Article

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Melamine Trisulfunic Acid: An Efficient and Recyclable Solid Acid Catalyst for the Synthesis of 4,4′-(Arylmethylene)-bis-(1*H*-pyrazol-5-ols)

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Melamine trisulfunic acid is employed as a recyclable catalyst for the condensation reaction of aromatic aldehydes with 3-methyl-l-phenyl-2-pyrazolin-5-one. This condensation reaction was performed in ethanol under refluxing conditions giving 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in 80-96% yields.

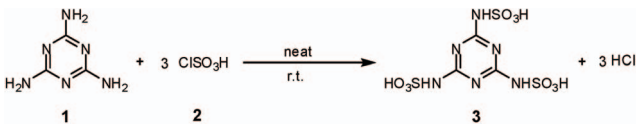
Keywords: Melamine trisulfunic acid; Aldehydes; 3-Methyl-l-phenyl-2-pyrazolin-5-one; 4,4′-(Arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols).

INTRODUCTION

Pyrazoles are an important class of bio-active drug targets in the pharmaceutical industry, as they are the core structure of numerous biologically active compounds.[1-3] For example, they exhibit antianxiety, antipyretic, analgesic, and anti-inflammatory properties. 2,4-Dihydro-3*H*-pyrazol-3-one derivatives including 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) have a broad spectrum of approved biological activity, being used as anti-inflammatory,[4] antipyretic,[5] gastric secretion stimulatory,[6] antidepressant,[7] antibacterial,[8] andantifilarial agents.[9] Moreover, the corresponding 4,4′-(arylmethylene)-bis-(1*H*-pyrazol-5-ols) are applied as fungicides,[10] pesticides,[11] insecticides,[12] and dyestuffs,[13-15] and as the chelating and extracting reagents for different metal ions.[16,17] The conventional chemical approach to 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-pyrazol-5-ols) involves the successive Knoevenagel synthesis of the corresponding arylidene pyrazolones and its base-promoted Michael reaction, and also one-pot tandem Knoevenagel-Michael reaction of arylaldehydes with 2 equiv of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one performed under a variety of reaction conditions.[18,19] The first set of procedures utilizes the catalysis of the components with piperidine in ethanolic solution.[20,21] The second set of methods involve the non-catalyzed tandem Knoevenagel-Michael reaction under neutral conditions in either ethanol[22] or benzene[23] solutions. Although it affords the corresponding 4,4′-(arylmethylene)-bis-(1*H*-pyrazol-5-ols) in reliable 70-90% yields, the reaction requires 3-12 h of initial reflux with a further 24 h under ambient temperature to go to completion.Wang et al,[24] reported its synthesis in water using sodium dodecyl sulfate as the surfactant catalyst over a one-hour period, but the process needs a temperature of 100 °C. Finally, Elinson et al. utilized electrocatalytic procedure for its synthesis.[25] Further, Perumal and coworkers reported the synthesis and antiviral activity of 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) using CAN as a catalyst,[26] also Niknam and coworker reported the synthesis of these compounds using silica-bonded S-sulfonic acid (SBSSA) and sulfuric acid ([3-(3-silicapropyl)sulfanyl]propyl) ester (SASPSPE) in ethanol under refluxing conditions.[27,28] However, most of the methods suffer from at least one limitation that may include moderate yields, long reaction times, harsh reaction conditions, or tedious workup procedures.

One of the efficient solid acid catalysts in organic transformations is melamine trisulfunic acid (MTSA),[29-34] (Scheme I) and in this article, we described a mild, efficient and environmentally friendly method for the preparation of 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives in the presence of catalytic amounts of melamine trisulfunic acid as catalyst.

Scheme I Preparation of Melamine trisulfunic acid



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EXPERIMENTAL SECTION

General

Aromatic aldehydes and 3-methyl-l-phenyl-2-pyrazolin-5-one were obtained from Fluka and were used without further purification**.** The IR spectra: Shimadzu IR-460 spectro meter; ^{1}H and ^{13}C NMR spectra: Bruker DRX-400 AVANC instrument; in DMSO-d_6 at 400 MHz and 100 MHz, respectively, δ in ppm, *J* in Hz; Elemental analyses (C, H, and N) were performed with a Heraeus CHN-O-Rapid analyzer. Melting points were determined using a Melting Point SMP1 apparatus in open capillary tubes and are uncorrected. All the products were characterized by comparing their spectral (IR, ^{1}H and ^{13}C NMR), TLC, and physical data with those reported in the literature[27,28] and obtained results showed that the analyses data were in agreement with the proposed structures.

