A Novel Diastereoselective Synthesis of 6-Aryl-5-hydroxy-2,3-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-ones

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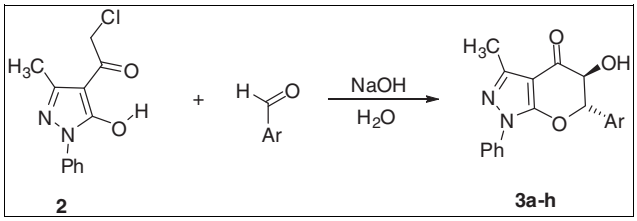

A novel one-pot diastereoselective synthesis of *trans*-6-aryl-5-hydroxy-2,3-dihydro[2,3-*c*]pyrazol-4(1*H*)-ones **3a–h** is described via the Darzens condensation reaction of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**2**) with different aromatic aldehydes in aqueous basic medium. The structures of the compounds prepared were determined by analytical and spectral analyses.

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INTRODUCTION

The 6-arylpyrano[2,3-*c*]pyrazol-4(1*H*)-one moiety is an attractive heterocyclic system as it represent as an isosteric system of flavone, 2-phenyl-4*H*-chromen-4-one, the latter being the parent system for a large variety of natural products that play important roles in numerous biological processes [1–5]. Moreover, pyrano[2,3-*c*]pyrazoles are of great synthetic interest because of their wide variety of medicinal applications or as the key intermediate for the synthesis of drugs. Especially, some 6-substituted pyrano [2,3-*c*]pyrazoles have been reported to have potent antimicrobial [6], molluscicidal [7,8], and bovine brain adenosine A_1 and A_{2A} receptor binding activities [9].

A literature survey reveals that there are four synthetic routes for pyrano[2,3-*c*]pyrazol-4(1*H*)-ones. These synthetic strategies include (1) *C*-acylation of 2-pyrazolin-5-ones with α,β-unsaturated acyl chlorides followed by ring closure using sulfuric acid [5,10], (2) acid-catalyzed cyclization of 1,3-diketones obtained either from 2-pyrazolin-5-ones by acetylation and subsequent Claisen condensation [3,11] (or treatment with lithium bis(trimethylsilyl)amide/benzoyl chloride [9,12]) or via ring transformation of phenylhydrazone derived from 3-acetyl-4-hydroxy-6-phenyl-2*H*-pyran-2-one [9,13], (3) reaction of 4-cinnamoyl-5-hydroxypyrazoles with bromine followed by treatment of the resulting bromo compounds with DBU [9,14], and (4) the base-catalyzed cyclization of 2-pyrazolin-5-ones with phenylpropynoyl chloride [2].

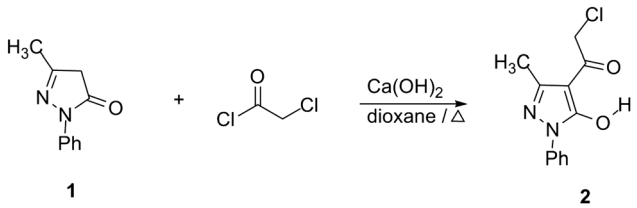
In the light of these findings and in continuation of our interest in the synthesis of heterocycles containing a pyrazole moiety [15–17], we felt that there is a real need for the synthesis of novel 6-aryl-5-hydroxy-5,6-dihydropyrano [2,3-*c*]pyrazol-4(1*H*)-ones. Meanwhile, considering the green process, it is of importance to perform this reaction in water because water is environmentally benign, and potential advantages of using water as a solvent are its low cost, safety, and ease of use. Therefore, herein, we would like to report the diastereoselective synthesis of a series of 6-aryl-5-hydroxy-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-ones via the Darzens condensation reaction of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**2**) with various aromatic aldehydes in aqueous basic medium.

