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Ascorbic Acid as an Eco-friendly Catalyst for the Efficient Synthesis of *Bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in Aqueous Media

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ABSTRACT One-pot, multi-component reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) and aryl aldehydes **2** or 5-substituted indoline-2,3-diones (**4a-c)** in the presence of ascorbic acid as a unique catalyst in aqueous media afforded the 4, 4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) **(3a-f)** and 3, 3-bis-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-substituted indolin-2-ones **(5a-c)**, respectively. This protocol provides several advantages such as environmental friendliness, excellent yields, and simple workup procedure

KEYWORDS 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one, 5-substituted indoline-2,3-diones, ascorbic acid, aryl aldehydes, bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol).

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INTRODUCTION

Nitrogen heterocycles are of unique interest due to the fact that they represent an important class of natural and synthetic products, among them, pyrazolone derivatives, which have an extensive variety of precise biological activities. Some of pyrazolone derivatives are now present in many commercial drugs for myocardial ischemia and brain ischemia.[1] Antipyrine, aminopyrine, dipyrone, benzpiperylon, propyl phenazone, morazone, and ramifenazone are widely used drugs available in the market.[2] Furthermore, bis-pyrazolylmethanes have an extensive spectrum of authorized biological activity, getting used as anti-inflammatory,[3] gastric secretion stimulatory,[4] antidepressant,[5] antibacterial,[5] and antipyretic agents.[6] Moreover, these compounds have been used as pesticides,[7] insecticides,[8] dyestuffs,[9] and chelating as well as extracting reagents for different metal ions.[10] Several synthetic strategies have been reported for the preparation of 4,4′-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) under classical or modified conditions.[11-24] However, some of these methods suffer from several drawbacks – expensive reagents, low yields, prolonged reaction times, use of poisonous organic solvents, and tedious workup procedures.[11-24] Therefore, a search for new reagents and the development of the latest methods are nevertheless of sensible importance. In the present study, we decided to explore the possibility of synthesizing bis-pyrazolylmethane derivatives through an one-pot, multi-component condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2 equiv.), and aromatic aldehydes or substituted isatins (1 equiv.) in water in the presence of ascorbic acid.

RESULTS AND DISCUSSION

Synthesis

Initially, we carried out the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) with benzaldehyde (**2a)** in the presence of different concentrations of ascorbic acid to produce 4, 4'-(phenylmethylene)

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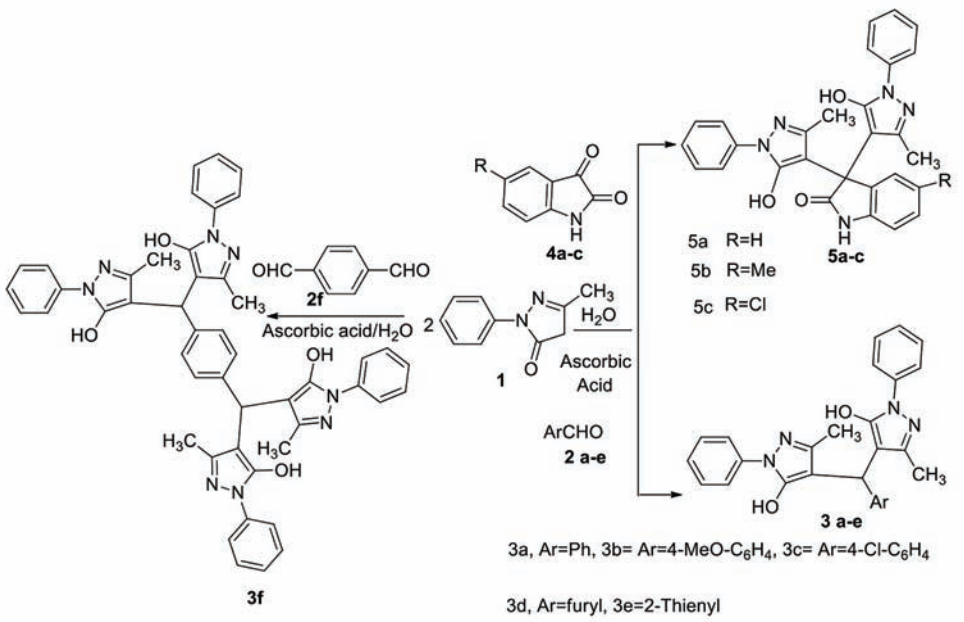

Scheme 1: Synthesis of 4, 4'-(arylmethylene)bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) (3a-f) and 3,3-bis-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-substitutedindolin-2-one (5a-c)

Table 1: The reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1) with benzaldehyde (2a) using different concentrations (10–25 mol%) of ascorbic acid

Entry	Conc. of ascorbic acid (mmole) (%)	Yield at 90°C	Time, min.
1	10	74	180
2	15	77	180
3	20	83	180
4	25	83	180

Table 2: The reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1) with the appropriate aldehydes 2a-f using 0.20 equivalents of ascorbic acid

Compounds	Ar	Yield at 90°C	Time, min
3a	C_6H_5	83	180
3b	4-$CH_3OC_6H_4$	90	120
3c	4-ClC_6H_4	91	80
3d	furan-2-yl	84	190
3e	thiophen-2-yl	81	200
3f	1,4-phenylene	92	90

bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) **(3**a) [**Scheme 1**]. The results summarized in **Table 1** revealed that raising the concentration of ascorbic acid more than 20 mol % has no marked effect on the reaction outcome.

