RESEARCH LETTER

Two efficient and green methods for synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) without use of any catalyst or solvent

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Two efficient and green methods for synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) without use of any catalyst or solvent have been developed simply by heating (at 120°C) or microwave irradiation (300 W) of intimate mixtures of 3-methyl-l-phenyl-5-pyrazolone and aldehyde in 2:1 mole ratio.

Keywords: 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols); 3-methyl-l-phenyl-5-pyrazolone; aromatic aldehydes; catalyst-free synthesis; solvent-free synthesis

1. Introduction

Pyrazolone derivatives are an important class of bioactive drug targets in the pharmaceutical industry as they constitute the core structure of numerous biologically active compounds (1–3). They have been paid much attention for their various biological activities such as antitumor (4, 5), selective COX-2 inhibitory (6), cytokine inhibitory (7), anti-inflammatory (8), antipyretic (9), gastric secretion stimulatory (10), antidepressant (11), antibacterial (12), and antifilarial activities (13). Moreover, they are capable of exhibiting prototropic tautomerism (14). The compounds which contain two pyrazolone rings can be used as extractant for some metal ions (15) and ligands (16–18). 4,4′-(Arylmethylene)bis (1H-pyrazol-5-ols) 3 are usually synthesized by condensing 3-methyl-l-phenyl-5-pyrazolone 1 with various aldehydes 2 (e.g., aromatic and heterocyclic) using different catalysts and media (19–28). Some of these methods require long reaction time, use of expensive catalysts, and organic solvents and tedious workup. The current trend toward development of catalyst-free (29–32) and solvent-free (26, 33–35) reaction conditions encouraged us to study the same reaction without using any catalyst or solvent. Our success in this endeavor resulted in development of two green methods for synthesis of the title compounds, which are presented herein.

2. Results and discussion

Our present methods involve subjecting of an intimate mixture of 3-methyl-l-phenyl-5-pyrazolone and aldehyde (2:1 mole ratio) directly to heat (120°C, 10 min) or microwave (60°C, 300 W, 3 min) irradiation. A range of structurally diverse aldehydes belonging to the categories aromatic and heterocyclic aldehydes were taken. To our delight, the target compounds were formed in most of the combinations of the reactants (Scheme 1). Under the optimized conditions (Table 1), very good to excellent yield of 3 was obtained (Table 2). In the combination 1+p-Me2N-C6H4-CHO (2:1 mole ratio), however, any product of the series 3 was not obtained; instead, a 1:1 condensation product 4 was formed (yield: 88%) (Scheme 2). Possibly, a greater stability of 4 as compared to its analogs (formed by use of other aldehydes) due to conjugative effect is responsible for this difference.

Recently, we have reported an efficient and green “on-water” synthesis of biscoumarins starting from 4-hydroxycoumarin, where use of 5M NaCl solution as the aqueous medium was found to be much beneficial (29). We carried out the present reaction under the same condition when it was observed that

![Scheme 1. Synthesis of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) 3 under catalyst-free and solvent-free conditions.](image-url)
Table 1. Optimization of reaction condition using 3-methyl-l-phenyl-5-pyrazolone 1 and benzaldehyde 2a (2:1 mole ratio) as reactants.\(^a\)

| Thermal process | MW-assisted process |
|-----------------|---------------------|
| Temperature (°C) | Yield of 3a (%)     | Temperature (°C) | Yield of 3a (%) |
| 60              | 10                  | 60              | 3               |
| 90              | 10                  | 45              | 5               |
| 110             | 10                  | 120             | 10              |
| 120             | 10                  | 60              | 2               |
| 125             | 10                  | 60              | 3               |
| 130             | 10                  | 60              | 4               |

\(^a\)Optimized values are given in bold.

Table 2. Catalyst- and solvent-free synthesis of 4,4'-((arylmethylene)bis(1H-pyrazol-5-ols) 3.