Catalyst Preparation

A 250-mL suction flask charged with chlorosulfonic acid (5 mL, 75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water). Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately. After completion of the addition of melamine, the mixture was shaken for 30 min; meanwhile, the the residual HCl was removed by suction. Melamine trisulfonic acid (7.9 g, 87%) was obtained as a white solid, which was stored in a capped bottle.

General Procedure for the Synthesis of 4,4′-(aryl methylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols)

A mixture of aromatic aldehyde (1 mmol), 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (2 mmol), and MTSA (0.05 gr), in ethanol (10 mL) were added to a flask and heated under reflux for an appropriate time. After completion of reaction, as indicated by thin layer chromatography (TLC, silica gel SILG/UV 254 plates), the reaction mixture was wash with warm ethanol (3 × 30 mL). After cooling the crude products were precipitated. The crude products were purified by recystallization from ethanol (95%) and observed as white or yellow powders. The recovered catalyst was washed with diethyl ether, dried, and reused in subsequent runs.

4,4′-(Phenylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6a)

Yield: 0.36 g (82%), mp 169-171 °C (171-172 °C.[27]). IR (KBr): $\bar{\nu}$ = 3400 (OH), 3050 (CH arom), 2900 (CH aliph), 1598 (C=C), 1496 (C=C), 1403 (C=C), 1270 (C=N), 1020, 730, 690 cm^{-1}. ^{1}H NMR: δ = 2.34 (6H, s, 2 CH_3), 4.99 (1H, s, CH), 7.16-7.32 (7H, m, 7CH), 7.45 (4H, t, *J* = 7.6 Hz, 4 CH), 7.73 (4H, d, *J* = 8.0 Hz, 4 CH), 13.98 (2H, br.s, 2 OH) ppm. ^{13}C NMR: δ = 12.12 (CH_3), 33.60 (CH), 121.0 (C), 126.04 (CH), 126.38 (CH), 127.67 (CH), 128.61 (C), 129.40 (CH), 142.68 (C), 146.81 (C) ppm.

4,4′-[(4-Methylphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6b)

Yield: 0.38 g (85%), mp 203-205 °C (203 °C[27]). IR (KBr): $\bar{\nu}$ = 3450 (OH), 3025 (CH arom), 2850 (CH aliph), 1598 (C=C), 1499 (C=C), 1410 (C=C), 1290 (C=N), 1022, 800, 745, 690. ^{1}H NMR: δ = 2.26 (3H, s, CH_3), 2.33 (6H, s, 2 CH_3), 4.93 (1H, s, CH), 7.08 (2H, d, *J* = 8.0 Hz, 2CH), 7.15 (2H, d, *J* = 8.0 Hz, 2 CH), 7.25 (2H, t, *J* = 7.6 Hz, 2 CH), 7.45 (4H, t, *J* = 7.6 Hz, 4 CH), 7.72 (4H, d, *J* = 7.6 Hz, 4 CH), 13.93 (2H, br.s, 2 OH). ^{13}C NMR: δ = 12.10 (CH_3), 21.01 (CH_3), 33.23 (CH), 120.95 (C), 126.02 (CH), 127.56 (CH), 129.17 (C), 129.40 (CH), 135.31 (CH), 139.55 (C), 146.78 (C) ppm.

4,4′-[(4-Chlorophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6c)

Yield: 0.43 g (92%), mp 211-213 °C (210 °C[27]). IR (KBr): $\bar{\nu}$ = 3400 (OH), 3050 (CH arom), 2900 (CH aliph), 1600 (C=C), 1590 (C=C), 1578 (C=C), 1498 (C=C), 1415 (C=C), 1280 (C=N), 808, 742, 685 cm^{-1} . ^{1}H NMR: δ = 2.34 (6H, s, 2 CH_3), 4.99 (1H, s, CH), 7.24-7.29 (4H, m, 4 CH), 7.35 (2H, d, *J* = 8.4 Hz, 2 CH), 7.46 (4H, t, *J* = 7.6 Hz, 4 CH), 7.72 (4H, d, *J* = 8 Hz, 4 CH), 13.89 (2H, br.s, 2 OH) ppm. ^{13}C NMR: δ = 12.07 (CH_3), 33.02 (CH), 121.01 (C), 126.11 (CH), 128.50 (C), 129.41 (CH), 129.63 (CH), 131.06 (CH), 141.58 (C), 149.76 (C) ppm.

