Mutual Influence of (Dimethylhydrazono)methyl Groups and α-Hydroxy Ketone Moieties in Hetaryl Analogues of Unsymmetric Benzoins

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Reactions between phenylglyoxal hydrate and the *N*,*N*-dimethylhydrazones of furfural and pyrrole-2-carbaldehyde run regioselectively at the 5-position of the heterocycle. The resulting hetaryl analogues of α-benzoins quantitatively isomerize to β-compounds, the (dimethylhydrazono)methyl group activating the hetaryl residue and thus affording faster isomerization than in their unfunctionalized counterparts. The (dimethylhydrazono)methyl group is easily convertible into the aldehyde or nitrile group and can also be involved in rehydrazonation.

Introduction

The chemical properties of benzoins and their hetaryl analogues studied so far are mainly associated with transformations of the α-hydroxy ketone moiety and the effect of the het(aryl) residues on its reactivity. The effect of the α-hydroxy ketone moiety on the reactivity of substituents in the het(aryl) residues of isomeric benzoins still remains to be investigated.

We have previously examined the synthesis[1] and isomerization in basic media[2] of α-benzoins. Our interest is in the study of hetaryl analogues of benzoins in which the het(aryl) residues contain functionalities modifiable over a wide range. A (dimethylhydrazono)methyl group appears to be very promising in this respect, as it is readily convertible into an aldehyde group.[3] At the same time, a (dimethylhydrazono)methyl group itself has been extensively applied in asymmetric synthesis[4] and represents an active nucleophilic substrate, like enamines,[5] in electrophilic substitution reactions.

Hydrazones of aldehydes derived from the most active π-excessive five-membered heterocycles (pyrrole, furan, thiophene), however, enter into trifluoroacetylation,[6] aminomethylation,[7] and reactions with electron-deficient unsaturated compounds[8] preferably at the 5-position of the ring. We attribute a certain degree of regioselectivity to the fact that the highly electron-donating (dialkylhydrazono)methyl group is efficiently conjugated with the ring, thus activating it to a sufficient degree to enable phosphorylation[9] and trinitrophenylation[10] (i.e., electrophilic substitutions with low-reactivity electrophiles).

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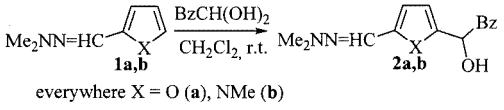
Results and Discussion

Hydroxyalkylation of *N*,*N*-dimethylhydrazones **1** with phenylglyoxal proceeds regioselectively at the 5-position of the heterocycle to give the corresponding hetaryl analogues of α-benzoins **2** (less stable than β-isomers) in high yields, as shown in Scheme 1. Because of the activation of the heterocyclic ring by the hydrazonomethyl group, the reaction can be performed smoothly with less active phenylglyoxal hydrate at room temp., which was found to be impossible for the unsubstituted heterocycles.[1] As a result of the higher electron-donor ability of pyrrole, the corresponding benzoin **2a** forms more rapidly.



Scheme 1

The α-benzoins **2** thus obtained quantitatively isomerize to the corresponding β-isomers **3** in the presence of a base (Et_3N), small amounts of benzoin oxidation products − the hetaryl benzil analogues **4** − forming in parallel through the action of atmospheric oxygen (Table 1, Entries 1 and 2; Scheme 2). Structural determination of the isomers was based on the previously revealed regularities[2] relating to the positions and shapes of ^1H NMR signals from the protons of the unsubstituted phenyl rings in the benzoins: these resonances of β-benzoins **3** are shifted upfield relative to those in the α-isomers **2**.

As demonstrated previously with derivatives of π-excessive heterocycles, an increased electron donor ability of a hetaryl residue favours α→β isomerization of unsymmetric

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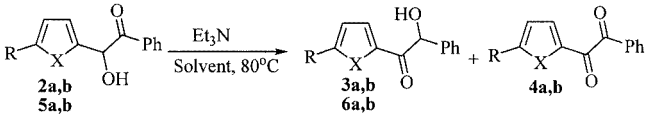
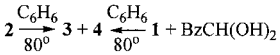
Table 1. Yields of β-benzoins **3** and benzils **4** under varied conditions

Entry	Reaction	Yield (%) Benzoins **3**	Benzils **4**
1	isomerization of α-benzoin in the presence of Et_3N	**a** (92)	**a** (5)
2		**b** (91)	**b** (5)
3	autoisomerization of α-benzoin	**a** (53)	**a** (33)
4		**b** (45)	**b** (38)
5	hydroxyalkylation of aldehyde *N*,*N*-dimethylhydrazone at 80 °C	**a** (22)	**a** (45)
6		**b** (10)	**b** (50)



Scheme 2



Scheme 3

benzoins.[2] Activation of the heterocyclic rings in α-benzoins **2** by the (dimethylhydrazono)methyl substituents reduces the isomerization time relative to those of their unfunctionalized counterparts **5**.

