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Article

In situ generation of trityl carbocation (Ph_3C^+) as a homogeneous organocatalyst for the efficient synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s

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Solvent-free synthesis

ABSTRACT

Trityl chloride (Ph_3CCl) efficiently catalyzes the condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and aromatic aldehydes under mild and solvent-free conditions, affording 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*- pyrazol-5-ol)s in high to excellent yields and in short reaction time. The presence of the requisite organocatalytic trityl carbocation (Ph_3C^+) species was confirmed by analysis of infrared, ^1H NMR, and ultra violet spectral data. A plausible mechanism was proposed for the reaction based on the observations and literature precedent.

1. Introduction

The use of small-molecule organocatalysts in organic synthesis has flourished over the past decade [1–15]. The advantages of organocatalysts over other catalysts, such as those based on transition-metal complexes, include greater air-stability and commercial availability, lower cost, lack of heavy metals, and lower inherent toxicity. Moreover, organocatalysts can enable access to reactions via different activation modes and often require relatively simple reaction conditions [1–15]. One novel class of small-molecule organocatalysts is triarylmethyl chlorides (Ar_3CCl), whose catalytic activity is mediated via in situ formation of triarylmethyl carbocations (Ar_3C^+) [9–15].

Pyrazole-based compounds have received much attention owing to their various biological activities, which include their acting as antitumor [16], antifilarial [17], antibacterial [18], antidepressant [19], and gastric-secretion stimulatory agents [20], as well as selective inhibitors of cycloxygenase-2 [21], and inhibitors of cytokines [22].

More specifically, derivatives such as 4'-(arylmethylene)-bis(1*H*-pyrazol-5-ol)s have been used as dyestuffs [23], fungicides [24], and pesticides [25]. A typical route to one class of these compounds, 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s (**1**), is via the condensation of two equivalents of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) with one equivalent of aromatic aldehydes **3** (Scheme 1) [26–34]. Numerous Lewis and Brönsted acid catalysts have been employed to promote this transformation, including cerium(IV) ammonium nitrate [26], $[Cu(3,4\text{-tmtppa})](MeSO_4)_4$ [27], 3-ami-

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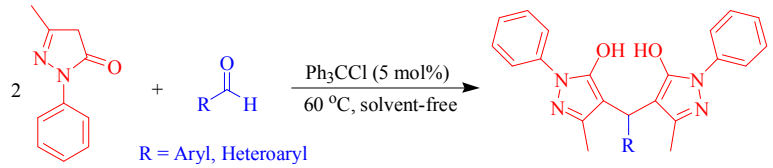


Scheme 1. Synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s using trityl chloride.

nopropylated silica gel [28], 1,3-disulfonic acid imidazolium tetrachloroaluminate [29], 1,3,5-tris(hydrogensulfato) benzene [30], silica-bonded S-sulfonic acid (SBSSA) [31], PEG-OSO_3H [32], xanthan sulfuric acid [33], and sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl)ester [34]. This reaction has been also performed in PEG-400 at 110 °C [35].

However, disadvantages of these methods include requirements for (1) difficult-to-prepare catalysts; (2) prolonged reaction times; (3) use of toxic organic solvents; (4) harsh reaction conditions; and (5) tedious work-up procedures. Furthermore, yields are often only moderate. To overcome these limitations, a more efficient, pH-neutral, and easily available catalyst capable of operating under mild conditions would be strongly desirable.

Here we describe our studies examining whether trityl chloride (Ph_3CCl) fulfills the above criteria, as an organocatalyst for the synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s from 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and aromatic aldehydes.

2. Experimental

2.1. General

All chemicals were purchased from Merck or Fluka and used as supplied. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel SIL G/UV 254 plates (Macherey-Nagel). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were acquired in DMSO-d_6 on Bruker Avance 300, 500, or 600 MHz DPX FT-NMR spectrometers. Chemical shifts (δ) are reported relative to residual CH_3SOCH_3 (δ_H = 2.50), and coupling constants (J) are reported in Hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet. Ultra violet (UV) spectra were recorded on a T80 UV-Vis spectrophotometer (PG Instruments Ltd).

