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Synthesis and reactivity of Mannich bases. Part 15: Synthesis of 3-(2-(1-pyrazolyl)ethyl)-1,2-benzisoxazoles

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Abstract—Four new Mannich bases derived from *ortho*-hydroxyacetophenones and containing pyrazoles as amine moieties have been subjected to oximation in alkaline medium. The selective acetylation to the oximino hydroxyl of the resulting oximes led to the corresponding oxime-acetates. These have been transformed via a ring closure reaction in refluxing benzene and in the presence of anhydrous K_2CO_3 into 3-(2-(1-pyrazolyl)ethyl)-1,2-benzisoxazoles, valuable as potential pharmacologically relevant compounds. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

A survey of the recent literature on 1,2-benzisoxazoles reveals the importance of the above-mentioned heterocyclic system as a moiety in pharmaceutically significant compounds. Moreover, studies suggest that 3-substituted 1,2-benzisoxazoles are more likely to display biological activities. Thus, a series of 1,2-benzisoxazoles-3-carboxamides was evaluated as potential atypical antipsychotic agents and presented affinity for serotonergic and dopaminergic receptors.[1,2] Iloperidone (HP 873), an 3-aryloxyalkylpiperidinyl-1,2-benzisoxazole derivative, was also shown to exhibit potent antipsychotic-like activity and efficiency against asociality, a negative symptom of schizophrenia.[3] Aminoalkyl 2-cyclic amino-2-(1,2-benzisoxazol-3-yl)acetates and their quaternary ammonium salts[4] along with 3-(*N*-benzylpiperidinylethyl)-1,2-benzisoxazoles[5] were investigated and found to selectively inhibit acetylcholinesterase, making them suitable candidates for the palliative treatment of Alzheimer's disease. A potent inhibitor of LTB_4 binding to human neutrophile belongs to a family of 3-amino-1,2-benzisoxazoles[6] whereas 3-(2-thienyl)- or 3-(2-imidazolyl)-1,2-benzisoxazoles inhibit arachidonic acid-induced platelet aggregation.[7] Recently, two patents[8] have claimed that substituted 3-(aminoalkylamino)-1,2-benzisoxazoles are useful for the treatment of various memory dysfunctions and as antidepressants by inhibiting monoamine oxidase.

The earlier successful synthesis[9] of 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles via the cyclization of 3-dialkylamino-1-(2-hydroxyphenyl)-1-propanone oxime acetates in refluxing benzene in the presence of anhydrous K_2CO_3 urged us to investigate the applicability of this procedure for the generation of other 1,2-benzisoxazoles, this time bearing a pyrazolylethyl substituent in position 3.

2. Results and discussions

The four step reaction scheme leading to 3-(2-(1-pyrazolyl)-ethyl)-1,2-benzisoxazoles **5** is presented in Scheme 1.

The starting 1-(2-hydroxyphenyl)-3-(1-pyrazolyl)-1-propanones **2** were prepared through an amine exchange reaction between the dimethylamine Mannich bases **1** (R^1=H or CH_3) derived from *ortho*-hydroxyacetophenones[11,12] and pyrazoles. As it has been previously shown for the similar reaction between the same Mannich bases and arylamines,[12,13] the displacement of the dimethylamino moiety was best accomplished by refluxing the reactants for 1 h in a 1:1 (v/v) mixture of ethanol and water, that dissolves both starting materials and allows a facile separation of the *N*-alkylated pyrazoles in the end. The resulting emulsion was cooled with good stirring in a dry ice–acetone refrigerating mixture in order to obtain the solid compounds **2** (yield 50–84%).

Oximation of *N*-(*ortho*-hydroxybenzoylethyl)pyrazoles **2** was conducted in an aqueous alkaline solution in which these compounds are soluble due to the phenolic hydroxyl in their structure. As the salts of the pyrazole-containing

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Keywords: β-aminoketones; pyrazoles; amine exchange reaction; oximes; benzisoxazoles.