4,4′-[(2-Chlorophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6d)

Yield: 0.38 g (80%), mp 233-235 °C (236-237 °C[27]). IR (KBr): $\bar{\nu}$ = 3450 (OH), 3060 (CH arom), 2905 (CH aliph), 1615 (C=C), 1595 (C=C), 1555 (C=C), 1496 (C=C), 1400 (C=C), 1350, 1295 (C=N), 836, 750, 690 cm^{-1}. ^{1}H NMR: δ = 2.30 (6H, s, 2 CH_3), 5.17 (1H, s, CH), 7.22-7.34 (4H, m, 4 CH), 7.40 (1H, d, *J* = 7.82 Hz, CH), 7.44 (4H, t, *J* = 8.0 Hz, 4 CH), 7.71 (4H, d, *J* = 8.0 Hz, 4 CH), 7.81 (1H, d, *J* = 7.2 Hz, CH), 13.92 (2H, br.s, 2 OH) ppm. ^{13}C NMR: δ = 12.33 (CH_3), 32.14 (CH), 121.07 (C), 126.13 (CH), 127.4 (CH), 128.55 (C), 129.41 (CH), 129.95 (CH), 130.71 (CH), 132.4 (CH), 137.63 (CH), 139.89 (C), 146.54 (C) ppm.

4,4′-[(2,4-Dichlorophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6e)

Yield: 0.42 g (84%), mp 229-231 °C (228-230 °C[27]). IR (KBr): $\bar{\nu}$ = 3480 (OH), 3050 (CH arom), 2900 (CH aliph), 1620 (C=C), 1590 (C=C), 1550 (C=C), 1499 (C=C), 1420 (C=C), 1380, 1290 (C=N), 850, 760, 680 cm^{-1}. ^{1}H NMR: δ = 2.33 (6H, s, 2 CH_3), 5.22 (1H, s, CH), 7.11 (1H, d, *J* = 7.8 Hz, CH), 7.25 (1H, d, *J* = 7.83 Hz, CH), 7.45 (2H, t, *J* = 7.72 Hz, 2 CH), 7.58 (4H, t, *J* = 7.76 Hz, 4 CH), 7.62 (4H, d, *J* = 7.75 Hz, 4 CH), 7.68 (1H, s, CH), 13.88 (2H, br.s, 2 OH) ppm. ^{13}C NMR: δ = 12.46 (CH_3), 33.54

(CH), 122.3 (C), 122.8 (CH), 126.54 (CH), 126.8 (CH), 128.76 (C), 129.85 (CH), 130.3 (CH), 131.8 (CH), 132.7 (C), 135.7 (C), 136.2 (C), 137.5 (C), 145.2 (C) ppm.

4,4′-[(4-Nitrophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6f)

Yield: 0.46 g (96%), mp 225-227 °C (224-226 °C[27]). IR (KBr): $\bar{\nu}$ = 3420 (OH), 3060 (CH arom), 2800 (CH aliph), 1598 (C=C), 1510 (C=C), 1490 (C=C), 1419 (C=C), 1400 (C=C), 1290 (C=N), 1342, 750, 690 cm^{-1}. ^1H NMR: δ = 2.37 (6H, s, 2 CH_3), 5.15 (1H, s, CH), 7.26 (2H, t, *J* = 7.6 Hz, 2 CH), 7.46 (4H, t, *J* = 8.0 Hz, 4 CH), 7.53 (2H, d, *J* = 8.4 Hz, 2 CH), 7.72 (4H, d, *J* = 8.0 Hz, 4 CH), 8.18 (2H, d, *J* = 8.8 Hz, 2 CH), 13.88 (2H, br.s, 2 OH) ppm. ^{13}C NMR: δ = 12.06 (CH_3), 33.65 (CH), 121.07 (C), 123.82 (CH), 126.2 (CH), 129.1 (C), 129.42 (CH), 137.64 (C), 146.4 (C), 146.79 (C), 151.79 (C) ppm.

4,4′-[(3-Nitrophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6g)

Yield: 0.41 g (86%), mp 152-154 °C (149-150 °C[27]). IR (KBr): $\bar{\nu}$ = 3400 (OH), 3050 (CH arom), 2915 (CH aliph), 1610 (C=C), 1590 (C=C), 1510 (C=C), 1498 (C=C), 1420 (C=C), 1345 (C=N), 760, 725, 690, 598 cm^{-1}. ^1H NMR: δ = 2.37 (6H, s, 2 CH_3), 5.17 (1H, s, CH), 7.27 (2H, t, *J* = 7.2 Hz, 2 CH), 7.46 (4H, t, *J* = 8.0 Hz, 4 CH), 7.62 (1H, t, *J* = 8.4 Hz, CH), 7.71-7.76 (5H, m, 5 CH), 8.09 (2H, d, *J* = 6.8 Hz, 2 CH), 13.89 (2H, br.s, 2 OH) ppm. ^{13}C NMR: δ = 12.09 (CH_3), 33.31 (CH), 121.10 (C), 121.69 (CH), 122.23 (CH), 126.23 (CH), 129.45 (C), 130.18 (CH), 134.83 (CH), 145.06 (C), 146.82 (C), 148.24 (C) ppm.