RESULTS AND DISCUSSION

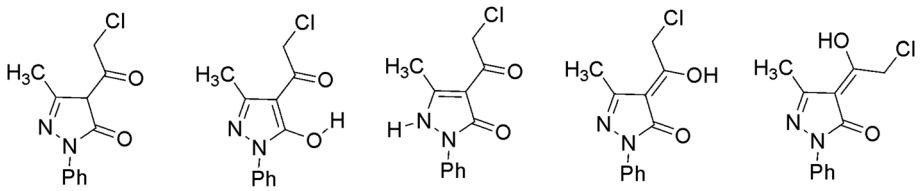
The starting material 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**2**) used in this study was prepared by refluxing 1-phenyl-3-methyl-2-pyrazolin-5-one (**1**) with chloroacetyl chloride in dioxane containing anhydrous calcium hydroxide as a basic catalyst following a procedure reported earlier by Jensen *et al*. [18] (Scheme 1).

Although compound **2** can exist in five prototropic tautomerism (**2a–2e**) (Fig. 1), the infrared and NMR spectra support the tautomeric form **2b**. The IR spectrum displayed a strong hydrogen-bonded carbonyl absorption at 1640 cm^{-1} and a weak broad hydroxyl absorption band at 3272 cm^{-1}. In the ^1H NMR spectrum, one proton singlet in a low magnetic field at δ 12.85 ppm was observed for **2b** that could be ascribed to hydroxyl proton. The ^{13}C NMR spectrum of **2b** revealed two characteristic signals at δ 159.6 and 188.9 ppm assigned to C-5 of pyrazole and a carbonyl carbon. Our result is in line with the published data by Kurkovskaya *et al*. [19], who found that in $CDCl_3$ solution and at low temperature, 4-acetylpyrazolones

Scheme 1. Synthesis of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)ethanone (**2**).



1 **2**



A **B** **C** **D** **E**

Figure 1. Tautomeric forms of compound **2**.

are mainly presented in the tautomeric 4-acetyl-5-hydroxy-pyrazoles structures.

Epoxides are particularly versatile synthetic intermediates that can readily be converted into a wide range of polyfunctional compounds. A useful method for the synthesis of α,β-epoxy-carbonyl compounds is the Darzens condensation between a carbonyl compound and an α-halo-carbonyl compound [20,21]. The presence of a hydroxyl group at C-2′ makes the α,β-epoxy-carbonyl compounds difficult to isolate as they undergo a cyclization to give dihydroflavonols formed by attack upon the β-carbon of the epoxides [22]. Within this context, we investigated the Darzens condensation reaction of compound **2** with aromatic aldehydes in a basic medium as a possible synthetic route to attain the diastereoselective *trans*-6-aryl-5-hydroxy-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-ones as flavonol analogs.

Firstly, we studied the Darzens condensation reaction of compound **2** with benzaldehyde in different basic aqueous medium to find the optimum basic condition (Scheme 2). As a basic medium, we used NaOH, KOH, LiOH, $Ca(OH)_2$, $Ba(OH)_2$, and K_2CO_3. Interestingly, in all basic medium, we obtain only one isolable product that was identified as *trans*-5-hydroxy-3-methyl-1,6-diphenyl-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one (**3a**) on the basis of microanalysis and spectral data (see Experimental). The results depicted in Table 1 revealed that the good yield was achieved in aqueous NaOH. However, reaction with relatively weaker bases, $Ba(OH)_2$ and K_2CO_3, gave **3a** in lower yields.

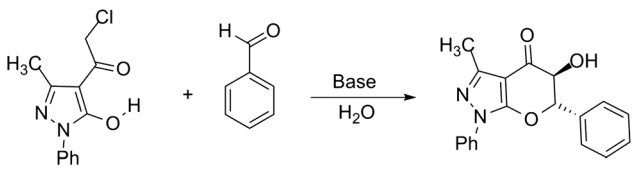
The forgoing result prompted us to investigate the Darzens condensation reaction of compound **2** with substituted benzaldehyde as well as heterocyclic aldehydes in aqueous NaOH solution to show the effect of electronic factor on the stereochemistry and yield of the product. Thus, treatment of **2** with a series of substituted benzaldehyde, namely, 4-methylbenzaldehyde, 4-methoxybenzaldehyde,

Table 1

Darzens condensation reaction of compound **2** with benzaldehyde in different basic medium.