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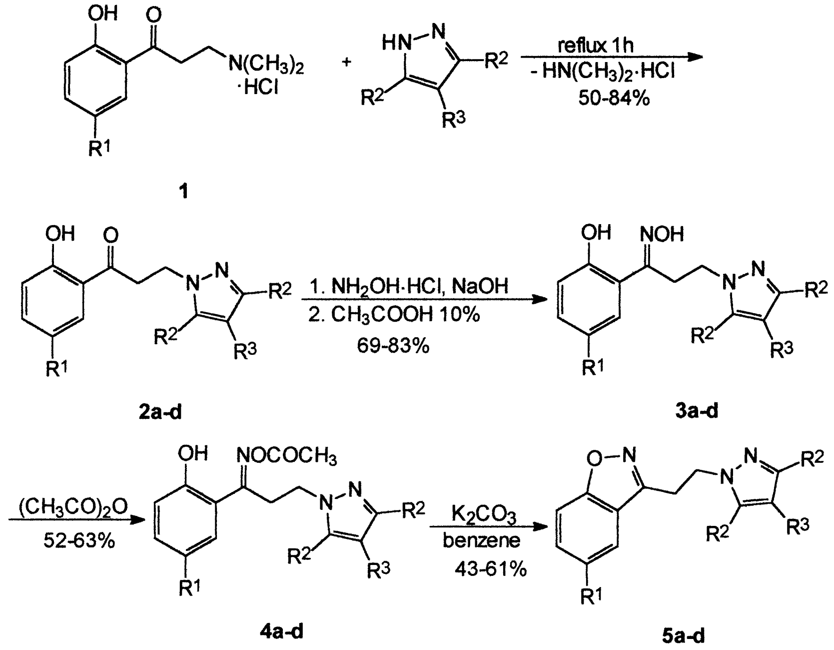

Compound	R^1	R^2	R^3
a	H	CH_3	H
b	CH_3	H	H
c	CH_3	CH_3	H
d	CH_3	CH_3	Br

Scheme 1. Three-step synthesis of 3-(2-(1-pyrazolyl)ethyl)-1,2-benzisoxazoles.

Mannich bases are not as soluble as their analogs bearing a dialkylamino moiety instead, larger volumes of dilute NaOH solution should be used. The alkaline medium also plays a key role in controlling the stereochemistry of the resulting oximes. It has been shown[14] that oximations in an alkaline medium leads to only one stereoisomer; furthermore, most aryl alkyl ketoximes exhibit a *syn*-alkyl configuration,[15] that is also important in the subsequent cyclization stage of oxime acetates to 1,2-benzisoxazoles. The molar ratio Mannich base/hydroxylamine hydrochloride/NaOH was 1:2:4. The reaction proceeded smoothly and with excellent yields (over 90%) in a homogeneous medium from which the oximes **3** were separated by adding acetic acid to the yellow solution of their salts until the pH reached 7.

The conversion of oximes **3** into oxime acetates **4** is recommendable since it is known that oxime esters are more reactive in cyclizations to 1,2-benzisoxazoles under less drastic conditions. Mannich base oxime esters have received little attention. To our knowledge, except for our earlier works,[9,10,16] only one paper deals with the preparation of several 2-dialkylaminocycloalkanone oxime benzoates as prodrug candidates with cytotoxic activity.[17] As previously reported,[16] the synthesis of the Mannich base oxime acetates can be achieved by selective acetylation using either acetyl chloride in THF or acetic anhydride. In the case of dialkylamine Mannich base oximes, acetic anhydride provided only oily oxime acetates, whereas the use of acetyl chloride afforded the solid corresponding oxime acetate hydrochlorides having the advantage to be easy to handle and purify prior to the ring closure stage. A preliminary experiment aiming at the preparation of the pyrazole-containing Mannich base oxime acetate **4b** as a hydrochloride using acetyl chloride as acylating agent did not led to the expected product, only some unchanged oxime being recovered. Instead, acetic anhydride proved efficient in the case of Mannich base oximes bearing a pyrazole as amine moiety, rendering good yields of solid desired oxime esters. Due to the Mannich base oxime acetates' remarkable solubility in most organic solvents, severe loss was incurred during recrystallization.

In the series of common salicylaldehydes and *ortho*-hydroxyacetophenones oximes, ring closure to 1,2-benzisoxazoles is frequently brought about thermally or in the presence of a base. Both elevated temperatures[18] and highly alkaline conditions[19,20] may cause unwanted secondary processes such as cyclization to 1,3-benzoxazoles or the hydrolysis of the oxime esters. The original method developed for the synthesis of 3-(2-dialkylaminoethyl)-1,2-benzisoxazoles[9] from dialkylamine Mannich bases oxime acetates under moderate reaction conditions minimized the extent of the hydrolysis and prevented 1,3-benzoxazole formation, making it a suitable alternative for further approaches in the preparation of other 1,2-benzisoxazoles substituted with nitrogen-containing basic functions. Thus, the ring closure reaction of the pyrazole-containing Mannich base oxime acetates **4** was effected with synthetically useful yields in refluxing benzene and in the presence of a mild base (anhydrous K_2CO_3). Only small amounts (3–6%) of oximes (that could be separated from the alkaline extract used in the work-up of the organic phase and identified by their melting points) resulted from the basic hydrolysis of oxime acetates. The yields of pure 1,2-benzisoxazoles **5** reduced substantially after

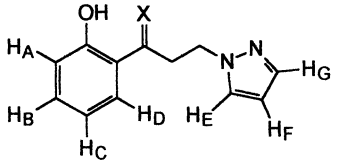

Figure 1. Representation of aromatic protons in the spectra of compounds **2**–**5**.

recrystallization because of these compounds' good solubility in common organic solvents.