4,4′-[(4-Hydroxyphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6h)

Yield: 0.38 g (84%), mp 153-155 °C (152-153 °C[27]). IR (KBr): $\bar{\nu}$ = 3480 (OH), 3050 (CH arom), 2900 (CH aliph), 1595 (C=C), 1585 (C=C), 1450 (C=C), 1360, 1280 (C=N), 750, 690, 600, 595 cm^{-1}. ^1H NMR: δ = 2.31 (6H, s, 2 CH_3), 4.86 (1H, s, CH), 6.67 (2H, d, *J* = 8.7 Hz, 2 CH), 7.06 (2H, d, *J* = 8.5 Hz, 2 CH), 7.25 (2H, t, *J* = 7.33 Hz, 2 CH), 7.45 (4H, t, *J* = 7.83 Hz, 4 CH), 7.72 (4H, d, *J* = 7.98 Hz, 4 CH), 9.16 (1H, s, OH), 12.2 (1H, br.s, OH), 13.96 (1H, br.s, OH) ppm. ^{13}C NMR: δ =12.50 (CH_3), 33.25 (CH), 115.73 (CH), 121.37 (C), 126.38 (CH), 128.96 (C), 129.77 (CH), 133.18 (CH), 147.04 (C), 156.37 (C) ppm.

4,4′-[(3-Hydroxyphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6i)

Yield: 0.40 g (88%), mp 169-170 °C (165-168 °C[27]). IR (KBr): $\bar{\nu}$ = 3460 (OH), 3050 (CH arom), 2950 (CH aliph), 1599 (C=C), 1580 (C=C), 1455 (C=C), 1369, 1250 (C=N), 790, 680, 600, 590 cm^{-1}. ^1H NMR: δ = 2.36 (6H, s, 2 CH_3), 4.91 (1H, s, CH), 6.76 (1H, d, *J* = 8.21Hz, CH), 6.91 (1H, d, *J* = 8.26 Hz, CH), 6.97 (1H, s, CH), 7.16 (1H, t, *J* = 8.0 Hz, CH), 7.48 (2H, t, *J* = 7.46 Hz, 2 CH), 7.56 (4H, t, *J* = 7.67 Hz, 4 CH), 7.62 (2H, d, *J* = 7.31 Hz, 2 CH), 9.43 (1H, s, OH), 12.5 (1H, br.s, OH), 13.88 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 13.3 (CH_3), 32.9 (CH), 112.9 (CH), 114.7 (CH), 121.3 (C), 121.6 (CH), 122.5 (CH), 126.2 (CH), 128.8 (C), 129.3 (CH), 130.0 (CH), 137.5 (C), 139.2 (C), 147.1(C), 156.7 (C) ppm.

4,4′-[(3,4-Dimethoxyphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6j)

Yield: 0.40 g (81%), mp 194-196 °C (195-197 °C[27]). IR (KBr): $\bar{\nu}$ = 3420 (OH), 3150 (CH arom), 3090 (CH arom), 2920 (CH aliph), 1590 (C=C), 1500 (C=C), 1420 (C=C), 1270 (C=N), 1120 (C-O), 745, 690 cm^{-1}. ^1H NMR: δ = 2.29 (6H, s, 2 CH_3), 3.63 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 4.86 (1H, s, CH), 6.78-6.83 (2H, m, 2 CH), 6.87 (1H, s, CH), 7.20 (2H, t, *J* = 6.8 Hz, 2 CH), 7.40 (4H, t, *J* = 7.4 Hz, 4 CH), 7.68 (4H, d, *J* = 7.8 Hz, 4 CH), 13.99 (1H, s, OH) ppm. ^{13}C NMR: δ =12.53 (CH_3), 33.82 (CH), 56.39 (OCH_3), 56.43 (OCH_3), 112.56 (CH), 112.68 (CH), 120.20 (C), 121.46 (CH), 126.44 (CH), 129.78 (C), 135.85 (CH), 138.19 (C), 147.07 (C), 148.15 (C), 149.32 (C) ppm.