Entry	Base	Yield (%)
1	NaOH	94
2	KOH	92
3	LiOH	91
4	$Ca(OH)_2$	92
5	$Ba(OH)_2$	75
6	K_2CO_3	50

Scheme 2. Darzens condensation reaction of compound **2** with benzaldehyde.



2 **3a**

2-chlorobenzaldehyde, 4-bromobenzaldehyde, and 4-fluorobenzaldehyde in aqueous NaOH at room temperature afforded, in each case, a single product that was formulated as **3b–f**. In a similar manner, treatment of **2** with heterocyclic aldehydes, namely, furfural and thiophene-2-carbaldehyde, under the same reaction condition afforded also a sole product, in each case, formulated as **3g** and **3h** (Scheme 3).

As shown in Table 2, some trends in the reactions of **2** with substituted benzaldehyde were noted, that is, the yields were slightly affected by the substituents of the investigated aldehydes. Those having electron-withdrawing halo substituents (e.g., Cl, Br, F) were efficiently reacted to give the corresponding pyrano[2,3-*c*]pyrazoles in good yields (entries 4, 5, and 6), whereas those having slightly electron-donating groups (e.g., Me, OMe) lower the yields under the same reaction conditions (entries 2 and 3). Surprisingly, both the electron-donating and electron-withdrawing groups have no effect on the stereochemistry of the product.

The chemical structure of all the 6-aryl-5-hydroxy-5, 6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-ones **3a–h** obtained during the present work was characterized by elemental analyses and spectral data. The IR spectra of new compounds **3a–h** displayed the characteristic absorption band for the hydroxyl group in the region 3437–3423 cm^{-1}, the pyrone ring carbonyl in the region 1676–1669 cm^{-1}, and the C-O-C stretching mode in the region 1172–1115 cm^{-1}. The ^1H NMR spectra were consistent with the structure of these new compounds. All new compounds displayed two doublet signals in the region δ 4.45–4.67 and 5.33–6.01 ppm assigned to H-5 and H-6. On the basis of the coupling constant between H-5 and H-6 ($J = 12$ Hz), we conclude that the relative configuration of compounds **3a–h** is *trans*-diastereoselectivity. The ^{13}C NMR spectrum of compound **3a**, for example, showed three characteristic signals at about δ 72.4, 88.3, and 188.1 ppm because of C-6, C-5, and a carbonyl carbon of C-4, respectively.

Scheme 3. Synthesis of *trans*-6-aryl-5-hydroxy-5,6-dihydropyrano [2,3-*c*]pyrazol-4(1*H*)-ones **3a–h**.

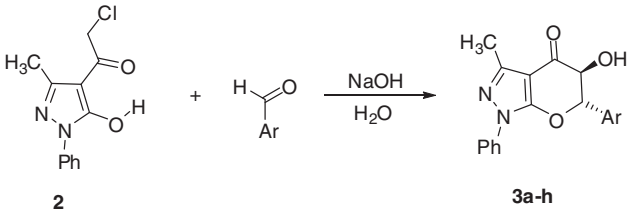


Table 2

Darzens condensation reactions of compound **2** with aromatic aldehydes in aqueous NaOH.

Entry	Ar	Product	Yield (%)
1	C_6H_5-	**3a**	94
2	4-Me-C_6H_4-	**3b**	90
3	4-MeO-C_6H_4-	**3c**	88
4	2-Cl-C_6H_4-	**3d**	96
5	4-Br-C_6H_4-	**3e**	93
6	4-F-C_6H_4-	**3f**	94
7	2-furyl	**3g**	96
8	2-thienyl	**3h**	96

The mechanistic scenario for the formation of the diastereoselective *trans*-6-aryl-5-hydroxy-5,6-dihydropyrano [2,3-*c*]pyrazol-4(1*H*)-ones **3a–h** is depicted in Scheme 4. The reaction is probably started with Darzens condensation via the nucleophilic addition of the deprotonated α-chloroketone **I** to aromatic aldehydes to give the intermediate **II** that undergoes an intramolecular SN^2 reaction to afford the nonisolable *trans*-epoxide intermediate **III**, which subsequently undergoes intramolecular nucleophilic addition of the hydroxyl group to the β-carbon of the epoxide **IV** to give the target compounds **3a–h**. We believe that the ring opening of the epoxide proceeded with retention of configuration, and the stereochemistry of product reveals the stereochemistry of the epoxide precursor.