The activating influence of the (dimethylhydrazono)methyl group proves to be more pronounced for the furan ring than for the pyrrole, which is likely to be the result of the transmission effect.[11] Thus, furfural *N*,*N*-dimethylhydrazone **2a** has the same reactivity in the isomerization as nonactivated pyrrole **5b** (Table 2, Entries 1 and 3; Scheme 2).

Activation of the hetaryl residue allows the hydrazone isomerization to be efficiently conducted in a nonpolar solvent (benzene), whereas unfunctionalized α-benzoins **5** need a more polar environment (EtOH) to be isomerized.[2] In EtOH, α-benzoins **2** are completely oxidized by atmospheric oxygen to the corresponding benzil analogues **4**; at the same time, the more stable β-benzoins **3** are resistant to oxidation in boiling EtOH.

α-Benzoins **2** can isomerize without addition of base, merely on heating of their benzene solutions, but in lower yields even under argon (Table 1, Entries 3 and 4). Interestingly, hydroxyalkylation of aldehyde hydrazones performed at elevated temperature yielded mainly β-benzoins **3** and the corresponding oxidation products **4** (Table 1, Entries 5 and 6; Scheme 3).

The formation of β-benzoins **3** probably proceeds as a consequence of the basic nature of the terminal dimethylamino moiety contained in the *N*,*N*-dimethylhydrazono group. It is evident that the basic nature of the terminal dimethylamino group in α-benzoins, giving rise to the autocatalytic α→β isomerization (conducted separately or instantaneously after the electrophilic substitution in the initial *N*,*N*-dimethylhydrazones), is drastically weakened in β-benzoins, due to the conjugation between the dimethylamino and the carbonyl group. This effect is corroborated by the spectroscopic data: the IR absorption bands of the >C=O and >C=N groups of β-benzoins are shifted 40−70 cm^{-1} towards lower frequencies relative to their α-benzoin counterparts, which is indicative of the fact that the mutual conjugation of the two groups through the heterocyclic ring, as in β-benzoins, is much more efficient and thus loosens the double bonds significantly more than the noninteracting carbonyl−phenyl and azomethine−hetaryl conjugations, as in α-benzoins.

At the same time, the long-wavelength absorption bands in the UV spectra of the β-benzoins are shifted bathochromically in relation to those of the α-isomers, suggesting a more extended π-chromophore in the former case.

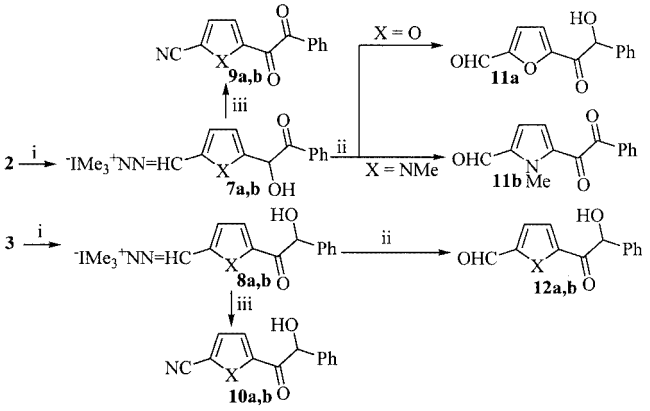
The involvement of electron density in the conjugation, and its consequent reduction on the terminal nitrogen atom of the *N*,*N*-dimethylhydrazono group, results in a reduced reactivity of β-benzoins **3** towards alkylating agents: the reaction with methyl iodide proceeds only on long heating, whereas α-benzoins **2** are readily alkylated even on heating for a short time. The salts obtained are easily convertible into nitriles or aldehydes if their aqueous solutions are heated slightly in a neutral or acid medium, respectively (Scheme 4). In most cases, α-benzoin salts **7** form benzil derivatives **9** and **11b** (since α-benzoins themselves have a pronounced tendency towards oxidation), whereas β-

Table 2. Isomerization time for α-benzoins **2** and **5** in the presence of Et_3N

Entry	Starting compound	Product	X	R	Solvent	Time [h][a]	Yields (%)
1	**2a**	**3a**	O	$CH=NNMe_2$	benzene	1.5	92
2	**2b**	**3b**	NMe	$CH=NNMe_2$	benzene	1.5	91
3[2]	**5b**	**6b**	NMe	H	EtOH	1.5	51
4[2]	**5a**	**6a**	O	Me	EtOH	9	90

[a] The time for full conversion of starting compound is monitored by TLC (every 30 min).