2.2. General procedure for synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1H-pyrazol-5-ol)s

Ph_3CCl (14 mg, 0.05 mmol) was added to a stirred mixture of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) (350 mg, 2.00 mmol) and arylaldehyde (1.00 mmol) at 60 °C. The resulting mixture was initially stirred magnetically, and then, following solidification of the reaction mixture, with a small glass rod. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature, and then diluted with petroleum ether (10 mL) [the catalyst is soluble in hot petroleum ether, but the products are not]. The resulting mixture was heated at reflux for 3 min, and filtered to remove the catalyst. The resulting precipitate was recrystallized from ethanol (EtOH) (>85%) to give the pure solid product.

2.3. Selected spectral data of the products

4,4'-(2-Phenylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 1). ^1H NMR (500 MHz, DMSO-d_6): δ 2.33 (s, 6H), 4.88 (s, 1H), 7.07 (m, 1H), 7.18 (m, 6H), 7.44 (t, J = 7.5 Hz, 4H), 7.58 (d, J = 7.8 Hz, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.0, 33.5, 121.4, 126.2, 126.8, 127.6, 128.2, 129.1, 137.3, 142.9, 146.1.

4,4'-((4-Nitrophenyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 2). ^1H NMR (500 MHz, DMSO-d_6): δ 2.35 (s, 6H), 5.13 (s, 1H), 7.25–7.27 (m, 2H), 7.43–7.46 (t, J = 7.0 Hz, 4H), 7.51–7.53 (d, J = 8.0 Hz), 7.70–7.72 (d, J = 8.0 Hz, 4H), 8.16–8.18 (d, J = 8.0 Hz, 2H), 12.64 (s, 1H, OH), 13.86 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.4, 34.0, 121.5, 124.2, 126.6, 129.5, 129.8, 146.8, 147.1, 151.2.

4-(Bis(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)methyl)benzonitrile (Table 3, entry 5). ^1H NMR (600 MHz, DMSO-d_6): δ 2.32 (s, 6H), 5.05 (s, 1H), 7.25 (d, J = 7.16 Hz, 2H), 7.42–7.45 (m, 6H), 7.68 (d, J = 7.88 Hz, 4H), 7.75 (d, J = 8.32 Hz, 2H), 12.46 (s, 1H, OH), 13.86 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.1, 33.2, 108.7, 118.9, 120.5, 128.3, 128.9, 132.0, 139.3, 142.4, 148.1.

4,4'-((4-Chloro-3-nitrophenyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 6). ^1H NMR (600 MHz, DMSO-d_6): δ 2.02 (s, 6H), 5.09 (s, 1H), 7.25 (t, J = 7.30 Hz, 2H), 7.44 (t, J = 7.76 Hz, 4H), 7.57 (d, J = 8.36 Hz, 1H), 7.68 (m, 5H), 7.85 (s, 1H), 12.47 (s, 1H, OH), 13.87 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.4, 32.5, 118.9, 120.5, 125.5, 128.8, 129.5, 130.8, 132.7, 141.6, 146.1.

4,4'-((4-Chlorophenyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 7). ^1H NMR (500 MHz, DMSO-d_6): δ 2.32 (s, 6H), 4.97 (s, 1H), 7.26 (d, J = 8.2 Hz, 4H), 7.34 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 7.1 Hz, 4H), 7.71 (d, J = 7.6 Hz, 4H).

4,4'-((3-Bromophenyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 11). ^1H NMR (500 MHz, DMSO-d_6): δ 2.30 (s, 6H), 4.89 (s, 1H), 6.82–7.71 (m, 14H), 12.40 (s, 1H, OH), 13.92 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 14.3, 33.2, 117.9, 123.6, 125.4, 127.2, 127.7, 128.3, 128.7, 129.7, 132.4, 133.6, 140.4, 145.9, 154.4.

4,4'-((2-Bromophenyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 12). ^1H NMR (600 MHz, DMSO-d_6): δ 2.28 (s, 6H), 5.10 (s, 1H), 7.14 (t, J = 7.64 Hz, 1H), 7.24 (t, J = 7.24 Hz, 2H), 7.33 (t, J = 7.88 Hz, 1H), 7.43 (t, J = 7.96 Hz, 4H), 7.56–7.57 (d, J = 7.16 Hz, 1H), 7.68 (d, J = 7.92 Hz, 4H),

7.81 (d, *J* = 7.08 Hz, 1H), 12.43(s, 1H, OH), 13.72 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.0, 34.2, 120.5, 127.4, 128.3, 128.8, 130.4, 132.7, 141.0.