It is worthwhile to mention that after taking specific rotation of compounds *trans*-**3a–h** at different concentration, it was found to be zero. So, we can conclude that compounds *trans*-**3a–f** may be racemic (5*S**,6*S**) and (5*R**,6*R**) and exist in equal quantities.

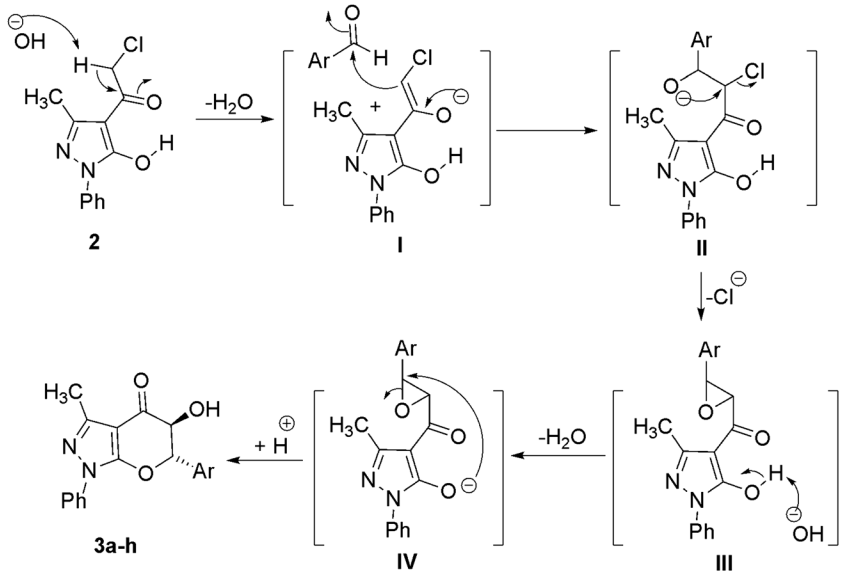
In conclusion, we have described a facial and clean one-pot synthesis of novel *trans*-6-aryl-5-hydroxy-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-ones **3a–h** via the Darzens condensation reaction of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (**2**) with aromatic aldehyde in aqueous sodium hydroxide solution.

EXPERIMENTAL

All chemicals were purchased from Fluka. All melting points were measured on an electrothermal 9100 Gallenkamp melting point apparatus (Germany). The infrared spectra were recorded in potassium bromide disks on a Mattson 5000 FTIR spectrometer (USA). The NMR spectra were recorded on a Brucker WP 300 NMR spectrometer (USA). ^1H spectra were run at 300 MHz, and ^{13}C spectra were run at 75.5 MHz in DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts were related to that of the solvent. The mass spectrum was recorded on Finnigan Incos 500 mass spectrometer (USA) at 70 ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt, and the results were in a good agreement (±0.3%) with the calculated values. The specific rotations were measured in a Perkin-Elmer 341 Polarimeter (USA) at room temperature and $\lambda = 589$ nm.

Synthesis of 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone (2). In a two-necked round-bottomed flask with magnetic stirrer, a reflux condenser, and a dropping funnel, 1-phenyl-3-methyl-2-pyrazolin-5-one (**1**) (17.07 g, 0.098 mol) was dissolved in dry dioxane (100 mL), and then $Ca(OH)_2$ (10.37 g, 0.14 mol) was added. Chloroacetyl chloride (7.97 mL, 0.1 mol)

Scheme 4. Plausible mechanism for the formation of compounds **3a–h**.



was added dropwise with precaution, as this reaction was exothermic. During this addition, the whole mass was converted into a thick paste. After the complete addition, the reaction mixture was heated to reflux for 4 h, and then, it was cooled to room temperature. The mixture was poured slowly into 2 M chilled HCl (200 mL) with constant stirring until the light yellow precipitate was formed. The colored crystals thus obtained were separated by filtration and recrystallized from methanol–chloroform mixture (MeOH:$CHCl_3$ = 80:20) to afford compound **2**.