4,4′-[(4-Methylthiophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6k)

Yield: 0.41 g (86%), mp 205-207 °C (201-203 °C[27]). IR (KBr): $\bar{\nu}$ = 3440 (OH), 3055 (CH arom), 2900 (CH aliph), 1590 (C=C), 1500 (C=C), 1450(C=C), 1300 (C=N), 1040, 790, 750, 680 cm^{-1}. ^1H NMR: δ = 2.52 (6H, s, 2 CH_3), 2.53 (3H, s, CH_3), 4.81 (1H, s, CH), 7.22 (2H, d, *J* = 7.92 Hz, 2 CH), 7.31 (2H, d, *J* = 7.81 Hz, 2 CH), 7.38 (2H, t, *J* = 7.1 Hz, 2 CH), 7.48 (4H, t, *J* = 7.5 Hz, 4 CH), 7.79 (4H, d, *J* = 7.72 Hz, 4 CH), 13.91 (2H, br.s, OH) ppm. ^{13}C NMR: δ = 12.62 (CH_3), 21.54 (CH_3), 34.24 (CH), 121.30 (C), 122.84 (CH), 122.09 (CH), 127.68 (CH), 128.98 (C), 129.33 (CH), 129.89 (CH), 134.39 (C), 134.85 (C), 137.54 (C), 138.65 (C), 145.84 (C) ppm.

4,4′-[(4-Cyanophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6l)

Yield: 0.43 g (93%), mp 206-208 °C (210-212 °C[27]). IR (KBr): $\bar{\nu}$ = 3400 (OH), 3050 (CH arom), 2900 (CH aliph), 2210 (CN), 1595 (C=C), 1500 (C=C), 1458 (C=C), 1410, 1280 (C=N), 808, 748, 682 cm^{-1}. ^1H NMR: δ = 2.36 (6H, s, 2 CH_3), 5.09 (1H, s, CH), 7.26 (2H, t, *J* = 7.2 Hz, 2 CH), 7.43-7.49 (6H, m, 6 CH), 7.73-7.79 (6H, m, 6 CH), 14.01 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 12.10 (CH_3), 33.81 (CH), 109.28 (C), 119.51 (C), 120.69 (C), 121.06 (CH) , 125.35 (CH), 126.12 (CH), 128.88 (C), 129.4 (CH), 132.58 (CH), 137.74 (C), 146.79 (C), 148.71(C) ppm.

4,4′-[(2-Hydroxyphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6m)

Yield: 0.36 g (80%), mp 228-230 °C (230-231 °C[28]). IR (KBr): $\bar{\nu}$ = 3400 (OH), 3050 (CH arom), 2900 (CH aliph), 1596

(C=C), 1570 (C=C), 1498 (C=C), 1450 (C=C), 1366, 1280 (C=N), 750, 687 cm^{-1}. ^1H NMR: δ = 2.32 (6H, s, 2 CH_3), 5.21 (1H, s, CH), 6.72-6.79 (2H, m, 2 CH), 6.99 (1H, t, *J* = 7.6 Hz, CH), 7.25 (2H, t, *J* = 7.2 Hz, 2 CH), 7.45 (4H, t, *J* = 7.6 Hz, 4 CH), 7.59 (1H, d, *J* = 7.6 Hz, CH), 7.72 (4H, d, *J* = 8.0 Hz, 4 CH), 9.58 (1H, br.s, OH), 12.33 (1H, br.s, OH), 14.39 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 12.24 (CH_3), 27.77 (CH), 115.29 (CH), 119.08 (C), 121.08 (CH), 125.97 (C), 127.39 (CH), 129.27 (C), 129.38 (CH), 129.69 (CH), 146.81 (C), 154.35 (C) ppm.

4,4′-[(4-Fluorophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6n)

Yield: 0.43 g (94%), mp 180-182 °C (182 °C[28]). IR (KBr): $\bar{\nu}$ = 3480 (OH), 3050 (CH arom), 2800 (CH aliph), 1600 (C=C), 1585 (C=C), 1498 (C=C), 1400 (C=C), 1370, 1318, 1219 (C=N), 1150 (C-F), 1020, 800, 790, 745, 680 cm^{-1}. ^1H NMR: δ = 2.34 (6H, s, 2 CH_3), 4.99 (1H, s, CH), 7.12 (2H, t, *J* = 8.8 Hz, 2 CH), 7.24-7.32 (4H, m, 4 CH), 7.45 (4H, t, *J* = 8.0 Hz, 4 CH), 7.73 (4H, d, *J* = 8.0 Hz, 4 CH), 13.95 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 12.09 (CH_3), 32.92 (CH), 115.11 (CH), 115.32 (CH), 121.02 (CH), 126.08 (CH), 129.4 (C), 129.47 (CH), 129.55 (C), 138.65 (C), 146.71 (C), 159.95-162.36 (C-F, $^1J_{CF}$ = 241 Hz) ppm.