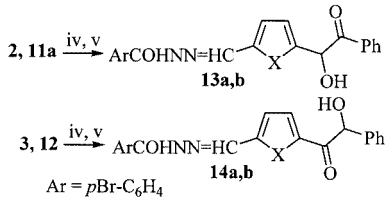
benzoin salts **8** smoothly furnish the α-hydroxy ketone derivative **10** and **12**.



Scheme 4. Reagents and conditions: i: MeI, MeCN, 82°C; ii: HCl (1:10), 50°C; iii: H_2O, 50°C

The dicarbonyl compounds obtained, **11a** and **12**, have two reaction centres capable of reacting with N-nucleophiles: namely, the aldehyde group and the α-hydroxy ketone moiety. The latter reacts with N-nucleophiles, so the oxygen atom of the carbonyl group or the hydroxy group can be substituted to afford α-hydroxy imines[12] or α-amino ketones, respectively. This twofold course of the reaction is associated with the isomerization of the intermediately forming α-hydroxy enamines.[13]

Compounds **11a** and **12** always react regioselectively at the more active aldehyde carbonyl group with *para*-bromobenzohydrazide in boiling EtOH. The reactivity of the carbonyl group contained in the α-hydroxy ketone moiety is lowered to such a degree that it is not involved in the reaction between hydrazones **2** or **3** and a hydrazide in a neutral or acid medium; as a consequence, only rehydrazonation products are obtained (Scheme 5).



Scheme 5. Reagents and conditions: iv: $H_2NNHCOAr$, EtOH, 78°C; v: $H_2NNHCOAr$, H^+, EtOH, 78°C (only for benzoins **2** and **3**)

As can be seen from Table 3, the reactivity of β-benzoins, aldehydes or hydrazones towards *para*-bromobenzohydrazide is higher than that of α-benzoins and does not depend on the reaction conditions. This effect is attributable to the acceptor influence exerted by the carbonyl group of the α-hydroxy ketone moiety, which in β-isomers is transmitted through the heterocyclic ring. It is noteworthy that furan derivatives are more reactive than their analogues containing the pyrrole ring both for α- and β-isomers, which is due to the lower electron-donor capability of the furan nucleus.

Conclusion

Reactions between phenylglyoxal hydrate and the *N*,*N*-dimethylhydrazones of furfural and pyrrole-2-carbaldehyde run regioselectively at the 5-positions of the heterocycles. The (dimethylhydrazono)methyl group activates the heterocyclic ring, thus reducing the α→β isomerization time for substituted benzoins in relation to those of their unfunctionalized counterparts. In β-benzoins, the acceptor carbonyl group of the α-hydroxy ketone moiety is conjugated with the donor (dimethylhydrazono)methyl group, which is therefore characterized by reduced electronic density on the terminal nitrogen atom and enhanced reactivity of the carbon atom towards nucleophiles.

Table 3. Formation times and yields of hydrazones **23**−**26** under varied conditions

Entry	Starting compound	Product	Method (Scheme 5)	Time [h]	Yield (%)
1	**11a**	**13a**	i	1.5	70
2	**12a**	**14a**	i	0.75	75
3	**12b**	**14b**	i	2	62
4	**2a**	**13a**	i	2	63
5	**2a**	**13a**	ii	1.5	89
6	**2b**	**13b**	i	5	55
7	**2b**	**13b**	ii	3	62
8	**3a**	**14a**	i	0.75	80
9	**3a**	**14a**	ii	0.75	99
10	**3b**	**14b**	i	2	91
11	**3b**	**14b**	ii	2	85

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded in [D_6]DMSO with a Varian VXR-300 instrument at 300 MHz with TMS as internal standard. IR spectra were measured with a UR-20 spectrometer in KBr tablets. UV spectra were scanned in 95% EtOH with a Specord M-40 apparatus with 1-cm cuvettes. MS spectra were run at an electronic ionization at 70 eV with an MX-1321 spectrometer. The course of the reaction and product purities were monitored by TLC on Silufol-UV-254 plates in a benzene/acetone (5:1) system.

General Procedure for Preparation of α-Benzoins 2: A solution of the aldehyde *N*,*N*-dimethylhydrazone (5.00 mmol) in CH_2Cl_2 (5 mL) was poured into a solution of phenylglyoxal hydrate (0.76 g, 5.00 mmol) in CH_2Cl_2 (5 mL). The resulting solution was allowed to stand at room temp. for 3 d and was then concentrated under reduced pressure. The residue crystallized.