Yellow crystals, yield 65%, mp. 80–81°C (Lit.[18] mp. 80°C). IR ($\bar{\nu}$/cm^{-1}): 3272 (OH), 1640 (C═O), 1600 (C═C). ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 7.29–7.82 (m, 5H, Ar-H), 12.85 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 15.4 (CH_3), 45.4 (CH_2), 102.2 (C-4), 121.1 (2CH_{Ar}), 127.2 (CH_{Ar}), 129.2 (2CH_{Ar}), 136.8 (C_{Ar}), 147.0 (C-3), 159.6 (C-5), 188.9 (C═O). *Anal*. For $C_{12}H_{11}ClN_2O_2$ (250.68) Calcd: C, 57.49; H, 4.42; N, 11.17, Found: C, 57.52; H, 4.41; N, 11.22.

General procedure for the synthesis of 6-aryl-5-hydroxy-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-ones (3a–h). A suspension of a mixture of aromatic aldehyde (1.94 mmol), 2-chloro-1-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone **2** (0.49 g, 1.94 mmol), and sodium hydroxide (0.08 g, 2 mmol) was stirred in water (3 mL) at room temperature for 2 h. The crystalline powder formed was collected by filtration, washed with water, and dried in a desiccator to give compounds **3a–h**. The crude compounds thus obtained were recrystallized from ethanol to give pure compounds.

***(5S*,6S*)-5-Hydroxy-3-methyl-1,6-diphenyl-5,6-dihydropyrano[2,3-c]pyrazol-4(1H)-one* (*3a*)**. Colorless crystals; yield 94%; mp 220–221°C; $[\alpha]_D^{25}$ = 0 (*c* = 1.5, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3433 (OH), 1674 (C ≡ O), 1597 (C═N), 1133 (C-O-C). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 2.53 (s, 3H, CH_3), 3.75 (bs, 1H, OH), 4.51 (d, *J* = 12 Hz, 1H, H-5), 5.35 (d, *J* = 12 Hz, 1H, H-6), 7.41–7.71 (m, 10H, Ar-H). ^{13}C NMR ($CDCl_3$): δ_{ppm} = 14.1 (CH_3), 72.4 (C-6), 88.3 (C-5), 102.6 (C-3a), 121.5 (2CH_{Ar}), 125.7 (CH_{Ar}), 126.9 (2CH_{Ar}), 127.6 (2CH_{Ar}), 128.3 (CH_{Ar}), 129.8 (2CH_{Ar}), 134.6 (C_{Ar}), 137.6 (C_{Ar}), 147.9 (C-3), 159.1 (C-7a), 188.1 (C-4). MS *m/z* (%): 320 (M^+, 4.2), 263 (3.8), 202 (12.8), 201 (93.1), 200 (69.1), 187.2 (3.9), 132.0 (16.1), 120.0 (32), 105 (5.8), 91 (100), 76 (17.6). *Anal*. For $C_{19}H_{16}N_2O_3$ (320.12) Calcd: C, 71.24; H, 5.03; N, 8.74%, Found: C, 71.30; H, 5.11; N, 8.76%.