IR spectra of the *N*-alkylated pyrazoles **2** presented an intense sharp absorption band at about 1650 cm^{-1} ($\nu_{C=O}$) as a result of the incorporation of 2-hydroxybenzoylethyl moiety in their structure. The involvement of the carbonyl group in an intramolecular hydrogen bond with the neighboring phenolic hydroxyl lowers to 1650 cm^{-1} the value for the $\nu_{C=O}$ band, usually situated at 1700–1675 cm^{-1} in other common acetophenones. The conversion of the keto group into oximino in compounds **3** led to the substitution of the intense $\nu_{C=O}$ band with the medium intense $\nu_{C=N}$ absorption band at 1630–1640 cm^{-1}. Acetylation of oximes **3** to oxime acetates **4** resulted in the IR spectra of the latter compounds in the intense $\nu_{C=O}$ ester absorption band at 1760–1790 cm^{-1}, that could no longer be detected in the IR spectra of benzisoxazoles **5**.

^{1}H NMR spectra of Mannich bases **2** displayed the expected number of protons (Fig. 1) at typical chemical shift values. It should be noted the off-set signal given by the phenolic proton that confirms its participation to the above-mentioned intramolecular hydrogen bond. The ^{1}H NMR spectra of the oximes **3** differed from the proton spectra of ketones **2** by the additional off-set peak assigned to the hydroxyl proton in the oximino group. This peak disappeared in the ^{1}H NMR spectra of oxime acetates **4**, that exhibited instead the supplementary singlet in the aliphatic region due to the methyl protons in the acetyl group. The absence of the before mentioned singlet in the proton spectra of 1,2-benzisoxazoles **5**, corroborated with the lack of any signals in the off-set, made certain the success of the ring closure reaction.

The structure of the synthesized compounds was further substantiated by ^{13}C NMR spectra. The carbon atom in the ketonic group of the pyrazole-containing Mannich bases **2** gave a signal at δ values higher than 200 ppm; the same carbon atom in the oximes **3** could be associated with the signal at near 160 ppm as a result of the oxygen atom replacement with a nitrogen atom. The ^{13}C NMR spectra of oximes **3** also gave valuable information on the configuration of these compounds. The δ value recorded[21] for the carbon atom in the methylene α to the oximino group of several acetophenone oximes lies at about 21 ppm in the case of *E* (*syn*-alkyl) isomer and at approximately 29 ppm in the case of *Z* (*syn*-aryl) isomer. The same carbon atom in the *E* isomer of the dialkylamine Mannich base oximes[10,11] gives a signal near 23 ppm as a consequence of the deshielding effect of the nitrogen atom in the β-amino moiety. It is reasonable to admit that the β-N^1-pyrazolyl ring in oximes **3** would exert an even greater deshielding effect, so that the δ values of 26–27 ppm recorded for the carbon atom in the methylene α to the oximino group are typical rather for the *E* (*syn*-alkyl) isomer than for the *Z* isomer. The same configuration was retained in the oxime acetates **4** and favored the ring closure reaction to 1,2-benzisoxazoles **5**.

3. Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analysis was done on a Carlo Erba 1106 analyzer. IR spectra were recorded on a Specord M80 spectrophotometer. NMR analyses were performed on a Varian INOVA or a Varian Gemini instrument. All chemical shifts are reported in ppm downfield from tetramethylsilane; the coupling constants are given in Hz. Low resolution mass spectra were recorded on V.G. Micromass 7070 HS instrument, while the high resolution mass spectra were registered on a Kratos Concept-IIA spectrometer. All commercially available reagents were used without further purification.

3.1. *N*-Alkylation of pyrazoles with Mannich bases derived from *ortho*-hydroxyacetophenones—general procedure

Mannich base hydrochloride **1** (10 mmol) and (un)substituted pyrazole (10 mmol) were refluxed in 1:1 (v/v) ethanol–water mixture (12 mL) for 1 h. The oily reaction product crystallized on cooling. The solid was filtered off, washed with water and recrystallized from ethanol.

3.1.1. 1-(2-Hydroxyphenyl)-3-(3,5-dimethylpyrazol-1-yl)-1-propanone 2a. 2.05 g (84%) of white crystals, mp 91–92 °C; (Found: C, 68.93; H, 6.37; N, 11.56. $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.55; N, 11.47); ν_{max} (KBr) 1649 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 2.20 and 2.28 (s, 3H, $-CH_3$), 3.59 (t, 2H, J=6.6 Hz, $-COCH_2-$), 4.36 (t, 2H, J=6.6 Hz, $-CH_2N<$), 5.75 (s, 1H, H_F), 6.84–6.89 (m, 1H, H_A), 6.94–6.97 (m, 1H, H_C), 7.42–7.48 (m, 1H, H_B), 7.72 (dd, 1H, $J_{1,3}$=1.5 Hz, $J_{1,2}$=8.1 Hz, H_D), 12.07 (s, 1H, Ar-OH); δ_C (75 MHz, CDCl$_3$) 10.99 and 13.50 ($-CH_3$), 38.35 and 42.66 ($-COCH_2CH_2N<$), 104.94, 118.46, 119.06, 130.01, 136.62, 139.29, 147.88, 162.31 (aromatic carbon atoms), 203.73 (>C=O).