2-{5-[(Dimethylhydrazono)methyl]furan-2-yl}-2-hydroxy-1-phenylethanone (2a): Yield 86%. Yellow powder (hexane). M.p. 136.5−137 °C. IR: $\tilde{\nu}$ = 3430, 3140, 3000, 2940, 2875, 2805, 1690, 1600, 1575, 1290, 1230 cm^{-1}. UV: λ (lg ε) = 244.9 (3.94), 308.3 (4.23) nm. ^{1}H NMR: δ = 2.87 (s, 6 H), 5.00 (d, J = 6.5, 1 H), 6.19 (d, J = 6.5 Hz, 1 H), 6.32 (d, J = 3.4 Hz Hz, 1 H), 6.45 (d, J = 3.4 Hz, 1 H), 7.05 (s,), 7.49 (t, J = 7.8 Hz, 2 H), 7.62 (d, J = 7.8 Hz Hz, 1 H), 8.05 (d, J = 7.8, 2 H) ppm. MS: *m*/*z* (%) = 272 (15) [M$^+$], 67 (100), 124 (10), 105 (14), 77 (13), 44 (32). $C_{15}H_{16}N_2O_3$ (272.12): calcd. C 66.16, H 5.92; found C 66.32, 5.81.

2-{5-[(Dimethylhydrazono)methyl]-1-methyl-1*H*-pyrrol-2-yl}-2-hydroxy-1-phenylethanone (2b): Yield 88%. Yellow powder (hexane). M.p. 136−137 °C. IR: $\tilde{\nu}$ = 3175, 2970, 2868, 1682, 1597, 1261, 1234, 1200, 1155, 1070, 1042, 1013, 990, 952, 920 cm^{-1}. UV: λ (lg ε) = 243.9 (4.06), 305.3 (4.20) nm. ^{1}H NMR: δ = 3.30 (s, 3 H), 3.81 (s, 1 H), 5.63 (d, J = 7.6 Hz, 1 H), 5.70 (d, J = 4.0 Hz, 1 H), 6.03 (d, J = 4.0 Hz, 1 H), 6.17 (d, J = 7.6 Hz, 1 H), 7.25 (s, 1 H), 7.43 (t, J = 8.6 Hz, 2 H), 7.57 (d, J = 8.6 Hz, 1 H), 7.90 (d, J = 8.6 Hz, 2 H) ppm. MS: *m*/*z* (%) = 285 (15) [M$^+$], 180 (100), 135 (9), 77 (8), 44 (10). $C_{16}H_{19}N_3O_2$ (285.15): calcd. C 67.35, H 6.71; found C 67.36, H 6.71.

Preparation of β-Benzoins 3 (Table 1). A) Isomerization of α-Benzoins 2: A solution of the α-benzoin (1.50 mmol) in benzene (6 mL), with or without added Et_3N (0.25 mL, 1.80 mmol), was heated to reflux for 1.5 h. The β-benzoin precipitating on cooling was filtered off and recrystallized. The filtrate was concentrated under reduced pressure, and the residue was treated with CCl_4 (5 mL). On concentration of the solution under reduced pressure, heterocyclic benzil analogues were obtained. **B) Treatment of Phenylglyoxal Hydrate with *N*,*N*-Dimethylhydrazones 1:** A solution of phenylglyoxal hydrate (0.76 g, 5.00 mmol) and the aldehyde *N*,*N*-dimethylhydrazone (5.00 mmol) in benzene (8 mL) was heated to reflux for 1.5 h. The further workup was performed as in method A.

1-{5-[(Dimethylhydrazono)methyl]furan-2-yl}-2-hydroxy-2-phenylethanone (3a): Yellow powder (benzene). M.p. 160−162 °C. IR: $\tilde{\nu}$ = 3425, 3115, 2955, 2880, 1650, 1560, 1510, 1350, 1275 cm^{-1}. UV: λ (lg ε) = 293.8 (3.88), 375.4 (4.14) nm. ^{1}H NMR: δ = 2.99 (s, 6 H), 5.70 (d, J = 5.1, 1 H), .06 d, J = 5.1 Hz, 1 H), 6.54 (d, J = 3.6 Hz, 1 H), 7.09 (s, 1 H), 7.28 (d, J = 7.5 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.65 (d, J = 3.6 Hz, 1 H) ppm. MS: *m*/*z* (%) = 272 (29) [M$^+$], 165 (100), 109 (13), 77 (12), 44 (10). $C_{15}H_{16}N_2O_3$ (272.12): calcd. C 66.16, H, 5.92; found C 66.15, H 5.89.