***(5S*,6S*)-5-Hydroxy-3-methyl-1-phenyl-6-p-tolyl-5,6-dihydropyrano[2,3-c]pyrazol-4(1H)-one* (*3b*)**. White powder; yield 90%; mp 202–203°C; $[\alpha]_D^{25}$ = 0 (*c* = 1, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3433 (OH), 1674 (C ≡ O), 1596 (C═N), 1120 (C-O-C). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.35 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.04 (bs, 1H, OH), 4.54 (d, *J* = 12.4 Hz, 1H, H-5), 5.62 (d, *J* = 12.4 Hz, 1H, H-6), 7.24 (d, *J* = 7.6 Hz, 2H, C_6H_4-4-CH_3), 7.31–7.49 (m, 5H, Ar-H), 7.70 (d, *J* = 7.6 Hz, 2H, C_6H_4-4-CH_3). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 14.3 (CH_3), 21.3 (CH_3), 72.8 (C-6), 88.1 (C-5), 102.1 (C-3a), 121.2 (2CH_{Ar}), 127.5 (CH_{Ar}), 127.8 (CH_{Ar}), 129.3 (CH_{Ar}), 129.5 (2CH_{Ar}), 129.9 (2CH_{Ar}), 134.1 (C_{Ar}), 137.3 (C_{Ar}), 138.9 (C_{Ar}), 147.8 (C-3), 158.2 (C-7a), 188.0 (C-4). MS *m/z* (%): 334 (M^+, 22.1), 316 ($M^+ - H_2O$, 11.3), 243 (13.5), 202 (9.8), 201 (100), 200 (50.7), 134 (26.3), 120 (32.9), 91 (80.8), 76 (15.2). *Anal*. For $C_{20}H_{18}N_2O_3$ (334.37) Calcd: C, 71.84; H, 5.43; N, 8.38%, Found: C, 71.80; H, 5.33; N, 8.29%.

***(5S*,6S*)-5-Hydroxy-6-(4-methoxyphenyl)-3-methyl-1-phenyl-5,6-dihydropyrano-[2,3-c]pyrazol-4(1H)-one* (*3c*)**. White powder; yield 88%; mp 198–199°C; $[\alpha]_D^{25}$ = 0 (*c* = 0.85, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3424 (OH), 1674 (C ≡ O), 1603 (C═N), 1172 (C-O-C). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 2.54 (s, 3H, CH_3), 3.71 (bs, 1H, OH), 3.87 (s, 3H, OCH_3), 4.53 (d, *J* = 11.7 Hz, 1H, H-5), 5.33 (d, *J* = 11.7 Hz, 1H, H-6), 7.02 (d, *J* = 6 Hz, 2H, C_6H_4-4-OCH_3), 7.39–7.73 (m, 5H, Ar-H), 7.75 (d, *J* = 6 Hz, 2H, C_6H_4-4-OCH_3). ^{13}C NMR ($CDCl_3$): δ_{ppm} = 14.2 (CH_3), 51.6 (OCH_3), 72.5 (C-6), 88.8 (C-5), 102.4 (C-3a), 121.6 (2CH_{Ar}), 127.8 (CH_{Ar}), 128.2 (CH_{Ar}), 129.6 (CH_{Ar}), 130.5 (2CH_{Ar}), 131.8 (2CH_{Ar}), 135.1 (C_{Ar}), 137.5 (C_{Ar}), 139.6 (C_{Ar}), 147.6 (C-3), 158.5 (C-7a), 187.8 (C-4). MS *m/z* (%): 350 (M^+, 35.6), 243 (13.5), 202 (22.5), 201 (90.1), 200 (100), 150 (33.2), 136 (19.7), 120.0 (3.2), 107 (35.8), 91 (60.8), 76 (15.3). *Anal*. For $C_{20}H_{18}N_2O_4$ (350.37) Calcd: C, 68.56; H, 5.18; N, 8.00%, Found: C, 68.63; H, 5.21; N, 8.11%.

***(5S*,6S*)-6-(2-Chlorophenyl)-5-hydroxy-3-methyl-1-phenyl-5,6-dihydropyrano-[2,3-c]pyrazol-4(1H)-one* (*3d*)**. White powder; yield 96%; mp 180–181°C; $[\alpha]_D^{25}$ = 0 (*c* = 0.75, $CHCl_3$),