4,4'-((4-Fluorophenyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 13). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.31 (s, 6H), 5.34 (s, 1H), 7.19–7.38 (m, 4H), 7.40-7.45 (m, 5H), 7.68–7.70 (m, 5H), 11.44 (s, 1H, OH), 13.93 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.3, 32.4, 114.7, 117.9, 120.5, 124.8, 125.5, 128.7, 128.8, 129.0. 138.1, 146.1, 159.4.

4,4'-(*p*-Tolylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 14). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.24 (s, 3H), 2.31 (s, 6H), 4.91 (s, 1H), 7.08–7.71 (m, 14H), 12.40 (s, 1H, OH), 13.92 (s, 1H, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.5, 21.4, 33.6, 121.4, 126.4, 127.9, 129.5, 129.8, 135.7, 140.0, 147.1.

4,4'-((2,5-Dimethoxyphenyl)methylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 15). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.03 (s, 3H), 2.49 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 5.02 (s, 1H), 7.11–7.13 (m, 2H), 7.19–7.24 (m, 3H), 7.41–7.45 (m, 4H), 7.68 (d, *J* = 7.96 Hz, 1H), 7.88 (d, *J* = 7.84 Hz, 2H), 7.98 (s, 1H), 12.28 (s, 1H, OH), 13.25 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.9, 27.4, 55.0, 55.9, 112.5, 116.2, 117.9, 118.4, 120.6, 121.2, 122.3, 124.6, 125.7, 128.8, 140.9, 151.6, 154.1.

4,4'-(Naphthalen-2-ylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 16). ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.36 (s, 6H), 5.13 (s, 1H), 7.25 (d, *J* = 7.24 Hz, 2H), 7.40–7.45 (m, 7H), 7.70–7.72 (m, 5H), 7.80–7.85 (m, 3H),12.41 (s, 1H, OH), 13.88 (s, 1H, OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 12.9, 33.3, 120.5, 124.8, 125.4, 125.9, 126.4, 127.2, 127.61, 127.68, 128.8, 131.6, 132.8, 139.6, 147.6.

4,4'-((2-Furyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 18). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.21 (s, 6H), 4.87 (s, 1H), 6.14 (s, 1H), 6.48 (s, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 4H), 7.53 (s, 1H), 7.78 (d, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.2, 28.6, 106.4, 110.2, 121.6, 126.4, 129.9, 142.4, 146.9, 154.4.

4,4'-((2-Pyridyl)methylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, entry 19). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.29 (s, 6H), 5.11 (s, 1H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.41 (m, 1H), 7.48 (t, *J* = 8.0 Hz, 4H), 7.66 (d, *J* = 8.2 Hz, 5H), 8.47 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.1, 31.6, 104.5, 121.0, 123.7, 126.5, 129.1, 136.3, 137.6, 138.1, 146.5, 147.8, 148.5.

3. Results and discussion

First, we explored the optimal reaction temperature and quantity of Ph_3CCl that was required for the synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s from 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) and benzaldehyde. As shown in Table 1, the best results were obtained with 5 mol% of the catalyst at 60 °C.

Next, the solvent demands of the same reaction were examined. A mixture of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**; 2 mmol), benzaldehyde (1 mmol), and Ph_3CCl (0.05 mmol) was reacted at 60 °C in solvent (5 mL) or under solvent-free conditions. As shown in Table 2, the solvent-free method was rapid and very high-yielding, whereas significantly lower yields were obtained from reactions performed in solvent, despite longer reaction times.

Table 1
Optimization of the catalyst amount and temperature on the solvent-free reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) with benzaldehyde.

Entry	Ph_3CCl amount (mol%)	Temperature (°C)	Time (min)	Yield [a] (%)
1	2.5	60	18	88
2	5	60	12	95
3	7	60	12	95
4	5	50	20	84
5	5	65	12	95
6	2.5	65	15	91

[a] Yield of isolated product.

Table 2
Effect of solvent on the Ph_3CCl-catalyzed condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) with benzaldehyde.

Entry	Solvent	Temperature (°C)	Time (min)	Yield [a] (%)
1	—	60	12	95
2	CH_3CN	60	60	53
3	$CHCl_3$	reflux	60	46
4	THF	60	60	50
5	EtOH	60	80	63
6	EtOAc	60	80	71

[a] Yield of isolated product.

To assess the efficiency and scope of the organocatalyst, 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s (**1**) were synthesized by the condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) with different arylaldehydes under the optimized reaction conditions (Table 3). As can be

Table 3
Solvent-free synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s (**1**) from 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) and (hetero)arylaldehydes catalyzed by Ph_3CCl at 60 °C.