3.1.2. 1-(2-Hydroxy-5-methylphenyl)-3-(pyrazol-1-yl)-1-propanone 2b. 1.79 g (78%) of yellowish crystals, mp 118–119 °C; (Found: C, 67.97; H, 5.91; N, 12.26. $C_{13}H_{14}N_2O_2$ requires C, 67.82; H, 6.08; N, 12.17); ν_{max} (KBr) 1648 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 2.23 (s, 3H, $-CH_3$), 3.57 (t, 2H, J=6.6 Hz, $-COCH_2-$), 4.54 (t, 2H, J=6.6 Hz, $-CH_2N<$), 6.18 (t, 1H, J=2.2 Hz, H_F), 6.83 (d, 1H, J=8.5 Hz, H_A), 7.23 (dd, 1H, $J_{1,3}$=1.7 Hz, $J_{1,2}$=8.5 Hz, H_B), 7.43 (d, 1H, J=2.2 Hz, H_G), 7.45 (d, 1H, J=2.2 Hz, H_E), 7.48 (d, 1H, J=1.7 Hz, H_D), 11.84 (s, 1H, Ar-OH); δ_C (75 MHz, CDCl$_3$) 20.34 ($-CH_3$), 38.31 and 46.13 ($-COCH_2CH_2N<$), 106.54, 118.12, 118.70, 128.16, 129.40, 129.98, 137.69, 139.60, 160.13 (aromatic carbon atoms), 202.98 (>C=O); *m/z* 160.9 (100%), 162.0 (100%), 230.1 (11%, M$^+$), 231.1 (1.7%, M+1); HRMS: found 230.10432. $C_{13}H_{14}N_2O_2$ requires 320.10556.

3.1.3. 1-(2-Hydroxy-5-methylphenyl)-3-(3,5-dimethylpyrazol-1-yl)-1-propanone 2c. 1.91 g (74%) of white plates, mp 133–134 °C; (Found: C, 69.89; H, 7.08; N, 10.63. $C_{15}H_{18}N_2O_2$ requires C, 69.76; H, 6.97; N, 10.85); ν_{max} (KBr) 1648 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.21, 2.26 and 2.27 (s, 3H, $-CH_3$), 3.58 (t, 2H, J=6.8 Hz, $-COCH_2-$), 4.37 (t, 2H, J=6.8 Hz, $-CH_2N<$), 5.75 (s, 1H, H_F), 6.87 (d, 1H, J=8.4 Hz, H_A), 7.27 (m, 1H, H_B), 7.48 (d, s, 1H, H_D), 11.91 (s, 1H, Ar-OH); δ_C (75 MHz, $CDCl_3$) 10.97, 13.49 and 20.41 ($-CH_3$), 38.36 and 42.76 ($-COCH_2CH_2N<$), 104.87, 118.11, 118.89, 128.18, 129.73, 137.67, 139.31, 147.85, 160.17 (aromatic carbon atoms), 203.63 (>C=O).

3.1.4. 3-(4-Bromo-3,5-dimethylpyrazol-1-yl)-1-(2-hydroxy-5-methylphenyl)-1-propanone 2d. 1.68 g (50%) of silky white needles, mp 130–131 °C; (Found: C, 53.63; H, 5.17; N, 8.14. $C_{15}H_{17}BrN_2O_2$ requires C, 53.41; H, 5.04; N, 8.30); ν_{max} (KBr) 1654 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.17, 2.26 and 2.27 (s, 3H, $-CH_3$), 3.55 (t, 2H, J=6.6 Hz, $-COCH_2-$), 4.38 (t, 2H, J=6.6 Hz, $-CH_2N<$), 6.85 (d, 1H, J=8.6 Hz, H_A), 7.24 (s, 1H, H_B), 7.43 (d, 1H, J=1.5 Hz, H_D), 11.80 (s, 1H, Ar-OH); δ_C (75 MHz, $CDCl_3$) 10.29, 12.31 and 20.45 ($-CH_3$), 38.01 and 43.83 ($-COCH_2CH_2N<$), 93.87, 118.22, 118.78, 128.25, 129.57, 137.55, 137.83, 146.44, 160.24 (aromatic carbon atoms), 203.10 (>C=O).