1-{5-[(Dimethylhydrazono)methyl]-1-methyl-1*H*-pyrrol-2-yl}-2-hydroxy-2-phenylethanone (3b): Yellow powder (hexane). M.p. 140−141 °C. IR: $\tilde{\nu}$ = 3390, 3136, 2940, 2885, 2800, 1616, 1568, 1494, 1446, 1400, 1360, 1340, 1297, 1207, 1180, 1056, 1000, 931, 909 cm^{-1}. UV: λ (lg ε) = 254.1 (3.74), 367.1 (4.42) nm. ^{1}H NMR: δ = 3.33 (s, 6 H), 3.69 (s, 3 H), 5.66 (d, J = 6.9, 1 H), 5.77 (d, J = 6.9 Hz, 1 H), 6.31 (d, J = 4.5 Hz, 1 H), 7.17 (s, 1 H), 7.23 (d, J = 4.5 Hz, 1 H), 7.30 (d, J = 9.0 Hz, 1 H), 7.37 (t, J = 9.0 Hz, 2 H), 7.46 (d, J = 9.0 Hz, 2 H) ppm. MS: *m*/*z* (%) = 285 (25) [M$^+$], 178 (100), 109 (20). $C_{16}H_{19}N_3O_2$ (285.15): calcd. C 67.35; H 6.71; found C 67.28, H 6.59.

1-{5-[(Dimethylhydrazono)methyl]furan-2-yl}-2-phenylethane-1,2-dione (4a): Red, viscous liquid. ^{1}H NMR: δ = 3.04 (s, 6 H), 6.67 (d, J = 3.9 Hz, 1 H), 7.14 (s, 1 H), 7.53 (d, J = 3.9 Hz, 1 H), 7.61 (t, J = 7.5 Hz, 2 H), 7.68 (d, J = 7.5 Hz, 1 H), 7.94 (d, J = 7.5 Hz, 2 H) ppm. $C_{15}H_{14}N_2O_3$ (270.10): calcd. C 66.66, H 5.22; found C 67.01, H 5.51.

1-{5-[(Dimethylhydrazono)methyl]-1-methyl-1*H*-pyrrol-2-yl}-2-phenylethane-1,2-dione (4b): Red powder (hexane). M.p. 82−83 °C. ^{1}H NMR: δ = 3.32 (s, 6 H), 4.15 (s, 3 H), 6.39 (d, J = 4.9 Hz, 1 H), 6.74 (d, J = 4.9 Hz, 1 H), 7.22 (s, 1 H), 7.59 (t, J = 8.1 Hz, 2 H), 7.74 (d, J = 8.1 Hz, 1 H), 7.93 (d, J = 8.1 Hz, 2 H) ppm. $C_{16}H_{17}N_3O_2$ (283.13): calcd. C 67.83, H 6.05; found C 67.82, H 6.04.

General Procedure for Alkylation of Benzoins 2 and 3: A solution of the benzoin (0.82 g, 3.00 mmol) in a mixture of MeCN (5 mL) and MeI (3 mL) was heated to reflux for 1 h for α-isomers **7** (precipitated during boiling) or 24 h for β-isomers **8**. On cooling, the resulting precipitate was filtered off or the solution was concentrated under reduced pressure, according to whether α- or β-isomers were involved.

***N*′-[5-(1-Hydroxy-2-oxo-2-phenylethyl)furan-2-ylmethylene]-*N*,*N*,*N*-trimethylhydrazinium Iodide (7a):** Yield 100%. White powder. M.p. 160−162 °C. ^{1}H NMR: δ = 2.08 (s, 9 H), 6.31 (d, J = 6.3 Hz, 1 H), 6.47 (d, J = 6.3 Hz, 1 H), 6.82 (d, J = 4.0 Hz, 1 H), 7.33 (d, J = 4.0 Hz, 1 H), 7.52 (t, J = 8.1 Hz, 2 H), 7.65 (d, J = 8.1 Hz, 1 H), 8.03 (d, J = 8.1 Hz, 2 H), 8.89 (s, 1 H) ppm. $C_{16}H_{19}IN_2O_3$ (412.03): calcd. C 46.39, H 4.62; found C 46.38, H 4.63.

***N*′-[5-(1-Hydroxy-2-oxo-2-phenylethyl)-1-methyl-1*H*-pyrrol-2-ylmethylene]-*N*,*N*,*N*-trimethylhydrazinium Iodide (7b):** Yield 100%. White powder. M.p. 199−201 °C. ^{1}H NMR: δ = 3.46 (s, 9 H), 3.92 (s, 3 H), 6.09 (d, J = 4.2 Hz, 1 H), 6.14 (d, J = 6.9 Hz, 1 H), 6.35 (d, J = 6.9, 1 H), 6.77 d, J = 4.2 Hz, 1 H), 7.49 (t, J = 8.1 Hz, 2 H), 7.62 (d, J = 8.1 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 2 H), 8.85 (s, 1 H) ppm. $C_{17}H_{22}IN_3O_2$ (425.06): calcd. C 47.79, H 5.19; found C 47.70, H 5.16.