4,4′-[(4-Isopropylphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6o)

Yield: 0.39 g (82%), mp 132-134 °C (132-134 °C[28]). IR (KBr): $\bar{\nu}$ = 3400 (OH), 3090 (CH arom), 2950-2850 (CH aliph), 1610 (C=C), 1598 (C=C), 1578 (C=C), 1495 (C=C), 1419, 1410, 1370, 1358, 1280 (C=N), 1020, 780, 745, 682 cm^{-1}. ^1H NMR: δ = 1.17 (6H, d, *J* = 6.8 Hz, 2 CH_3), 2.36 (6H, s, 2 CH_3), 2.83 (1H, sep, *J* = 6.8 Hz, CH), 4.93 (1H, s, CH), 7.15 (2H, d, *J* = 8.0 Hz, 2 CH), 7.19-7.27 (4H, m, 4 CH), 7.45 (4H, t, *J* = 7.6 Hz, 4 CH), 7.74 (4H, d, *J* = 8.0 Hz, 4 CH), 14.11 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 12.14 (CH_3), 24.40 (CH_3), 33.32 (CH), 33.47 (CH), 118.81 (C), 120.96 (CH), 125.98 (CH), 126.54 (CH), 127.55 (C), 129.38 (CH), 137.92 (C), 140.21 (C), 146.33 (C), 146.77 (C) ppm.

4,4′-[(4-Methoxyphenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6p)

Yield: 0.41 g (89%), mp 174-176 °C. IR (KBr): $\bar{\nu}$ = 3450 (OH), 3050 (CH arom), 2800 (CH aliph), 1605 (C=C), 1598 (C=C), 1577 (C=C), 1505 (C=C), 1490 (C=C), 1385, 1245 (C=N), 1180, 1110, 1038, 870, 812, 785, 750, 690 cm^{-1}. ^1H NMR: δ = 2.33 (6H, s, 2 CH_3), 3.71 (3H, s, OCH_3), 4.92 (1H, s, CH), 6.85 (2H, d, *J* = 8.8 Hz, 2 CH), 7.19 (2H, d, *J* = 8.4 Hz, 2 CH), 7.25 (2H, t, *J* = 7.2 Hz, 2 CH), 7.45 (4H, t, *J* = 7.6 Hz, 4 CH), 7.73 (4H, d, *J* = 8.0 Hz, 4 CH), 14.03 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 12.13 (CH_3), 32.87 (CH), 55.46 (OCH_3), 113.98 (CH), 120.94 (C), 125.97 (C), 128.65 (C), 129.38 (CH), 134.61 (CH), 137.91 (CH), 146.68 (C), 157.99 (C) ppm. Anal. Calcd for $C_{27}H_{26}N_4O_3$: C, 72.09; H, 5.62; N, 12.01 (%). Found: C, 72.03; H, 5.45; N, 12.14 (%).

4,4′-[(2-Bromophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6q)

Yield: 0.44 g (86%), mp 201-204 °C (198- 200 °C[28]). IR (KBr): $\bar{\nu}$ = 3450 (OH), 3050 (CH arom), 2900 (CH aliph), 1618 (C=C), 1596 (C=C), 1565 (C=C), 1550 (C=C), 1495 (C=C), 1395, 1365, 1310 (C=N), 1020, 900, 838, 790, 750, 690 cm^{-1}. ^1H NMR: δ = 2.31 (6H, s, 2 CH_3), 5.12 (1H, s, CH), 7.15 (1H, t, *J* = 7.2 Hz, CH), 7.6 (2H, t, *J* = 7.2 Hz, 2 CH), 7.35 (1H, t, *J* = 7.6 Hz, CH), 7.45 (4H, t, *J* = 7.6 Hz, 4 CH), 7.55 (1H, d, *J* = 8.0 Hz, CH), 7.71 (4H, d, *J* = 8.0 Hz, 4 CH), 7.83 (1H, m, CH), 12.58 (1H, br.s, OH), 13.76 (1H, s, OH) ppm. ^{13}C NMR: δ =12.55 (CH_3), 34.82 (CH), 121.03 (CH), 123.30 (CH), 126.06 (C), 127.92 (CH), 128.84 (C), 129.41 (CH), 131.01 (CH), 133.30 (CH), 141.48 (C), 146.53 (C) ppm.