Entry	R	Time (min)	Yield [a] (%)	M.p. (°)	
				Found	Reported
1	C_6H_5	12	95	168–170	169–171 [30]
2	4-$NO_2C_6H_4$	6	93	228–230	225 [30]
3	3-$NO_2C_6H_4$	5	94	147–149	151–154 [30]
4	2-$NO_2C_6H_4$	9	95	221–223	221–223 [32]
5	4-CNC_6H_4	15	92	216–218	212–214 [30]
6	4-Cl-3-$NO_2C_6H_4$	6	95	235–237	237–238 [30]
7	4-ClC_6H_4	10	95	213–215	212–214 [32]
8	3-ClC_6H_4	9	92	151–153	150–152 [35]
9	2-ClC_6H_4	13	94	234–236	236–237 [32]
10	4-BrC_6H_4	9	95	181–183	183–185 [30]
11	3-BrC_6H_4	9	92	172–174	172–175 [32]
12	2-BrC_6H_5	6	91	248–250	—
13	4-FC_6H_4	10	97	175–177	182–184 [30]
14	4-MeC_6H_4	10	96	202–204	203–205 [32]
15	2,5-$(MeO)_2C_6H_4$	4	94	133–141	—
16	2-Naphthyl	22	94	203–205	204–206 [30]
17	2-Thienyl	17	88	192–194	190–192 [35]
18	2-Furyl	10	74	189–191	189–191 [35]
19	2-Pyridyl	7	86	229–231	230–232 [35]

[a] Yield of isolated product.

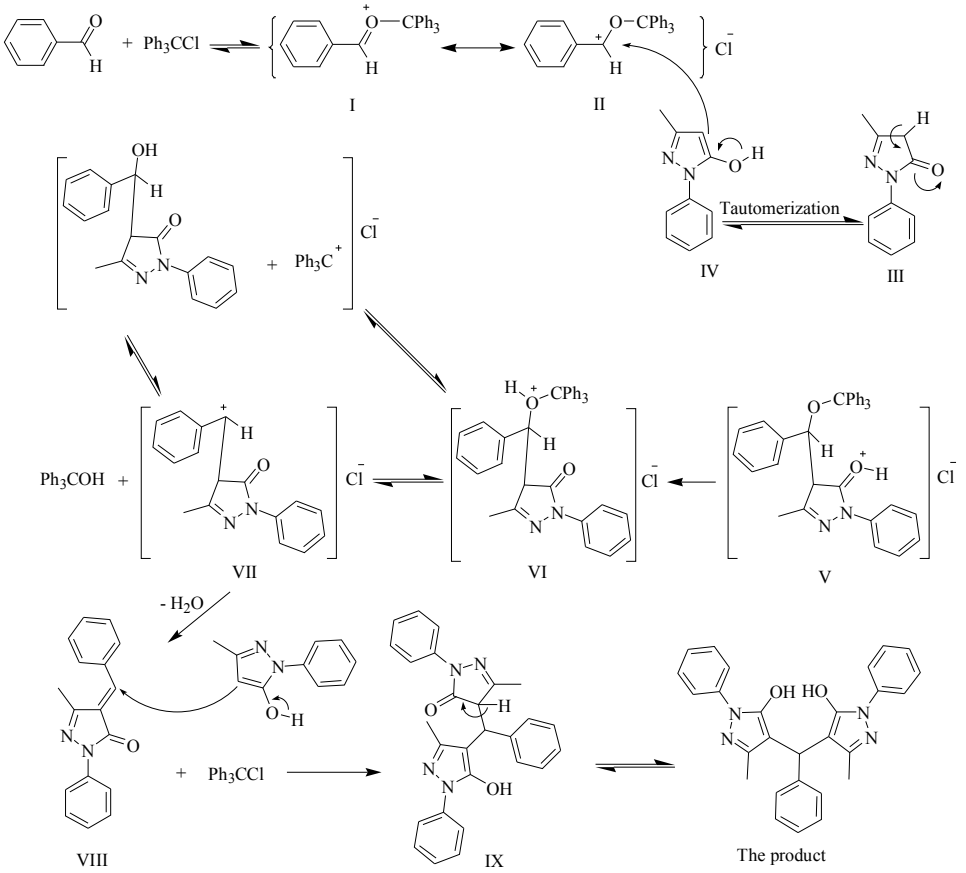
seen, the electronic character of substituents on the aromatic ring of the aldehyde had a negligible effect on the efficiency of the reaction, with all desired products being obtained in high to excellent yields in short reaction time (Table 3, entries 1–15). Moreover, Ph_3CCl successfully catalyzed the reaction when heteroaromatic aldehydes were used, affording **1x**, **1y**, and **1z**. Thus, Ph_3CCl catalysis was efficient and general.