IR ($\bar{\nu}$/cm^{-1}): 3437 (OH), 1676 (C≡O), 1594 (C=N), 1118 (C-O-C). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 2.51 (s, 3H, CH_3), 3.35 (bs, 1H, OH), 4.67 (d, *J* = 11.8 Hz, 1H, H-5), 5.97 (d, *J* = 11.8 Hz, 1H, H-6), 7.31–7.97 (m, 9H, Ar-H). ^{13}C NMR ($CDCl_3$): δ_{ppm} = 14.5 (CH_3), 72.8 (C-6), 88.3 (C-5), 102.1 (C-3a), 123.5 ($2CH_{Ar}$), 126.8 (CH_{Ar}), 127.8 (CH_{Ar}), 128.4 ($2CH_{Ar}$), 129.3 (CH_{Ar}), 129.9 (CH_{Ar}), 131.4 (CH_{Ar}), 134.1 (C_{Ar}), 137.8 (C_{Ar}), 138.9 (C_{Ar}), 147.2 (C-3), 158.9 (C-7a), 188.6 (C-4). MS *m*/*z* (%): 356 (M^+ + 2, 2.3), 354 (M^+, 3.3), 297 (5.5), 243 (6.6), 201 (81.5), 200 (91.6), 155 (4.9), 153 (11.5), 132 (22.1), 125 (21.3), 111 (25.6), 91 (100), 77 (19.6). *Anal*. For $C_{19}H_{15}ClN_2O_3$ (354.79) Calcd: C, 64.32; H, 4.26; N, 7.90%, Found: C, 64.27; H, 4.17; N, 8.04%.

(5*S,6*S**)-6-(4-Bromophenyl)-5-hydroxy-3-methyl-1-phenyl-5,6-dihydropyrano-[2,3-*c*]pyrazol-4(1*H*)-one (3e)**. White powder; yield 93%; mp 230–231°C; $[\alpha]_D^{25} = 0$ (*c* = 1.75, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3430 (OH), 1675 (C≡O), 1596 (C=N), 1125 (C-O-C). ^{1}H NMR ($CDCl_3$): δ_{ppm} = 2.50 (s, 3H, CH_3), 3.98 (bs, 1H, OH), 4.62 (d, *J* = 11.9 Hz, 1H, H-5), 5.85 (d, *J* = 11.9 Hz, 1H, H-6), 7.23 (d, *J* = 6.5 Hz, 2H, C_6H_4-4-Br), 7.41–7.80 (m, 5H, Ar-H), 7.86 (d, *J* = 6.5 Hz, 2H, C_6H_4-4-Br). ^{13}C NMR ($CDCl_3$): δ_{ppm} = 14.2 (CH_3), 72.4 (C-6), 88.9 (C-5), 102.7 (C-3a), 125.5 ($2CH_{Ar}$), 126.8 (CH_{Ar}), 127.8 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 131.4 ($2CH_{Ar}$), 134.1 (C_{Ar}), 136.9 (C_{Ar}), 139.2 (C_{Ar}), 147.5 (C-3), 158.7 (C-7a), 188.9 (C-4). *Anal*. For $C_{19}H_{15}BrN_2O_3$ (399.24) Calcd: C, 57.16; H, 3.79; N, 7.02%, Found: C, 57.24; H, 3.68; N, 7.21%.

(5*S,6*S**)-6-(4-Flurophenyl)-5-hydroxy-3-methyl-1-phenyl-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one (3f)**. White crystals; yield 94%; mp 224–225°C; $[\alpha]_D^{25} = 0$ (*c* = 1, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3423 (OH), 1675 (C≡O), 1599 (C=N), 1147 (C-O-C). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.51 (s, 3H, CH_3), 3.08 (bs, 1H, OH), 4.45 (d, *J* = 12 Hz, 1H, H-5), 5.66 (d, *J* = 12 Hz, 1H, H-6), 7.12 (d, *J* = 6.8 Hz, 2H, C_6H_4-4-F), 7.27–7.71 (m, 5H, Ar-H), 7.99 (d, *J* = 6.8 Hz, 2H, C_6H_4-4-F). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 14.2 (CH_3), 72.8 (C-6), 87.3 (C-5), 102.2 (C-3a), 115.7 (CH_{Ar}), 115.9 (CH_{Ar}), 121.3 ($2CH_{Ar}$), 127.6 (CH_{Ar}), 129.9 ($2CH_{Ar}$), 130.8 (CH_{Ar}), 130.9 (CH_{Ar}), 133.4 (C_{Ar}), 137.2 (C_{Ar}), 137.5 (C_{Ar}), 147.9 (C-3), 158.1 (C-7a), 187.9 (C-4). *Anal*. For $C_{19}H_{15}FN_2O_3$ (338.33) Calcd: C, 67.45; H, 4.47; N, 8.28%, Found: C, 67.36; H, 4.38; N, 8.39%.