3.2. Oximation of the pyrazole-containing ketonic Mannich bases—general procedure

N-alkylated pyrazole **2** (10 mmol) was dissolved in 10% aqueous NaOH (1.6 g, 40 mmol) and to the stirred solution hydroxylamine hydrochloride (1.39 g, 20 mmol) in water (5 mL) was added in portions. The mixture was stirred at room temperature overnight and then 10% aqueous acetic acid was added dropwise to the cooled solution until the pH reached 6.5–7.0. The precipitate was filtered off and washed with water. Recrystallization from ethanol afforded pure oximes **3** in 69–83% yield.

3.2.1. 1-(2-Hydroxyphenyl)-3-(3,5-dimethylpyrazol-1-yl)-1-propanone oxime 3a. 2.15 g (83%) of pinkish crystals, mp 205–206 °C; (Found: C, 64.64; H, 6.74; N, 16.34. $C_{14}H_{17}N_3O_2$ requires C, 64.86; H, 6.56; N, 16.21); ν_{max} (KBr) 1638 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.05 and 2.11 (s, 3H, $-CH_3$), 3.16 (t, 2H, J=7.1 Hz, $-C(=NOH)CH_2-$), 4.15 (t, 2H, J=7.1 Hz, $-CH_2N<$), 5.69 (s, 1H, H_F), 6.78–6.87 (m, 2H, H_A and H_D), 7.17–7.26 (m, 2H, H_B and H_C), 11.29 (s, 1H, >N–OH), 11.79 (s, 1H, Ar-OH); δ_C (75 MHz, $CDCl_3$) 10.26 and 13.28 ($-CH_3$), 26.78 and 44.32 ($-C(=NOH)CH_2CH_2N<$), 104.65, 116.52, 118.89, 119.00, 127.84, 130.22, 138.37, 146.03, 157.77 (aromatic carbon atoms), 157.03 (>C=N–).

3.2.2. 1-(2-Hydroxy-5-methylphenyl)-3-(pyrazol-1-yl)-1-propanone oxime 3b. 1.81 g (74%) of white plates, mp 138–139 °C; (Found: C, 63.79; H, 6.28; N, 17.04. $C_{13}H_{15}N_3O_2$ requires C, 63.67; H, 6.12; N, 17.14); ν_{max} (KBr) 1630 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H, $-CH_3$), 3.37 (t, 2H, J=7.2 Hz, $-C(=NOH)CH_2-$), 4.53 (t, 2H, J=7.2 Hz, $-CH_2N<$), 6.23 (t, 1H, J=2.2 Hz, H_F), 6.78 (d, 1H, J=8.3 Hz, H_A), 6.82 (s, 1H, H_D), 6.97 (dd, 1H, $J_{1,3}$=1.6 Hz, $J_{1,2}$=8.3 Hz, H_B), 7.43 (dd, 1H, $J_{1,3}$=0.6 Hz, $J_{1,2}$=2.2 Hz, H_G), 7.51 (dd, 1H, $J_{1,3}$=0.6 Hz, $J_{1,2}$=2.2 Hz, H_E), 10.65 (bs, 1H, >N–OH), 11.18 (s, 1H, Ar-OH); δ_C (75 MHz, $CDCl_3$) 20.53 ($-CH_3$), 27.13 and 48.52 ($-C(=NOH)CH_2CH_2N<$), 106.02, 116.93, 117.46, 126.95, 127.93, 129.75, 131.17, 139.36, 155.41 (aromatic carbon atoms), 158.18 (>C=N–).

3.2.3. 1-(2-Hydroxy-5-methylphenyl)-3-(3,5-dimethylpyrazol-1-yl)-1-propanone oxime 3c. 1.88 g (69%) of white crystals, mp 193–194 °C; (Found: C, 65.77; H, 7.18; N, 15.47. $C_{15}H_{19}N_3O_2$ requires C, 65.93; H, 6.96; N, 15.38); ν_{max} (KBr) 1636 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.21, 2.22 and 2.31 (s, 3H, $-CH_3$), 3.29 (t, 2H, J=7.4 Hz, $-C(=NOH)CH_2-$), 4.35 (t, 2H, J=7.4 Hz, $-CH_2N<$), 5.80 (s, 1H, H_F), 6.79–6.97 (m, 3H, H_A, H_B and H_D), 11.49 (s, 1H, >N–OH), 12.51 (s, 1H, Ar-OH); δ_C (75 MHz, $CDCl_3$) 10.87, 13.14 and 20.66 ($-CH_3$), 26.57 and 44.81 ($-C(=NOH)CH_2CH_2N<$), 105.43, 116.98, 117.74, 126.74, 127.64, 130.85, 138.94, 147.53, 155.73 (aromatic carbon atoms), 157.52 (>C=N–).

