NH), 1615 (C=N), 1320 (C–N stretch of *sec.* aryl amine), 1294, 1252, 1132 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.04 (s, 3H, $(Ar–CH_3)$, 2.73 (m, 4H, $(CH_2)_2$–N), 3.31 (d, 2H, 4-H_2), 3.75 (s, 3H, $ArOCH_3$), 5.35 (m, 1H, 5-*H*), 7.21 – 7.67 (m, 13H, aromatic), 9.58 (s, 1H, ArN*H*). – $C_{25}H_{27}N_3O$ (385.50): calcd. C 77.89, H 7.06, N 10.90; found C 77.78, H 6.88, N 10.79.

*1-(p-Anisyl)-1,2-dibromo-5-(piperidin-1-yl)pentan-3-one (**10**)*

A solution of **9** (0.82 g, 3 mmol) in carbon tetrachloride (40 mL) was cooled and bromine (0.5 g, 6 mmol) was added with stirring. After standing for 30 min, the product was filtered and washed with hot ethanol (2 × 10 mL). Crystallization from benzene-ethanol (2 : 1) gave **10**. M. p.

208 °C. – Yield 90 % (white crystals). – IR (KBr): ν = 1656 (CO), 1601, 1512, 1459, 1364, 1256, 1223, 1019 cm^{-1}. – $C_{17}H_{23}Br_2NO_2$ (433.18): calcd. C 47.14, H 5.35, N 3.23; found C 47.02, H 5.22, N 3.02.

*5-(p-Anisyl)-3-[β-(piperidin-1-yl)ethyl]-4-(piperidin-1-yl)-1-phenyl-2-pyrazoline (**12**)*

A solution of **10** (0.87 g, 2 mmol) and piperidine (0.5 g, 6 mmol) in absolute ethanol (30 mL) was stirred at r. t. for 24 h, to give **11** which was not isolated, and then phenylhydrazine (0.22 g, 2 mmol) and acetic acid (1 mL) were added. The reaction mixture was heated on a steam bath for 45 min. The crystals obtained on cooling were filtered and crystallized from ethanol to give **12**. M. p. 165 °C. Yield 63 % (yellow crystals). – IR (KBr): ν = 1615 (C=N), 1598, 1462, 1345, 1256, 1173, 1030 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.45 – 1.58 (2 × m, 12H, 2 × (3-H_2, 4-H_2, 5-H_2) of piperidine units), 2.38 (t, 2H, CH_2CH_2N), 2.45 (m, 4H, 2H_2, 6H_2 of piperidine at side chain), 2.58 (t, 2H, CH_2CH_2N), 2.65 (m, 4H, 2H_2, 6H_2 of 4-(piperidin-1-yl)), 3.40 (d, 1H, 4-*H*), 3.75 (s, 3H, $ArOCH_3$), 4.88 (d,1H, 5-*H*), 7.15 – 7.52 (m, 9H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 446 (3) $[M]^+$, 369 (31) $[M-Ph]^+$, 362 (40) $[M-C_5H_{10}N]^+$, 348 (100) $[M-C_5H_{10}N-CH_2]^+$, 264 (13) $[M-(C_5H_{10}N + C_5H_{10}N-CH_2)]^+$, 112 (37) $[C_5H_{10}N-CH_2-CH_2]^+$, 108 (43) $[C_6H_4OMe + H]^+$, 105 (32) $[PhN{=}N]^+$, 98 (8) $[C_5H_{10}N-CH_2]^+$, 77 (28) $[Ph]^+$, 65 (24) $[C_3H_3N_2 - 2H]^+$. – $C_{28}H_{38}N_4O$ (446.63): calcd. C 75.30, H 8.58, N 12.54; found C 75.15, H 8.28, N 12.22.

*1-(Biphenyl-4-yl)-2,3-di(morpholin-4-yl)-3-phenylpropan-1-one (**19b**)*

To a suspension of **18b** (1.3 g, 3 mmol) in absolute ethanol (50 mL), morpholine (0.9 g, 10 mmol) was added with stirring. After standing at r. t. for 24 h, the yellow crystals obtained were filtered and washed with water (4 × 10 mL). The product was crystallized from ethanol to give **19b**. M. p. 120 °C. Yield 66 % (yellow crystals). – IR (KBr): ν = 1665 (CO), 1596, 1449, 1320, 1250, 1113, 1071 cm^{-1}. – $C_{29}H_{32}N_2O_3$ (456.58): calcd. C 76.29, H 7.06, N 6.14; found C 76.12, H 6.93, N 5.94.