***N*′-{5-[(Hydroxy)(phenyl)acetyl]furan-2-ylmethylene}-*N*,*N*,*N*-trimethylhydrazinium Iodide (8a):** Yield 86%. Pale brown powder. M.p. 117−118 °C. ^{1}H NMR: δ = 3.33 (s, 9 H), 5.82 (d, J = 5.7, 1 H), 6.37 (d, J = 5.7 Hz, 1 H), 7.26 (d, J = 4.2 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 1 H), 7.46 (t, J = 8.1 Hz, 2 H), 7.47 (d, J = 8.1 Hz, 2 H), 7.81 (d, J = 4.2 Hz, 1 H), 9.05 (s, 1 H) ppm. $C_{16}H_{19}IN_2O_3$ (412.03): calcd. C 46.39, H 4.62; found C 46.29, H 4.60.

***N*′-{5-[(Hydroxy)(phenyl)acetyl]-1-methyl-1*H*-pyrrol-2-ylmethylene}-*N*,*N*,*N*-trimethylhydrazinium Iodide (8b):** Yield 87%. Pale brown powder. M.p. 115−117 °C. ^{1}H NMR: δ = 3.57 (s, 9 H), 4.04 (s, 3 H), 5.86 (d, J = 5.7 Hz, 1 H), 5.88 (d, J = 5.7 Hz, 1 H), 6.89 (d, J = 4.5 Hz, 1 H), 7.26 (d, J = 6.9 Hz, 1 H), 7.33 (t, J = 6.9 Hz, 2 H), 7.41 (d, J = 4.5 Hz, 1 H), 7.44 (d, J = 6.9 Hz,

2 H), 8.98 (s, 1 H) ppm. $C_{17}H_{22}IN_3O_2$ (425.06): calcd. C 47.79, H 5.19; found C, 47.65, H 5.08.

General Procedure for Preparation of Nitriles 9 and 10: A solution of the salt **7** or **8** (0.80 mmol) in H_2O (15 mL) was heated in a water bath at 50 °C (bath temperature) for 1 h. The precipitate resulting on cooling was filtered off and was then either chromatographed on a column (alumina, CH_2Cl_2) in the case of α-isomers or recrystallized in the case of β-isomers.

5-[Oxo(phenyl)acetyl]furan-2-carbonitrile (9a): Yield 82%. Yellow powder (hexane). M.p. 107−108 °C. IR: $\tilde{\nu}$ = 3150, 3129, 2248, 1663, 1594, 1491, 1445, 1366, 1315, 1237, 1205, 1180, 1041 cm^{-1}. ^1H NMR: δ = 7.63 (t, J = 8.1 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 4.2 Hz, 1 H), 7.86 (d, J = 4.2 Hz, 1 H), 8.01 (d, J = 8.1 Hz, 2 H) ppm. $C_{13}H_7NO_3$ (225.04): calcd. C 69.33, H 3.13; found C 69.27, H 3.10.

1-Methyl-5-[(oxo)(phenyl)acetyl]-1*H*-pyrrole-2-carbonitrile (9b): Yield 75%. Pale brown powder (hexane). M.p. 105−107 °C. ^1H NMR: δ = 4.13 (s, 3 H), 6.98 (d, J = 5.1 Hz, 1 H), 7.09 (d, J = 5.1, 1 H), 7.62 (t, J = 8.7 Hz, 2 H), 7.79 (d, J = 8.7 Hz, 1 H), 7.98 (d, J = 8.7, 2 H) ppm. $C_{14}H_{10}N_2O_2$ (238.07): calcd. C 70.58, H 4.23; found C 70.49, H 4.22.

5-[(Hydroxy)(phenyl)acetyl]furan-2-carbonitrile (10a): Yield 83%. Yellow powder (hexane). M.p. 140−141 °C. IR: $\tilde{\nu}$ = 3449, 3415, 3151, 3113, 2252, 1674, 1493, 1452, 1395, 1269, 1228, 1210, 1187, 1045, 1024, 972 cm^{-1}. ^1H NMR: δ = 5.90 (d, J = 6.0 Hz, 1 H), 6.40 (d, J = 6.0 Hz, 1 H), 7.30 (d, J = 8.1 Hz, 1 H), 7.36 (t, J = 8.1 Hz, 2 H), 7.46 (d, J = 8.1 Hz, 2 H), 7.74 (d, J = 4.2 Hz, 1 H), 7.78 (d, J = 4.2 Hz, 1 H) ppm. $C_{13}H_9NO_3$ (227.06): calcd. C 68.72, H 3.99; found C 68.70, H 3.95.