3.2.4. 3-(4-Bromo-3,5-dimethylpyrazol-1-yl)-1-(2-hydroxy-5-methylphenyl)-1-propanone oxime 3d. 2.64 g (75%) of yellowish crystals, mp 217–219 °C; (Found: C, 51.36; H, 4.95; N, 12.11. $C_{15}H_{18}BrN_3O_2$ requires C, 51.13; H, 5.11; N, 11.93); ν_{max} (KBr) 1641 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 2.007, 2.01 and 2.17 (s, 3H, $-CH_3$), 3.16 (t, 2H, J=6.9 Hz, $-C(=NOH)CH_2-$), 4.25 (t, 2H, J=6.9 Hz, $-CH_2N<$), 6.74 (d, 1H, J=8.2 Hz, H_A), 6.83 (d, 1H, J=2 Hz, H_D), 7.00 (dd, 1H, $J_{1,3}$=2 Hz, $J_{1,2}$=8.2 Hz, H_B), 10.95 (bs, 1H, >N–OH), 11.71 (s, 1H, Ar-OH); δ_C (75 MHz, d_6-DMSO) 9.47, 11.87 and 20.05 ($-CH_3$), 26.38 and 45.92 ($-C(=NOH)CH_2CH_2N<$), 92.68, 116.11, 118.60, 127.14, 127.84, 130.60, 136.84, 144.47, 154.56 (aromatic carbon atoms), 157.63 (>C=N–).

3.3. Preparation of pyrazole-containing Mannich base oxime acetates—general procedure

Mannich base oxime **3** (10 mmol) was stirred with a three-fold amount of acetic anhydride at 40–50 °C until the solid dissolves. The mixture was then allowed to stay at room temperature for 2 h. In the case of compounds **4a** and **4d**, crystallization occurred on cooling in a freezer and they were filtered and washed with water. Oxime acetates **4b** and **4c** were separated by pouring the reaction mixture into ice-cold water and bringing the pH to 8 with Na_2CO_3. The initial oily product turned to a solid that was filtered off and washed with water. Recrystallization from small volumes of ethanol provided the pure oxime acetates **4** in 52–63% yield.

3.3.1. 1-(2-Hydroxyphenyl)-3-(3,5-dimethylpyrazol-1-yl)-1-propanone oxime acetate 4a. 1.35 g (45%) of white crystals, mp 104–106 °C; (Found: C, 63.53; H, 6.14; N, 14.12. $C_{16}H_{19}N_3O_3$ requires C, 63.78; H, 6.31; N, 13.95); ν_{max} (KBr) 1620, 1778 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 2.19 (s, 3H, $-COCH_3$), 2.03 and 2.17 (s, 3H, $-CH_3$), 3.39 (t, 2H, J=6.7 Hz, $-C(=NOCOCH_3)CH_2-$), 4.25 (t, 2H, J=6.7 Hz, $-CH_2N<$), 5.68 (s, 1H, H_F), 6.87 (dd, 1H, $J_{1,3}$=1.1 Hz, $J_{1,2}$=7.8 Hz, H_A), 7.01 (dd, 1H, $J_{1,3}$=1.1 Hz, $J_{1,2}$=7.8 Hz, H_B), 7.24–7.36 (m, 2H, H_B and H_C), 11.12 (s, 1H, Ar-OH); δ_C (75 MHz, $CDCl_3$)10.50 and 13.31 ($-CH_3$), 18.94 ($-OCOCH_3$), 27.90 and 45.28

(–C(═NOCOCH$_3$)CH_2CH_2N<), 105.26, 115.86, 118.18, 119.22, 128.18, 132.56, 138.88, 147.88, 158.82 (aromatic carbon atoms), 164.45 (>C═N–), 166.28 (–OCOCH$_3$).

3.3.2. 1-(2-Hydroxy-5-methylphenyl)-3-(pyrazol-1-yl)-1-propanone oxime acetate 4b. 1.81 g (63%) of white needles, mp 76–77 °C; (Found: C, 62.93; H, 6.14; N, 14.47. $C_{15}H_{17}N_3O_3$ requires C, 62.71; H, 5.92; N, 14.63); ν_{max} (KBr) 1618, 1762 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 2.13 (s, 3H, –CH$_3$), 2.21 (s, 3H, –OCOCH$_3$), 3.40 (t, 2H, J=6.5 Hz, –C(═NOCOCH$_3$)CH_2–), 4.40 (t, 2H, J=6.5 Hz, –CH$_2$N<), 6.11 (s, 1H, H$_F$), 6.88 (d, 1H, J=8.3 Hz, H$_A$), 6.94 (s, 1H, H$_D$), 7.08 (d, 1H, J=8.3 Hz, H$_B$), 7.19 (s, 1H, H$_G$), 7.49 (s, 1H, H$_E$), 10.87 (s, 1H, Ar-OH); δ_C (75 MHz, CDCl$_3$) 19.01 (–OCOCH$_3$), 20.40 (–CH$_3$), 28.10 and 49.10 (–C(═NOCOCH$_3$)CH_2CH_2N<), 105.81, 115.35, 117.97, 127.99, 128.32, 129.50, 133.46, 139.88, 156.42 (aromatic carbon atoms), 164.22 (>C═N–), 166.32 (–OCOCH$_3$).