| Reaction condition | Entry | Aldehyde 2 | Product 3 | Δ 120°C yield (%) | MW (300 W) yield (%) | Melting point |
|-------------------|-------|------------|-----------|-------------------|----------------------|---------------|
|                   | 1     | ![Diagram](#) | 3a        | 91                | 92                   | 173–174°C [Ref. (20), 171–172°C] |
|                   | 2     | ![Diagram](#) | 3b        | 93                | 93                   | 201–202°C [Ref. (20), 203–204°C] |
|                   | 3     | ![Diagram](#) | 3c        | 90                | 90                   | 174–176°C [Ref. (36), 173–175°C] |
| Entry | Aldehyde 2 | Product 3 | Reaction condition |
|-------|------------|-----------|--------------------|
| 4     | Cl-Ph-CHO  | ![](image) | 94/94: 209–210°C [Ref. (20), 207–209°C] |
| 5     | Br-Ph-CHO  | ![](image) | 96/92: 185–186°C [Ref. (37), 183–185°C] |
| 6     | O₂N-Ph-CHO | ![](image) | 95/91: 231–232°C [Ref. (20), 230–232°C] |
| 7     | O₂N-Ph-CHO | ![](image) | 92/92: 148–149°C [Ref. (20), 149–150°C] |
| Entry | Aldehyde 2 | Product 3 | Reaction condition |
|-------|------------|-----------|-------------------|
|       |            |           | Δ 120°C yield (%) | MW (300 W) yield (%) | Melting point |
| 8     | ![Aldehyde 2](image1) | ![Product 3](image2) | 91 | 93 | 225–226°C [Ref. (20), 224–225°C] |
| 9     | ![Aldehyde 2](image3) | ![Product 3](image4) | 90 | 92 | 229–230°C [Ref. (38), 230–231°C] |
| 10    | ![Aldehyde 2](image5) | ![Product 3](image6) | 92 | 93 | 201–203°C [Ref. (20), 200–201°C] |
| 11    | ![Aldehyde 2](image7) | ![Product 3](image8) | 91 | 91 | 183–184°C [Ref. (19), 181–183°C] |
very good to excellent yield of 3 was obtained within 1 h (Table 3). However, after completion of our work of this “on-water” method, it came to our notice that Tale et al. have reported an analogous method in 2011 using pure water as medium (36), where the reaction time was somewhat longer (6–8 h).

3-Methyl-1-phenyl-5-pyrazolone 1 can have two other tautomers 1A and 1B. In solution, this compound is known to remain in equilibrium with its tautomers (39). Though in chloroform solution the 4H-5-keto form 1 is reported to exist preferentially, the 1H NMR spectrum of 3a recorded by us in CDCl3 was found to be very complicated, which is possibly due to existence of the equilibria shown in Scheme 3.

It is reported that between the tautomers 1 and 1A the latter is favored in pyridine (39), and such a situation would be expected in another polar solvent DMSO also. The 1H NMR spectral data of 4,4′-(arylmethylene)bis(1H-pyrazol-5-ols) 3 reported in the literature are mostly recorded in DMSO-d6. In the papers incorporating the 1H NMR spectral data of 3 in DMSO-d6, there are different types of reports about the position of their OH signals. In some papers, it has been mentioned that they appear as a two-proton broad singlet in the downfield region (δ13.5–14.0; 19, 22, 23). This is quite unexpected, and the two hydroxyl protons of 3 would be expected to appear at two different positions, just like those of the biscoumarins (29). We recorded the 1H NMR spectra of 3a–m in DMSO-d6 and found that for none of these compounds a two-proton signal in the δ13.5–14.0 region was obtained.

In the method for synthesis of 3 being reported here, it was a common observation that the reactions

| Entry | Aldehyde 2 | Product 3 | Δ 120°C yield (%) | MW (300 W) yield (%) | Melting point |
|-------|------------|-----------|------------------|----------------------|--------------|
| 12    | ![3l](image) | ![3l](image) | 92               | 92                   | 235–236°C [Ref. (37), 235–237°C] |
| 13    | ![3m](image) | ![3m](image) | 94               | 91                   | 258–260°C [Ref. (37), 258–259°C] |

Table 2 (Continued)
were very clean, and no side product was formed in any run. In fact, the crude products obtained were of high purity and did not require any chromatographic separation. Their crystallization from ethanol provided analytically pure samples. More significantly, the whole operation did not require any solvent, organic or inorganic, at any stage. Furthermore, the reaction condition has been found to be mild enough to tolerate a variety of functionalities such as NO₂, Cl, Br, OH, OMe, etc.

3. Conclusion
In summary, we have developed two very simple, efficient, and environmentally benign methods for synthesis of 4,4'-arylmethylene-bis(3-methyl-1H-pyrazol-5-ols) without use of any catalyst, solvent, surfactant, or solid support. We feel that this protocol is a good addition to the currently reported methods.

4. Experimental
4.1. Materials and methods
Chemicals were purchased from Merck, Aldrich, and Spectrochem chemical companies. Melting points were recorded on a Köfler block. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX II) in KBr pellets. ¹H NMR spectra were recorded in CDCl₃ on a Bruker AV-300 (300 MHz) spectrometer and HRMS on a Waters HRMS instrument [Xevo G2QToF] spectrometer. Analytical samples were routinely dried in vacuo at room temperature. Microanalytical data were recorded on a Perkin-Elmer 2400 Series II C, H, N analyzer. A mono-mode microwave reactor, manufactured by CEM Corporation, USA, was used for this study.

4.2. General procedure for the synthesis of 4,4'-arylmethylene-bis(3-methyl-1H-pyrazol-5-ols) 3

Thermal method
An intimate mixture of 3-methyl-l-phenyl-5-pyrazolone 1 (4 mmol) and an aldehyde 2 (2 mmol) was taken in a round-bottomed flask fitted with an air condenser, and it was heated in an oil bath at 120°C for 10 min. The reaction mixture was then cooled and crystallized from ethanol in order to obtain 3 in perfectly pure state.