5-[(Hydroxy)(phenyl)acetyl]-1-methyl-1*H*-pyrrole-2-carbonitrile (10b): Yield 74%. Pale brown powder (hexane). M.p. 112−114 °C. IR: $\tilde{\nu}$ = 3390, 3360, 3120, 2919, 2895, 2238, 1682, 1475, 1444, 1382, 1334, 1273, 1236, 1210, 1189, 1103, 1050, 1004, 919 cm^{-1}. ^1H NMR: δ = 3.91 (s, 3 H), 5.84 (d, J = 5.1 Hz, 1 H), 6.07 (d, J = 5.1 Hz, 1 H), 6.99 (d, J = 5.1 Hz, 1 H), 7.25 (d, J = 8.7 Hz, 1 H), 7.33 (t, J = 8.7 Hz, 2 H), 7.37 (d, J = 5.1 Hz, 1 H), 7.45 (d, J = 8.7 Hz, 2 H) ppm. $C_{14}H_{12}N_2O_2$ (240.09): calcd. C 69.99, H 5.03; found C 69.95, H 4.98.

General Procedure for the Preparation of Aldehydes 11 and 12: A solution of the salt **7** or **8** (0.80 mmol) in dilute (1:10) hydrochloric acid (15 mL) was heated in a water bath at 50 °C (bath temperature) for 1 h. The precipitate resulting on cooling was filtered off and recrystallized.

5-(1-Hydroxy-2-oxo-2-phenylethyl)furan-2-carbaldehyde (11a): Yield 76%. Straw-coloured needles (hexane). M.p. 87−88 °C. IR: $\tilde{\nu}$ = 3391, 3378, 3127, 2948, 2820, 1675, 1591, 1516, 1456, 1393, 1270, 1222, 1200, 1175, 1098, 1025, 980, 959 cm^{-1}. ^1H NMR: δ = 6.31 (d, J = 6.3 Hz, 1 H), 6.51 (d, J = 6.3 Hz, 1 H), 6.76 (d, J = 3.9 Hz, 1 H), 7.49 (d, J = 3.9 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 2 H), 7.64 (d, J = 7.8 Hz, 1 H), 8.02 (d, J = 7.8 Hz, 2 H), 9.51 (s, 1 H) ppm. $C_{13}H_{10}O_4$ (230.06): calcd. C 67.82, H 4.38; found C 67.80, H 4.37.

1-Methyl-5-[(oxo)(phenyl)acetyl]-1*H*-pyrrole-2-carbaldehyde (11b): Yield 61%. Orange powder (hexane). M.p. 74−75 °C. ^1H NMR: δ = 4.32 (s, 3 H), 6.92 (d, J = 4.5 Hz, 1 H), 7.08 (d, J = 4.5 Hz, 1 H), 7.62 (t, J = 7.5 Hz, 2 H), 7.79 (d, J = 7.5 Hz, 1 H), 7.97 (d, J = 7.5., 2 H), 9.95 (s, 1 H) ppm. $C_{14}H_{11}NO_3$ (241.07): calcd. C 69.70, H 4.60; found C 6.68, H 4.55.

5-[(Hydroxy)(phenyl)acetyl]furan-2-carbaldehyde (12a): Yield 83%. Straw-coloured needles (hexane). M.p. 165−166 °C. IR: $\tilde{\nu}$ = 3463, 3428, 3152, 3110, 2820, 1680, 1650, 1252, 1214, 1183, 1060, 1025, 970 cm^{-1}. ^1H NMR: δ = 5.82 (d, J = 4.8 Hz, 1 H), 6.34 (d, J = 4.8 Hz, 1 H), 7.29 (d, J = 7.5 Hz, 1 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.58 (d, J = 4.2 Hz, 1 H), 7.74 (d, J = 4.2 Hz, 1 H), 9.75 (s, 1 H) ppm. $C_{13}H_{10}O_4$ (230.06): calcd. C 67.82, H 4.38; found C 67.79, H 4.38.

5-[(Hydroxy)(phenyl)acetyl]-1-methyl-1*H*-pyrrole-2-carbaldehyde (12b): Yield 89%. Pale brown powder (hexane). M.p. 108−109 °C. IR: $\tilde{\nu}$ = 3500, 3130, 2965, 2830, 2800, 1679, 1655, 1488, 1452, 1413, 1377, 1336, 1280, 1235, 1210, 1174, 1097, 1060, 1007 cm^{-1}. ^1H NMR: δ = 4.08 (s, 3 H), 5.82 (d, J = 4.9 Hz, 1 H), 5.88 (d, J = 4.9 Hz, 1 H), 7.01 (d, J = 4.8 Hz, 1 H), 7.25 (d, J = 9.00 Hz, 1 H), 7.35 (t, J = 9.0 Hz, 2 H), 7.36 (d, J = 4.8 Hz, 1 H), 7.45 (d, J = 9.0 Hz, 2 H), 9.77 (s, 1 H) ppm. $C_{14}H_{13}NO_3$ (243.09): calcd. C 69.12, H 5.39; found C 69.07, H 5.31.