*4-(1,3,5-Triaryl-4,5-dihydro-1H-pyrazol-4-yl)morpholines **20a, b***

A solution of **19a** (1.2 g) or **19b** (1.4 g, 3 mmol) and phenylhydrazine (0.33 g, 3 mmol) in 15 mL of 50 % acetic acid was heated on a steam bath. The reaction time was 30 min for **20a**, and 90 min for **20b**. The crystals obtained on cooling were filtered and crystallized from ethanol to give **20a**,**b**.

*4-(1,3,5-Triphenyl-4,5-dihydro-1H-pyrazol-4-yl)morpholine (**20a**)*

M. p. 141 °C. Yield 53 % (yellow crystals). – IR (KBr): ν = 1610 (C=N), 1594, 1490, 1294, 1258, 1134, 1056 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.83 – 2.96 (m, 4H, CH_2–N–CH_2 of morpholine), 3.12 – 3.25 (m, 4H, CH_2–O–CH_2 of morpholine), 3.25 (d, 1H, 4-*H*), 5.12 (d, 1H, 5-*H*), 7.05 – 7.56 (m, 15H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 383 (3) $[M]^+$, 196 (100) $[PhNH-N{=}CHPh]^+$, 195 (79) $[PhN{=}N{=}CHPh]^+$, 92 (66) $[PhNH]^+$, 77 (28) $[Ph]^+$, 66 (18) $[C_3H_2N_2]^+$, 65 (44) $[C_3H_2N_2 - H]^+$. – $C_{25}H_{25}N_3O$ (383.49): calcd. C 78.30, H 6.57, N 10.96; found C 78.11, H 6.38, N 10.77.

*4-[(3-Biphenyl-4-yl)-1,5-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)]morpholine (**20b**)*

M. p. 150 °C. Yield 58 % (yellow crystals). – IR (KBr): ν = 1613 (C=N), 1595, 1442, 1385, 1347, 1281, 1154 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.80 – 2.95 (m, 4H, CH_2–N–CH_2 of morpholine), 3.15 – 3.25 (m, 4H, CH_2–O–CH_2 of morpholine), 3.30 (d, 1H, 4-*H*), 5.15 (d, 1H, 5-*H*), 6.85 – 7.40 (m, 19H, aromatic). – $C_{31}H_{29}N_3O$ (459.58): calcd. C 81.02, H 6.36, N 9.14; found C 80.92, H 6.21, N 9.01.

*1-Methyl-4-[(1,3,5-triphenyl)-4,5-dihydro-1H-pyrazol-4-yl] piperazine (**20c**)*

A solution of **18a** (1.1 g, 3 mmol) and *N*-methylpiperazine (1.2 g, 12 mmol) in ethanol (50 mL) was stirred at r. t. for 24 h, to give **19c** which was not isolated. Then phenylhydrazine (0.33 g, 3 mmol) and acetic acid (1 mL) were added, and the reaction mixture was heated on a steam bath for 45 min. The yellow crystals obtained on cooling were filtered and crystallized from ethanol to give **20c**. M. p. 118 °C. Yield 65 % (yellow crystals). – IR (KBr): ν = 1605 (C=N), 1592, 1459, 1373, 1244, 1174 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.22 (s, 3H, NCH_3), 2.54 (m, 4H, $MeN(CH_2CH_2)_2N$)), 3.12 (m, 4H, $MeN(CH_2CH_2)_2N$)), 3.28 (d, 1H, 4-*H*), 5.13 (d, 1H, 5-*H*), 7.10 – 7.57 (m, 15H, aromatic). – MS (EI, 70 eV): *m/z* (%) = 396 (3) $[M]^+$, 319 (28) $[M-Ph]^+$, 242 (38) $[M-2Ph]^+$, 195 (79) $[PhNH-N{=}CHPh-H]^+$, 194 (100) $[PhNH-N{=}CHPh-2H]^+$, 165 (30) $[M-3Ph]^+$, 104 (8) $[PhCH{=}CH_2]^+$, 99 (68) $[MeN(CH_2CH_2)_2N]^+$, 66 (19) $[C_3H_2N_2]^+$, 65 (45) $[C_3H_2N_2 - H]^+$. – $C_{26}H_{28}N_4$ (396.53): calcd. C 78.75, H 7.12, N 14.13; found C 78.61, H 6.98, N 13.89.