4,4′-[(3-Bromophenyl)methylene)]-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (6r)

Yield: 0.45 g (88%), mp 164-166 °C. IR (KBr): $\bar{\nu}$ = 3400 (OH), 3050 (CH arom), 2950-2800 (CH aliph), 1610 (C=C), 1595 (C=C), 1578 (C=C), 1563 (C=C), 1490, 1450, 1398, 1362, 1318, 1299 (C=N), 1000, 862, 790, 768, 755, 684 cm^{-1}; ^1H NMR: δ = 2.35 (6H, s, 2 CH_3), 5.02 (1H, s, CH), 7.24-7.32 (4H, m, 4 CH), 7.39-7.48 (6H, m, 6 CH), 7.73 (4H, d, *J* = 8.4 Hz, 4CH), 14.01 (1H, br.s, OH) ppm. ^{13}C NMR: δ = 12.10 (CH_3), 33.37 (CH), 121.06 (C), 122.08 (CH), 126.13 (C), 126.96 (CH), 129.42 (C), 130.37 (CH), 130.81 (CH), 137.75 (CH), 145.67 (CH), 146.76 (C), 157.66 (C) ppm. Anal. Calcd for $C_{27}H_{23}BrN_4O_2$: C, 62.92; H, 4.50; N, 10.87 (%). Found: C, 62.64; H, 4.59; N, 10.78 (%).

RESULTS AND DISCUSSION

The reaction of aromatic aldehydes with 2 equivalents of 3-methyl-l-phenyl-2-pyrazolin-5-one in the presence of catalytic amounts of melamine trisulfunic acid in ethanol under refluxing conditions produce 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in good yields after purification (Scheme II).

Scheme II Synthesis of 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives catalyzed by MTSA

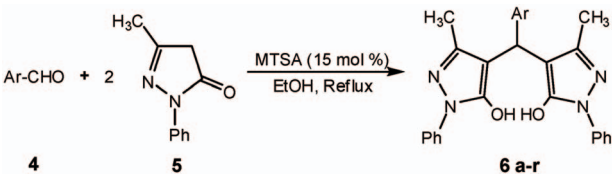

Table 1. Condensation reaction of *p*-nitrobenzaldehyde with 3-methyl-l-phenyl-2-pyrazolin-5-one in the presence of different amounts of catalyst[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	No catalyst	30 h	< 10
2	5	30	85
3	10	20	76
4	15	32	96
5	20	60	90
6	25	120	87

[a] Reaction conditions: *p*-nitrobenzaldehyde (1 mmol), 3-methyl-l-phenyl-2-pyrazolin-5-one (2 mmol), EtOH (10 mL), reflux conditions.
[b] Isolated yield.

Table 2. Condensation reaction of *p*-chlorobenzaldehyde with 3-methyl-l-phenyl-2-pyrazolin-5-one in the presence of different catalysts[a]

Entry	Catalyst	Catalyst loading (gr)	Time (min)	Yield[b] (%)[27,28]
1	MTSA	0.05	45	92
2	SBSSA	0.05	100	80
3	SBSSA	0.1	50	90
4	SASPSPE	0.1	132	85
5	Zeolite-HY	0.1	120	45
6	Zeolite-HY	0.2	120	71
7	Zeolite-HY	0.3	120	87
8	Amberlyst	0.1	120	35
9	Amberlyst	0.2	120	55
10	Amberlyst	0.3	120	73

[a] Reaction conditions: *p*-chlorobenzaldehyde (1 mmol), 3-methyl-l-phenyl-2-pyrazolin-5-one (2 mmol), EtOH (10 mL), reflux conditions.
[b] Isolated yield.

To study the effect of catalyst loading and in order to find optimum amount of the catalyst on the condensation reaction of aromatic aldehydes with 3-methyl-l-phenyl-2-pyrazolin-5-one, the reaction of *p*-nitrobenzaldehyde and 3-methyl-l-phenyl-2-pyrazolin-5-one was chosen as a model reaction and different molar ratios of catalyst was examined in the model reaction (Table 1). The obtained results clearly show that the best amount to prepare the products was achieved when 15 mol% of melamine trisulfunic acid was used , and in absence of MTSA the condensation reaction gaves very low yield after 30 h. Although 20 mol% of MTSA accomplished this condensation, however, 15 mol% of MTSA per 1mmol of aldehyde was optimum in terms of reaction time and isolated yield. Therefore, we employed the optimized conditions (0.1 $gmmol^{-1}$ of MTSA in ethanol under refluxing conditions) for the condensation

Table 3. Synthesis of 4,4'-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) derivatives catalyzed by MTSA in ethanol under reflux conditions[a]