3.3.3. 1-(2-Hydroxy-5-methylphenyl)-3-(3,5-dimethylpyrazol-1-yl)-1-propanone oxime acetate 4c. 1.86 g (59%) of white microcrystals, mp 114–116 °C; (Found: C, 64.96; H, 6.49; N, 13.51. $C_{17}H_{21}N_3O_3$ requires C, 64.76; H, 6.66; N, 13.33); ν_{max} (KBr) 1621, 1790 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 2.03, 2.07 and 2.15 (s, 3H, –CH$_3$), 2.20 (s, 3H, –OCOCH$_3$), 3.23 (t, 2H, J=6.7 Hz, –C(═NOCOCH$_3$)CH_2–), 4.16 (t, 2H, J=6.7 Hz, –CH$_2$N<), 5.70 (s, 1H, H$_F$), 6.82 (d, 1H, J=8.3 Hz, H$_A$), 7.05 (s, 1H, H$_D$), 7.12 (d, 1H, J=8.3 Hz, H$_B$), 10.43 (s, 1H, Ar-OH); δ_C (75 MHz, CDCl$_3$) 7.37, 10.42 and 17.13 (–CH$_3$), 16.39 (–OCOCH$_3$), 26.66 and 41.79 (–C(═NOCOCH$_3$)CH_2CH_2N<), 101.84, 113.67, 115.84, 124.89, 126.82, 129.63, 135.64, 143.20, 151.61 (aromatic carbon atoms), 162.22 (>C═N–), 164.64 (–OCOCH$_3$); m/z 109.1 (100%), 315.1 (5.5%, M$^+$), 316.1 (1.1%, M+1); HRMS: found 315.15758. $C_{17}H_{21}N_3O_3$ requires 315.1583.

3.3.4. 3-(4-Bromo-3,5-dimethylpyrazol-1-yl)-1-(2-hydroxy-5-methylphenyl)-1-propanone oxime acetate 4d. 2.05 g (52%) of white crystals, mp 128–129 °C; (Found: C, 51.57; H, 4.90; N, 10.83. $C_{17}H_{20}BrN_3O_3$ requires C, 51.77; H, 5.07; N, 10.66); ν_{max} (KBr) 1620, 1783 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 2.04, 2.19 and 2.24 (s, 3H, –CH$_3$), 2.20 (s, 3H, –OCOCH$_3$), 3.35 (t, 2H, J=6.5 Hz, –C(═NOCOCH$_3$)CH_2–), 4.31 (t, 2H, J=6.5 Hz, –CH$_2$N<), 6.918 (d, 1H, J=8 Hz, H$_A$), 6.923 (s, 1H, H$_D$), 7.13 (dd, 1H, $J_{1,3}$=2 Hz, $J_{1,2}$=8 Hz, H$_B$), 10.87 (s, 1H, Ar-OH); δ_C (75 MHz, CDCl$_3$) 10.01, 12.26 and 20.54 (–CH$_3$), 19.09 (–OCOCH$_3$), 27.79 and 46.85 (–C(═NOCOCH$_3$)CH_2CH_2N<), 94.36, 115.41, 118.11, 128.02, 128.41, 133.70, 137.39, 146.68, 156.52 (aromatic carbon atoms), 164.52 (>C═N–), 166.32 (–OCOCH$_3$).

3.4. Cyclization of pyrazole-containing Mannich base oxime acetates 4 to 1,2-benzisoxazoles 5—general procedure

Oxime acetate **4** (10 mmol) was dissolved in benzene (30 mL) and treated with finely grounded anhydrous K$_2$CO$_3$ (1.38 g, 10 mmol) under reflux for 3 h. The suspension was cooled to room temperature and the solid inorganic salts were filtered away. The organic phase was extracted with aqueous 10% NaOH, washed with water, dried on anhydrous Na$_2$SO$_4$. The removal of benzene under reduced pressure gave an oil that solidified on standing in a freezer. The solid substances were recrystallized from aqueous methanol, except for benzisoxazole **5d**, when little ethanol was employed as solvent.