*2-Hydroxy-3-(morpholin-4-yl)-1,3-diphenylpropan-1-one (**21**)*

A solution of chalcone epoxide [28] (2.24 g, 10 mmol) and morpholine (1.75 g, 20 mmol) in ethanol (50 mL) was re-

fluxed for 3 h. The solvent was evaporated and the oily product was purified by preparative chromatography on Al_2O_3 using pet. ether 40 – 60 °C / ethyl acetate (3 : 1) as eluent. The product was crystallized from ethanol to give **21**. M. p. 135 °C. Yield 45 % (yellow crystals). – IR (KBr): ν = 3475 (OH), 1660 (CO), 1596, 1447, 1376, 1270, 1114, 1065 cm^{-1}. – $C_{19}H_{21}NO_3$ (311.37): calcd. C 73.29, H 6.80, N 4.50; found C 73.11, H 6.62, N 4.22.

*4-Hydroxy-3,5-diphenyl-2-pyrazolines **22a, b***

A solution of **21** (0.62 g, 2 mmol), hydrazine hydrate (0.1 g, 2 mmol) or phenylhydrazine (0.22 g, 2 mmol) in ethanol (25 mL) containing acetic acid (1 mL), was refluxed for 3 h. After standing at r. t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **22a**,**b**.

*4-Hydroxy-3,5-diphenyl-2-pyrazoline (**22a**)*

M. p. 201 °C. Yield 65 % (yellow crystals). – IR (KBr): ν = 3387 (OH), 3183 (NH), 1610 (C=N), 1577, 1466, 1343, 1255, 1038 cm^{-1}. – $C_{15}H_{14}N_2O$ (238.28): calcd. C 75.61, H 5.92, N 11.76; found C 75.50, H 5.81, N 11.58.

*4-Hydroxy-1,3,5-triphenyl-2-pyrazoline (**22b**)*

M. p. 124 °C. Yield 72 % (yellow crystals). – IR (KBr): ν = 3262 (OH), 1608 (C=N), 1596, 1495, 1323, 1136, 1033 cm^{-1}. – $C_{21}H_{18}N_2O$ (314.37): calcd. C 80.23, H 5.77, N 8.91; found C 80.10, H 5.59, N 8.71.

*4-Hydroxy-1-(piperidin-1-ylmethyl)-3,5-diphenyl-2-pyrazoline (**23**)*

A solution of **22a** (1.2 g, 5 mmol), formalin (37 %, 0.5 mL, 6 mmol) and piperidine (0.43 g, 5 mmol) in ethanol (40 mL) was refluxed for 6 h. The crystals obtained on cooling were filtered off and recrystallized from ethanol to give **23**. M. p. 170 °C. Yield 55 % (yellow crystals). – IR (KBr): ν = 3383 (OH), 1612 (C=N), 1433, 1352, 1267, 1141, 1043 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.55 – 1.58 (m, 6H, 3-H_2, 4-H_2, 5-H_2 of piperidine), 2.63 (m, 4H, CH_2–N–CH_2 of piperidine), 3.75 (d, 1H, 4-*H*), 4.73 (s, 1H, O*H*), 5.15 (s, 2H, N–CH_2–N of side chain), 5.75 (m, 1H, 5-*H*), 7.19 – 7.75 (m, 10H, aromatic). – $C_{21}H_{25}N_3O$ (335.44): calcd. C 75.19, H 7.51, N 12.53; found C 75.02, H 7.32, N 12.33.

*1,4-Bis(4-hydroxy-3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-ylmethyl)piperazine (**24**)*

A solution of **22a** (2.4 g, 10 mmol), formalin (37 %, 1.2 mL, 15 mmol) and piperazine (0.44 g, 5 mmol) in ethanol (50 mL) was refluxed for 6 h. After standing at r. t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **24**. M. p. > 250 °C. Yield 58 % (yellow crystals). – IR (KBr): ν = 3373 (OH), 1605 (C=N), 1588, 1454, 1371, 1271, 1113, 1073 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.35 – 2.60 (m, 8H, N(CH_2 CH_2)$_2$N), 3.85 (d, 2H, 2 (4-*H*)), 4.75 (s, 2H, 2 O*H*), 5.15 (s, 4H, 2 (N–CH_2–N) of side chain), 5.71 (m, 2H, 2 (5-*H*)), 6.92 – 7.43 (m, 20H, aromatic). – $C_{36}H_{38}N_6O_2$ (586.73): calcd. C 73.69, H 6.53, N 14.32; found C 73.55, H 6.35, N 14.12.