To establish the generality, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1**) was treated with various aromatic aldehydes **2a-f** under the catalytic influence of ascorbic acid **2** [**Scheme 1**] (0.20 equivalents, **Table 2**). Excellent results **3a-f** (81–92% yields) were obtained and the reactions were completed during 80–200 min (thin-layer chromatography [TLC]). The assignment of the structure of compounds **3**a-e and **3**f was based on analytical and spectroscopic data (c.f. Exp. Part).

The dual role of ascorbic acid, that is, generates the enol form (I) of the 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **1** and activates the aldehyde carbonyl carbon by coordination with H^+ of ascorbic acid [**Figure 1**]. Proton migration from ascorbic acid (present in catalytic amount) generates the enol **I**, which coordinated with the aldehyde carbonyl carbon, forms the six-membered cyclic transition state **II.** Proton transfer of intermediate **II** gave the *β*-hydroxy ketone **III**, dehydration of intermediate **III** gave arylidene **IV**. **IV** subsequently abstracts a proton from ascorbic acid and undergoes Michael addition with the enol form **I** to generate the oxonium ion **V**, which loses a proton to complete the catalytic cycle and generate the target compound **3a-f** [**Scheme 2**]. In another study conducted by Zarghani *et al*.[25] sulfonated nanohydroxyapatite functionalized with 2-aminoethyl dihydrogen phosphate (HAP at $AEPH_2$-SO_3H) was used as a recyclable and eco-friendly catalyst for rapid one-pot synthesis of 4, 4′-(aryl methylene) bis (3-methyl-1 *H*-pyrazol-5-ols), The mechanism of the reaction was in line with our mechanism.[17,25]

This method additionally was extended to the synthesis of 3,3-bis-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-substituted indolin-2-ones **(5a-c)** through the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **1** with 5-substituted indoline-2, 3-dione **4** in the presence of 0.20 equivalent of ascorbic acid [**Scheme 1**]. Reaction occurred according to expectations affording products **5a-c** in 81–91% [**Table 3**]. The structures of **5a-c** were confirmed by various spectral data, including infrared (IR), ^{1}H-NMR, and mass spectroscopy. The IR spectra of compounds **5a-c** showed characteristic absorption bands in the region within 3447-3409 and 3184-3134 cm^{-1} due to the stretching vibrations of NH and OH groups. The strong bands due to C=O