3.4.1. 3-(2-(3,5-Dimethylpyrazol-1-yl)ethyl)-1,2-benzisoxazole 5a. 1.06 g (44%) of colorless needles, mp 40–41 °C; (Found: C, 69.94; H, 6.44; N, 17.24. $C_{14}H_{15}N_3O$ requires C, 69.71; H, 6.22; N, 17.42); ν_{max} (KBr) 1624 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 1.99 and 2.19 (s, 3H, –CH$_3$), 3.47 (t, 2H, J=7.1 Hz, ≡C–CH$_2$–), 4.40 (t, 2H, J=7.1 Hz, –CH$_2$N<), 5.66 (s, 1H, H$_F$), 7.17–7.24 (m, 1H), 7.37 (d, 1H, J=8 Hz), 7.45–7.49 (m, 2H); δ_C (75 MHz, CDCl$_3$) 10.71 and 13.40 (–CH$_3$), 26.32 and 46.25 (≡CCH_2CH_2N<), 105.04, 109.66, 121.11, 121.44, 123.28, 129.89, 139.14, 147.94, 156.0 (aromatic carbon atoms), 162.84 (>C═N–).

3.4.2. 5-Methyl-3-(2-(pyrazol-1-yl)ethyl)-1,2-benzisoxazole 5b. 1.18 g (52%) of white plates, mp 59–61 °C; (Found: C, 68.49; H, 5.89; N, 18.33. $C_{13}H_{13}N_3O$ requires C, 68.72; H, 5.72; N, 18.50); ν_{max} (KBr) 1627 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 2.41 (s, 3H, –CH$_3$), 3.54 (t, 2H, J=7 Hz, ≡C–CH$_2$–), 4.63 (t, 2H, J=7 Hz, –CH$_2$N<), 6.18 (t, 1H, J=2.1 Hz, H$_F$), 7.16 (d, 1H, J=1.7 Hz, H$_D$), 7.32 (d, 1H, J=2.1 Hz, H$_G$), 7.34 (dd, 1H, $J_{1,3}$=1.7 Hz, $J_{1,2}$=8.5 Hz, H$_B$), 7.42 (d, 1H, J=8.5 Hz, H$_A$), 7.56 (d, 1H, J=2.1 Hz, H$_E$); δ_C (75 MHz, CDCl$_3$) 20.99 (–CH$_3$), 26.66 and 49.83 (≡CCH_2CH_2N<), 105.54, 109.36, 120.23, 121.61, 129.89, 131.65, 133.20, 139.89, 155.42 (aromatic carbon atoms), 161.67 (>C═N–).

3.4.3. 5-Methyl-3-(2-(3,5-dimethylpyrazol-1-yl)ethyl)-1,2-benzisoxazole 5c. 1.55 g (61%) of silky white needles, mp 52–54 °C; (Found: C, 70.32; H, 6.54; N, 16.23. $C_{15}H_{17}N_3O$ requires C, 70.58; H, 6.66; N, 16.47); ν_{max} (KBr) 1622 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 1.98, 2.25 and 2.40 (s, 3H, –CH$_3$), 3.48 (t, 2H, J=7 Hz, ≡C–CH$_2$–), 4.41 (t, 2H, J=7 Hz, –CH$_2$N<), 5.59 (s, 1H, H$_F$), 7.09 (d, 1H, J=1.7 Hz, H$_D$), 7.32 (dd, 1H, $J_{1,3}$=1.7 Hz, $J_{1,2}$=8.5 Hz, H$_B$), 7.40 (d, 1H, J=8.5 Hz, H$_A$); δ_C (75 MHz, CDCl$_3$) 10.75, 13.47 and 20.98 (–CH$_3$), 26.42 and 46.52 (≡CCH_2CH_2N<), 105.08, 109.16, 120.49, 121.71, 131.54, 133.03, 139.35, 147.97, 155.83 (aromatic carbon atoms), 161.59 (>C═N–).

3.4.4. 3-(2-(4-Bromo-3,5-dimethylpyrazol-1-yl)ethyl)-5-methyl-1,2-benzisoxazole 5d. 1.44 g (43%) of white microcrystals, mp 77–78 °C; (Found: C, 54.06; H, 4.91; N, 12.29. $C_{15}H_{16}BrN_3O$ requires C, 53.89; H, 4.79; N, 12.57); ν_{max} (KBr) 1628 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 1.92, 2.20 and 2.36 (s, 3H, –CH$_3$), 3.43 (t, 2H, J=7 Hz, ≡C–CH$_2$–), 4.41 (t, 2H, J=7 Hz, –CH$_2$N<), 6.96 (d, 1H, J=1 Hz, H$_D$), 7.30 (d, 1H, J=1 Hz, H$_B$), 7.35 (s, 1H, H$_A$); δ_C (75 MHz, CDCl$_3$) 9.94, 12.20 and 20.94 (–CH$_3$), 26.17 and 47.64 (≡CCH_2CH_2N<), 94.03, 109.17, 120.08, 121.49, 131.58, 133.10, 137.50, 146.51, 155.40 (aromatic carbon atoms), 161.54 (>C═N–).

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