General Procedure for the Preparation of Hydrazones 13 and 14 (Table 3): A solution of the corresponding compound (see Scheme 5) (0.90 mmol) and *p*-bromobenzohydrazide (0.19 g, 0.90 mmol) in EtOH (8 mL), with or without added concentrated sulfuric acid (0.05 mL), was boiled for an appropriate time indicated in Table 3. The precipitate resulting on cooling was filtered off and recrystallized from EtOH.

4-Bromo-*N*′-{[5-(1-hydroxy-2-oxo-2-phenylethyl)-2-furyl]methylene}benzohydrazide (13a): Pale brown powder. M.p. 165−166 °C. ^1H NMR: δ = 6.25 (d, J = 6.3 Hz, 1 H), 6.29 (d, J = 6.3 Hz, 1 H), 6.59 (d, J = 3.0 Hz, 1 H), 6.89 (d, J = 3.0 Hz, 1 H), 7.51 (t, J = 7.2 Hz, 2 H), 7.63 (d, J = 7.2 Hz, 1 H), 7.75 (d, J = 8.5 Hz, 2 H), 7.84 (d, J = 8.5 Hz, 2 H), 8.02 (d, J = 7.2 Hz, 2 H), 8.23 (s, 1 H), 11.84 (s, 1 H) ppm. $C_{20}H_{15}BrN_2O_4$ (426.02): calcd. C 56.22, H 3.54; found C 56.20, H 3.54.

4-Bromo-*N*′-{[5-(1-hydroxy-2-oxo-2-phenylethyl)-1-methyl-1*H*-pyrrol-2-yl]methylene}benzohydrazide (13b): Brown powder. M.p. 164−165 °C. ^1H NMR: δ = 3.01 (s, 3 H), 5.65 (d, J = 3.5 Hz, 1 H), 5.75 (d, J = 5.3 Hz, 1 H), 6.13 (d, J = 5.3 Hz, 1 H), 6.80 (d, J = 3.5 Hz, 1 H), 7.49 (t, J = 7.7 Hz, 2 H), 7.65 (d, J = 7.7 Hz, 1 H), 7.77 (d, J = 8.1 Hz, 2 H), 7.91 (d, J = 8.1 Hz, 2 H), 8.00 (d, J = 7.7 Hz, 2 H), 8.37 (s, 1 H), 11.77 (s, 1 H) ppm. $C_{21}H_{18}BrN_3O_3$ (429.05): calcd. C 57.29, H 4.12; found C 57.19, H 4.08.

4-Bromo-*N*′-({5-[hydroxy(phenyl)acetyl]-2-furyl}methylene)-benzohydrazide (14a): Orange powder. M.p. 176−177 °C. ^1H NMR: δ = 5.78 (d, J = 4.6 Hz, 1 H), 6.25 (d, J = 4.6 Hz, 1 H), 7.10 (d, J = 3.0 Hz, 1 H), 7.25 (d, J = 3.0 Hz, 1 H), 7.30 (t, J = 7.2 Hz, 2 H), 7.35 (d, J = 7.2 Hz, 1 H), 7.49 (d, J = 7.2 Hz, 2 H), 7.76 (d, J = 7.6 Hz, 2 H), 7.86 (d, J = 7.6 Hz, 2 H), 8.36 (s, 1 H), 12.13 (s, 1 H) ppm. $C_{20}H_{15}BrN_2O_4$ (426.02): calcd. C 56.22, H 3.54; found C 56.19, H 3.50.

4-Bromo-*N*′-({5-[hydroxy(phenyl)acetyl]-1-methyl-1*H*-pyrrol-2-yl}-methylene)benzohydrazide (14b): Orange powder. M.p. 178−179 °C. ^1H NMR: δ = 3.34 (s, 3 H), 5.83 (d, J = 5.7 Hz, 1 H), 5.87 (d, J = 5.7 Hz, 1 H), 6.64 (d, J = 3.3 Hz, 1 H), 7.25 (d, J = 7.5 Hz, 1 H), 7.32 (t, J = 7.5 Hz, 2 H), 7.40 (d, J = 3.3 Hz, 1 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.75 (d, J = 7.8 Hz, 2 H), 7.85 (d, J = 7.8 Hz, 2 H), 8.49 (s, 1 H), 11.93 (s, 1 H) ppm. $C_{21}H_{18}BrN_3O_3$ (439.05): calcd. C 57.29, H 4.12; found C 57.15, H 4.10.

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