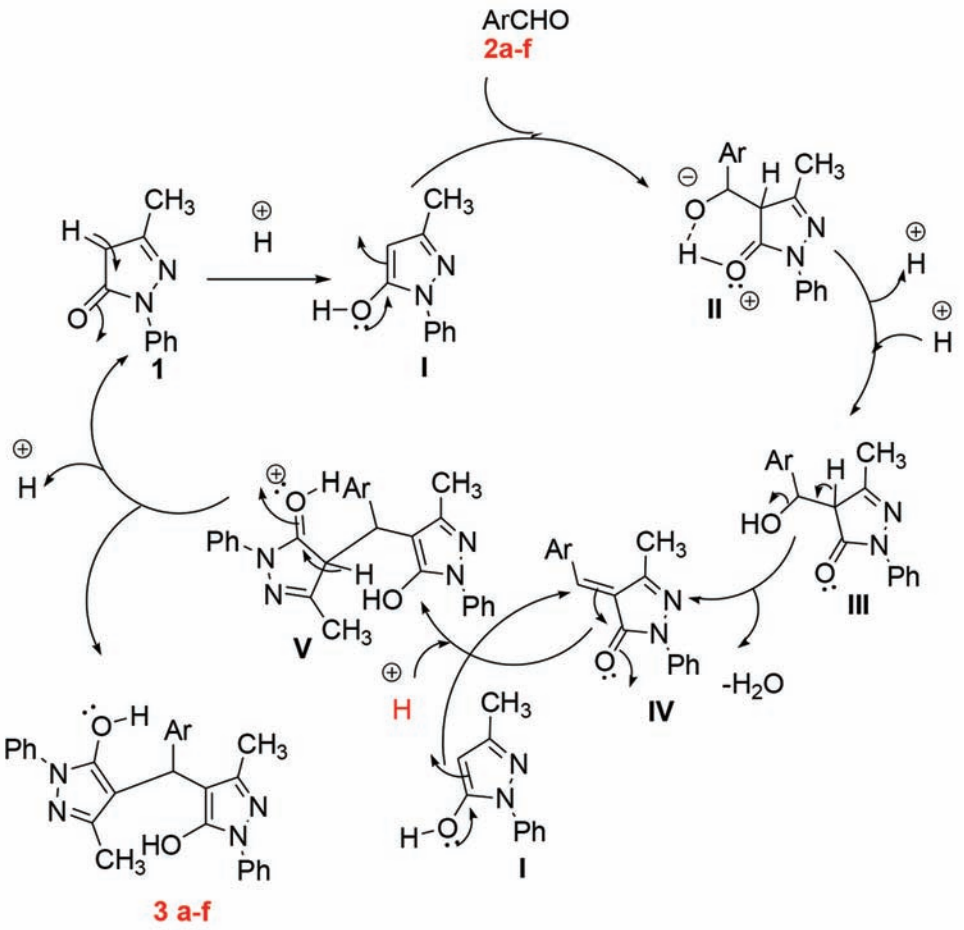

Figure 1: Dual activation role of ascorbic acid during synthesis of 4,4'-(aryl-methylene)-*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s (3a-f)

Table 3: The reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1) with the appropriate 5-substituted indoline-2, 3-diones (5a-c) using 0.20 equivalents of ascorbic acid

Compd. no	R	Yield at 90°C	Time, h
5a	H	90	5
5b	CH_3	81	4.5
5c	Cl	88	4

stretching appeared in the region within 1710-1700. The ^{1}HNMR spectra of **5a-c** showed two broad signals within δ = 2.21-2.10, δ = 12.96-11.01, and δ = 14.01-11.15 ppm due to $2CH_3$ and 2OH group protons, respectively. In addition to the NH and aromatic protons within δ=7.86-6.81 ppm. The mass spectra of compound **5a-c** showed the molecular ion peaks at *m/z* 400 (M^+), 491 (M^+), and 409 (M^+-2), respectively, which were in agreement with the molecular formula of the compound $C_{28}H_{23}N_5O_3$, $C_{29}H_{25}N_5O_3$, and $C_{28}H_{22}ClN_5O_3$.

EXPERIMENTAL

All melting points are recorded on Gallenkamp electric. IR spectra were recorded on a Shimadzu FTIR Affinity-1S apparatus, wave numbers are quoted in cm^{-1}. All compounds were measured neat directly on the crystal of the IR machine. Mass spectrometric measurements were performed using Advion CMS machine. Ions were generated by the Atmospheric Pressure Ionization Techniques. The ^{1}H NMR spectra were obtained on Bruker DPX 500 apparatus using TMS as an internal reference and $CDCl_3$ as the solvent. Elemental analyses (C, H, and N) were carried out at the National Research Center, Dokki, Giza, Egypt.

General procedure for the synthesis of *bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)

A mixture of substituted aryl aldehyde **2**a-f or substituted isatin derivatives **4**a-c (5 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **1** (0.87 g, 5 mmol), and ascorbic acid (0.352 g, 1 mmol, 20 mol%) in water (50 mL) was stirred at 90°C., progress of the reaction was monitored by (TLC). After completion of the reaction, the reaction mixture was cooled. The resultant precipitates were collected by filtration, washed with water, and recrystallized from ethanol/benzene to provide the desired products **3a-f** and **5a-c**, respectively.

4,4'-(Phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) 3a; Colorless powder; Yield (83.0%); MP 168–170°C [Lit.[26], 170–172°C); FT-IR (cm^{-1}): 3371 (br, 2OH), ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.31 (brs, 6H, CH_3), 4.93 (s, 1H, CH), 7.13–7.69 (m, 15H, $H_{aromatic}$), 12.44 (s, 1H, OH), 13.90 (s, 1H, OH).

4,4'-((4-Methoxyphenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) 3b; Colorless powder; Yield (90.0%); MP 174–176°C [Lit.[27], 176–178°C]. FT-IR (cm^{-1}): 3437(OH); ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.40 (brs, 6 H, 2 CH_3), 3.82 (s, 3 H, OCH_3), 4.81 (s, 1 H, CH), 7.07–7.58 (m, 14H, $H_{aromatic}$), 12.36 (1H, s), 13.43(1H, s).

4,4'-((4-Chlorophenyl)methylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) 3c; Colorless powder; Yield (91.0%); MP 213–215°C [Lit.[26], 215–217°C]. FT-IR (cm^{-1}): 3463 (OH); ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.30 (s, 6H, CH_3), 4.95 (s, 1H, CH), 7.22–7.70 (m, 14H, $H_{aromatic}$), 12.50 (s, 1H, OH), 13.87 (s, 1H, OH).