(5*S,6*R**)-6-(Furan-2-yl)-5-hydroxy-3-methyl-1-phenyl-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one (3g)**. Pale brown crystals; yield 96%; mp 179–180°C; $[\alpha]_D^{25} = 0$ (*c* = 0.85, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3437 (OH), 1669 (C≡O), 1597 (C=N), 1115 (C-O-C). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.51 (s, 3H, CH_3), 3.38 (bs, 1H, OH), 4.55 (d, *J* = 14.1 Hz, 1H, H-5), 5.65 (d, *J* = 14.1 Hz, 1H, H-6), 6.43 (d, *J* = 4 Hz, 1H, furan-H-3), 6.65 (t, *J* = 4 Hz, 1H, furan-H-4), 7.28 (d, *J* = 5.2 Hz, 1H, furan-H-5), 7.34–7.94 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 14.4 (CH_3), 73.3 (C-6), 84.0 (C-5), 102.6 (C-3a), 121.5 ($2CH_{Ar}$), 127.9 (furan-C-4), 128.8 (furan-C-3), 129.0 (furan-C-5), 129.6 (CH_{Ar}), 130.2 ($2CH_{Ar}$), 137.8 (furan-C-2), 139.2 (C_{Ar}), 148.2 (C-3), 157.2 (C-7a), 187.0 (C-4). MS *m*/*z* (%): 310 (M^+, 15.7), 292 ($M^+ - H_2O$, 29.2), 243 (19.3), 214 (56.2), 202 (20.9), 201 (100.0), 200 (55.0), 156 (30.5), 96 (67.8), 76 (37.6), 67 (52.7). *Anal*. For $C_{17}H_{14}N_2O_4$ (310.30) Calcd: C, 65.80; H, 4.55; N, 9.03%, Found: C, 65.71; H, 4.39; N, 9.24%.

(5*S,6*R**)-5-Hydroxy-3-methyl-1-phenyl-6-(thiophen-2-yl)-5,6-dihydropyrano[2,3-*c*]pyrazol-4(1*H*)-one (3h)**. Pale yellow needles; yield 96%; mp 196–197°C; $[\alpha]_D^{25} = 0$ (*c* = 1.5, $CHCl_3$), IR ($\bar{\nu}$/cm^{-1}): 3431 (OH), 1671 (C≡O), 1594 (C=N), 1117 (C-O-C). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.52 (s, 3H, CH_3), 3.50 (bs, 1H, OH), 4.46 (d, *J* = 11.9 Hz, 1H, H-5), 6.01 (d, *J* = 11.9 Hz, 1H, H-6), 7.09 (d, *J* = 3.5 Hz, 1H, thiophene-H-3), 7.31 (t, *J* = 3.5 Hz, 1H, thiophene-H-4), 7.37 (d, *J* = 4.0 Hz, 1H, thiophene-H-5), 7.51–7.73 (m, 5H, Ar-H). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 14.2 (CH_3), 73.1 (C-6), 83.9 (C-5), 102.0 (C-3a), 121.3 ($2CH_{Ar}$), 127.6 (thiophene-C-4), 127.7 (thiophene-C-3), 128.0 (thiophene-C-5), 128.8 (CH_{Ar}), 130.0 ($2CH_{Ar}$), 137.2 (thiophene-C-2), 138.9 (C_{Ar}), 148.1 (C-3), 157.3 (C-7a), 186.8 (C-4). MS *m*/*z* (%): 326 (M^+, 25.6), 308 ($M^+ - H_2O$, 10.2), 243 (17.6), 214 (9.6), 202 (26.1), 201 (92.0), 200 (67.2), 156 (32.5), 120.0 (43.2), 105 (8.8), 91 (100), 83 (65.6), 76 (24.6). *Anal*. For $C_{17}H_{14}N_2O_3S$ (326.37) Calcd: C, 62.56; H, 4.32; N, 8.58%, Found: C, 62.68; H, 4.29; N, 8.49%.

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