Entry	Ar (4)	Product (6)	Time (min)	Yield[b] (%)	m.p. (°C)	Lit.m.p. (°C) [27,28]
a	C_6H_5-	6a	100	82	169-171	171-172
b	4-Me-C_6H_4-	6b	56	85	203-205	203
c	4-Cl-C_6H_4-	6c	45	92	211-213	210
d	2-Cl-C_6H_4-	6d	70	80	233-235	236-237
e	2,4-$(Cl)_2$-C_6H_3-	6e	180	84	229-231	228-230
f	4-NO_2-C_6H_4-	6f	32	96	225-227	224-226
g	3-NO_2-C_6H_4-	6g	60	86	152-154	149-150
h	4-OH-C_6H_4-	6h	80	84	153-155	152-153
i	3-OH-C_6H_4-	6i	135	88	169-170	165-168
j	3,4-$(MeO)_2$-C_6H_3-	6j	90	81	194-196	195-197
k	4-MeS-C_6H_4-	6k	35	86	205-207	201-203
l	4-CN-C_6H_4-	6l	55	93	206-208	210-212
m	2-OH-C_6H_4-	6m	110	80	228-230	230-231
n	4-F-C_6H_4-	6n	20	94	180-182	182
o	4-^{i}Pr-C_6H_4-	6o	60	82	132-134	132-134
p	4-MeO-C_6H_4-	6p	50	89	174-176	-
q	2-Br-C_6H_4-	6q	90	86	201-204	198-200
r	3-Br-C_6H_4-	6r	100	88	164-166	-

[a] Reaction conditions: aromatic aldehyde (1 mmol), 3-methyl-l-phenyl-2-pyrazolin-5-one (2 mmol), EtOH (10 mL), reflux conditions.
[b] Isolated yield.

reaction of various aryl aldehydes with 3-methyl-l-phenyl-2-pyrazolin-5-one into the corresponding 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) (Scheme II).

Herein, as sample, the results of the presented protocol in comparison with the different available solid acids such as SBSSA, amberlyst and zeolite-HY in condensation reaction of *p*-chlorobenzaldehyde with 3-methyl-l-phenyl-2-pyrazolin-5-one are shown in Table 2. The information of this table show that MTSA presented better result in comparison with the other solid acids in this condensation reaction and probably, this is due to existing of three acidulous function in the structure of MTSA.

The results of this synthetic method is presented in Table 3. As shown in this table, all aromatic aldehydes reacted with 3-methyl-l-phenyl-2-pyrazolin-5-one to afford 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) in excellent yields. On the other hand, benzaldehydes with electrondonating or electron-withdrawing groups, that is, 3,4-dimethoxybenzaldehyde **4j** or 4-nitrobenzaldehyde **4f**, were condensed into the corresponding 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) **6j** and **6f** in high yields.

The reusability of catalyst is important for the large scale operation and industrial point of view. Therefore, the possibility of recycling the catalyst was examined using the reaction of *p*-nitrobenzaldehyde and 3-methyl-l-phenyl-2-pyrazolin-5-one under the optimized conditions. Upon completion, the reaction mixture was washed with warm ethanol (3 × 30 mL). The recovered catalyst was washed with diethyl ether, dried, and reused for subsequent runs.[34] The recycled catalyst could be reused five times without any additional treatment (Fig. 1).

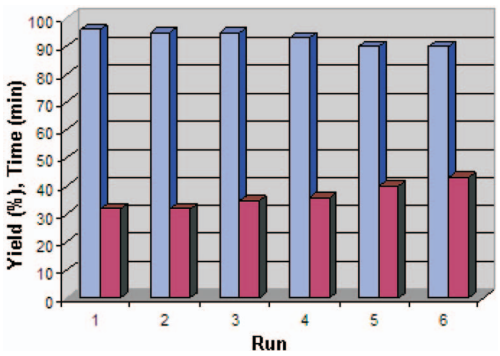

Fig. 1. Recyclability of MTSA (15 mol %, 0.05 gr) in the reaction of *p*-nitrobenzaldehyde (1 mmol) and 3-methyl-l-phenyl-2-pyrazolin-5-one (2 mmol) in EtOH under refluxing conditions. Series 1: Yield (%), Series 2: Time (min).

CONCLUSIONS

In conclusion, we have prepared some 4,4′-(arylmethylene)-bis-(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) by a tandem condensation reaction of aromatic aldehydes with 2 equiv of 3-methyl-l-phenyl-2-pyrazolin-5-one in the presence of melamine trisulfunic acid in refluxing ethanol. This catalyst synthetic method seems facile, good yields, workup procedure is easy and gives pure target compounds containing several potential centers for further modification.

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