4,4'-(Furan-2-ylmethylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) 3d; Colorless powder; Yield (84.0%); MP 189–191°C [Lit.[27], 188–190°C]. FT-IR (cm^{-1}): 3427(OH); ^{1}H-NMR (500-MHz; DMSO-d_6): δ: 2.23 (s, 6H, 2CH_3), 4.88 (s, 1H, CH), 6.06-7.69 (m, 13H, Ar-H), 12.56 (br, 1H, OH),13.97 (br, 1H, 2OH).

4,4'-(Thiophen-2-ylmethylene)*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) 3e; White cream powder; Yield (81.0%); MP 184–186°C, [Lit.[28], 181–183°C]. FT-IR (cm^{-1}):3434(OH); ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.30 (6H, s, 2 × CH_3), 4.95 (1H, s, CH), 6.75–7.71 (m, 13H, Ar-H), 12.52 (br, 1H, OH), 14.01 (br, 1H, OH).

4,4',4'',4'''-(1,4-Phenylenebis(methanetriyl)) tetrakis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)) 3f; White cream powder; Yield (90.0%); MP 216–218°C, [Lit.[29], 214–216°C]. FT-IR (cm^{-1}): 3415 (OH); ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.28 (s, 6H, 2CH_3), 2.30 (s, 6H, 2CH_3), 5.02 (s, 1H, CH), 5.03 (s, 1H, CH), 7.17–7.69 (m, 24H, Ar-H) 12.43 (br, 2H, OH) 14.10 (2H, s, OH).

3,3-*Bis*(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)indolin-2-one 5a; White powder; Yield (90.0%); MP 178–179°C, [Lit.[30], 174–176°C]. FT-IR (cm^{-1}): 3409, 3184 (NH, 2OH), 1710.(C=O); (500 MHz; DMSO-d_6): δ: 2.10 (br, 6H, 2CH_3), 7.01–7.86 (m, 15H, Ar-H, NH),12.96 (br, 1H, OH) 14.01 (br, 1H, OH); MS (70 ev, %) m/z 477 (M^+, 0.8), 400 (M+, 1.7), 304 (20.8), 280(8.7), 230(6.1), 175 (100), 157 (28.4), 133 (19.0), 115 (26.2), 94(23.8), 77(25.3), 69(40.5). **3,3-*Bis*(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-5-methylindolin-2-one 5**b; White powder; Yield (81.0%); MP 200°C. FT-IR (cm^{-1}): 3447, 3150 (NH, OH), 2885 (CH-Ali), 1706 (C=O); ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.21 (br, 6H, 2CH_3), 2.29(s, 3H, CH_3), 6.81–7.75 (14H, m, ArH, NH), 11.01 (br, 1H, OH), 11.15 (br,1H,OH). MS (70 ev, %) m/z 491 (M^+, 1.2), 402 (5.4), 320 (12.5) 302 (6.8), 255 (9.7), 235 (9.1), 175 (100), 157 (73.1), 149 (32.2) 115 (31.1), 105 (27.0), 93 (22.1), 77 (43.1). Analysis calculated for $C_{29}H_{25}N_5O_3$ (491.20): C, 70.86; H, 5.13; N, 14.25. Found: C, 70.78; H, 5.05; N, 14.34%.

5-Chloro-3,3-*bis*(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)indolin-2-one 5c; White powder; Yield (88.0%); MP 240°C. FT-IR (cm^{-1}):3429, 3134 (NH, OH),1700 (C=O); ^{1}H-NMR (500 MHz; DMSO-d_6): δ: 2.15 (6H, br, 2CH_3), 6.91–7.85 (14H, m, ArH, NH), 11.08 (br,1H,OH) 11.43 (br,1H,OH). MS (70 ev, %) m/z 509 (M^+-2, 3.2), 400 (2.5), 300 (5.1), 280 (17.3), 233 (10.2), 175 (12.5), 157 (56.8), 149 (26.4), 139 (23.2), 115 (31.1), 91 (22.1), 77 (18.7), 69 (48.6), 43 (100). Analysis calculated for $C_{28}H_{22}ClN_5O_3$ (511.96): C, 65.69; H, 4.33; N, 13.68. Found: C, 65.80; H, 4.21; N, 13.79%.

CONCLUSION

Ascorbic acid is an efficient catalyst for the synthesis of *bis*-pyrazolylmethane derivatives **3a-f** and **5a-c**, respectively. The advantages are – (i) use of cheap and easily available catalyst, (ii) requirement of a small amount of the catalyst, (iii) short reaction times, (iv) high product yields, and (v) clean product. Eco-friendly reaction conditions make this methodology a valid contribution to the existing processes in the field of *bis*(1*H*-pyrazol-5-ols) derivatives synthesis.

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