In another study, recyclability of the catalyst was investigated. For this purpose, several reactions of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) with benzaldehyde in the presence of Ph_3CCl were performed in parallel, and the reaction mixtures were then combined and worked up as per the general method (see Experimental section). The filtrate obtained during the work-up was concentrated to dryness to afford the remaining Ph_3CCl catalyst, which was recycled in another subsequent run of the reaction. The catalytic activity of Ph_3CCl was found to be retained, within the limits of the experimental error, for three successive recycle runs.

In a plausible mechanism (Scheme 2), resonance forms **I** and **II** can first be generated from arylaldehyde and Ph_3CCl in a reversible reaction [9–15]. To confirm our proposal, benzaldehyde was treated with Ph_3CCl, and then FT-IR, ^{1}H-NMR, and UV spectra of the resulting mixture were compared with those of benzaldehyde. It was found that: (1) in the FT-IR spectrum, the stretching vibration of aldehyde carbonyl group shifts to a slightly lower frequency because of increased dipole moment character of the carbonyl functionality (IR (nujol): ν_{max} of C=O in benzaldehyde (1705 cm^{-1}) decreased to 1697 cm^{-1} in the mixture of benzaldehyde and Ph_3CCl [11–15]); (2) in the ^{1}H-NMR spectrum, the aldehyde hydrogen was deshielded, which is in agreement with the increased single-bond character of the carbonyl functional group observed in the FT-IR spectra (^{1}H-NMR (300 MHz, $CDCl_3$): δ of the aldehydic hydrogen (9.78) increased to 10.04 in the mixture [11–15]); (3) in the ^{13}C NMR spectrum, δ of the carbonyl carbon (191.8) increased to 195.2 in the reaction mixture [11]; (4) in the UV spectrum (*n*-hexane), λ_{max} of absorption of benzaldehyde and Ph_3CCl appeared at 240 and 222 nm, respectively; however, λ_{max} of the absorption of the complexes of benzaldehyde and trityl carbocation was observed at 245 nm [14,15].

These results confirmed that resonance forms **I** and **II** are present in equilibrium in the reaction medium, as first reported by Kusumoto et al. [36]. These resonance forms act as an activated aldehyde, reacting with tautomer **IV** of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**I**) providing **V**, which converts to **VI** by proton transfer. Intermediate **VI** can interconvert to **VII** by loss of Ph_3COH. **VII** and Ph_3COH then react to give Michael acceptor **VIII**, Ph_3CCl, and H_2O. **VIII** subsequently reacts with another molecule of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**2**) (as tautomer **IV**) to produce **IX**. Finally, tautomerization of **IX** gives the product **1**.

This suggested mechanism is supported by data from previous literature [9–15,28,29,36,37] and also by the fact that Ph_3CCl was quantitatively recovered, with no Ph_3COH being detectable (as confirmed by LCMS analysis of the reaction mixture and of an authentic sample of Ph_3COH).



Scheme 2. Proposed mechanism for the condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one with arylaldehydes catalyzed by Ph_3CCl.

Graphical Abstract

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In situ generation of trityl carbocation (Ph_3C^+) as a homogeneous organocatalyst for the efficient synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s

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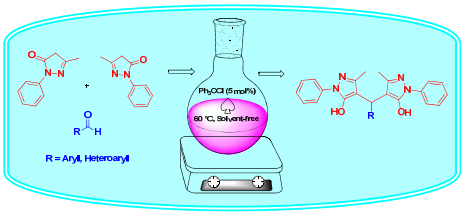
Efficient synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s from 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and arylaldehydes using Ph_3CCl under solvent-free conditions is described. A plausible reaction mechanism for the process based on the experimental data and that from similar literature studies is proposed.



4. Conclusions

We have developed a novel method for the synthesis of 4,4'-(arylmethylene)-bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol)s using commercially available Ph_3CCl as a low-cost and pH-neutral organocatalyst under solvent-free conditions. The advantages of this new method are its efficiency, simplicity, and generality with the high yields and ease of work up and purification being particularly notable.

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