Microwave method
In a typical experiment, an intimate mixture of 3-methyl-l-phenyl-5-pyrazolone 1 (4 mmol) and an aldehyde 2 (2 mmol) was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 60°C (300 W) for 3 min (as monitored by TLC). The reaction mixture was then cooled and crystallized from ethanol, which gave 3 in perfectly pure state.

4.2.1. 4,4'-Phenylmethylene-bis(3-methyl-1-phenyl-1H-pyrazol-5-ols) 3a
IR (KBr, cm⁻¹): 3400, 3080, 2900, 1593, 1494, 1410, 1275, 1020, 730, 690. ¹H NMR (CDCl₃, 300 MHz) δ: 7.86 (d, 1H, Ar-H), 7.46 (t, 2H, Ar-H), 7.30-7.20 (m, 5H, Ar-H), 6.81-6.71 (m, 2H, Ar-H), 5.84 (s, 1H, OH), 2.33 (s, 6H, OCH₃), 1.97 (s, 6H, OCH₃).

Scheme 3. Tautomers of 3-methyl-l-phenyl-5-pyrazolone 1 and 4,4'-arylmethylene-bis(1H-pyrazol-5-ols) 3.
NMR (300 MHz, DMSO-d6): δ (ppm): 13.95 (br, s, 1H, OH), 7.69 (d, J = 7.8 Hz, 4H), 7.43 (t, J = 7.8 Hz, 4H), 7.15–7.29 (m, 7H), 4.94 (s, 1H), 2.30 (s, 6H). HRMS: Calcd. for C22H23N2O2: [M+H]+: m/z 437.1989; found: 437.2031. Anal. Calcd. for C22H23N2O2: C, 74.29; H, 5.54; N, 12.84; Found C, 74.02; H, 5.32; N, 12.70%.

4.2.2. 4.4’-[4-Methylphenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]3b. IR (KBr, cm⁻¹): 3440, 3075, 3830, 1590, 1495, 1408, 1294, 1020, 800, 744, 688. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 13.91 (br, s, 1H, OH), 7.69 (d, J = 7.9 Hz, 4H), 7.42 (t, J = 7.6 Hz, 4H), 7.22 (br. t, J = 6.9 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 4.89 (s, 1H), 2.29 (s, 6H), 2.23 (s, 3H).

4.2.3. 4.4’-[4-Methylphenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5b. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 7.68 (d, J = 8.0 Hz, 4H), 7.43 (t, J = 7.7 Hz, 4H), 7.23 (t, J = 7.1 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.87 (s, 1H), 3.68 (s, 3H), 2.29 (s, 6H).

4.2.4. 4.4’-[4-Chlorophenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5c. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 7.68 (d, J = 8.0 Hz, 4H), 7.43 (t, J = 7.7 Hz, 4H), 7.32 (d, J = 8.2 Hz, 2H), 7.19–7.25 (m, 4H), 4.95 (s, 1H), 2.30 (s, 6H).

4.2.5. 4.4’-[4-Bromophenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5c. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 13.86 (br, s, 1H, OH), 7.68 (d, J = 7.9 Hz, 4H), 7.40–7.47 (m, 6H), 7.23 (br. t, J = 6.7 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 4.93 (s, 1H), 2.30 (s, 6H).

4.2.6. 4.4’-[4-Nitrophenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5d. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 13.84 (br, s, 1H, OH), 8.15 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.4 Hz, 4H), 7.50 (d, J = 8.6 Hz, 2H), 7.43 (t, J = 7.6 Hz, 4H), 7.24 (t, J = 7.2 Hz, 2H), 5.11 (s, 1H), 2.33 (s, 6H).

4.2.7. 4.4’-[3-Nitrophenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5g. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 13.90 (br, s, 1H, OH), 8.07 (br, s, 2H), 7.67–7.73 (m, 5H), 5.79 (t, J = 8.3 Hz, 1H), 7.43 (t, J = 7.6 Hz, 4H), 7.24 (t, J = 7.1 Hz, 2H), 5.13 (s, 1H), 2.33 (s, 6H).

4.2.8. 4.4’-[2-Nitrophenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5h. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 13.35 (br, s, 1H, OH), 7.60–7.71 (m, 7H), 7.40–7.47 (m, 5H), 7.23 (t, J = 6.9 Hz, 2H), 5.41 (s, 1H), 2.22 (s, 6H).

4.2.9. 4.4’-[2-Hydroxyphenyl)methylene]bis[3-methyl-1-phenyl-1H-pyrazol-5-ol]5i. ¹H NMR (300 MHz; DMSO-d6): δ (ppm): 7.68 (d, J = 7.8 Hz, 4H), 7.54 (br. d, J = 7.4 Hz, 1H), 7.42 (t, J = 6.9 Hz, 4H), 7.25 (br. t, J = 6.6 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 6.67–6.75 (m, 2H), 5.15 (s, 1H), 2.27 (s, 6H).

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