*1-(p-Anisyl)-5-(phenylthio)-1-penten-3-one (**26a**)*

A mixture of **9** (0.62 g, 2 mmol) and thiophenol (0.22 g, 2 mmol) in toluene (20 mL) was refluxed for 90 min. The solvent was removed under reduced pressure, and the oily product was crystallized from ethanol to give **26a**. M. p. 80 °C. Yield 65 % (white powder). – IR (KBr): ν = 1644 (α,β-unsaturated CO), 1599, 1460, 1373, 1239, 1169, 1030 cm^{-1}. – $C_{18}H_{18}O_2S$ (298.40): calcd. C 72.45, H 6.08; found C 72.38, H 6.01.

*1-(p-Anisyl)-1,5-di(phenylthio)-1-pentan-3-one (**27**)*

A solution of **9** (0.93 g, 3 mmol) and thiophenol (0.83 g, 7.5 mmol) in 50 % aq. ethanol (25 mL) was refluxed for 1 h. The product obtained on cooling was filtered off and crystallized from ethanol to give **27**. M. p. 60 °C. Yield 75 % (white powder). – IR (KBr): ν = 1701 cm^{-1} (CO), 1610, 1582, 1462, 1364, 1260, 1179, 1028 cm^{-1}. – $C_{24}H_{24}O_2S_2$ (408.58): calcd. C 70.55, H 5.92; found C 70.35, H 5.81.

*5-(p-Anisyl)-1-phenyl-3-(β-phenylthioethyl)-2-pyrazoline (**28a**)*

Procedure A: A solution of **26a** (0.6 g, 2 mmol), phenylhydrazine (0.22 g, 2 mmol) and 0.1 mL of conc. HCl in ethanol (25 mL) was heated on a water bath for 30 min. After standing at r. t. for 24 h, the product obtained was filtered and crystallized from ethanol to give **28a**. M. p. 70 °C. Yield 80 % (white crystals). – IR (KBr): ν = 1610 (C=N), 1593, 1456, 1325, 1252, 1168, 1090 cm^{-1}. – ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.64 – 2.76 (m, 4H, (CH_2)$_2$–SPh), 3.21 – 3.46 (d, 2H, 4-H_2), 3.79 (s, 3H, ArOCH_3), 4.91 – 5.02 (m, 1H, 5-*H*), 7.12 – 7.52 (m, 14H, aromatic). – $C_{24}H_{24}N_2OS$ (388.53): calcd. C 74.19, H 6.23, N 7.21; found C 74.01, H 6.11, N 7.03.

Procedure B: A mixture of **27** (0.82 g, 2 mmol), phenylhydrazine (0.22 g, 2 mmol) and 0.1 mL of conc. HCl in ethanol (25 mL) was refluxed for 1 h, and worked up as above to give **28a**. M. p. 69 – 70 °C. Yield 65 %. The structure was confirmed by a comparison of ^{1}H NMR data, m. p. and TLC with that from procedure A.

*1,5-Diphenyl-3-(β-phenylthioethyl)-2-pyrazoline (**28b**)*

This compound was obtained in the same manner as described for **28a** (procedure A), but using **26b** (0.54 g,

2 mmol) instead of **26a**. The product crystallized from ethanol to give **28b**. M. p. 73 °C. Yield 66 % (white crystals). – IR (KBr): ν = 1615 (C=N), 1600, 1510, 1447, 1319, 1260, 1120 cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.69 – 2.75 (m, 4H, $(CH_2)_2$–SPh), 3.24 – 3.38 (d, 2H, 4-H_2), 5.27 – 5.34 (m, 1H, 5-*H*), 7.15 – 7.55 (m, 15H, aromatic). – $C_{23}H_{22}N_2S$ (358.50): calcd. C 77.06, H 6.19, N 7.81; found C 76.93, H 6.01, N 7.67.

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