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Glycerol assisted eco-friendly strategy for the facile synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) and 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones under catalyst-free conditions

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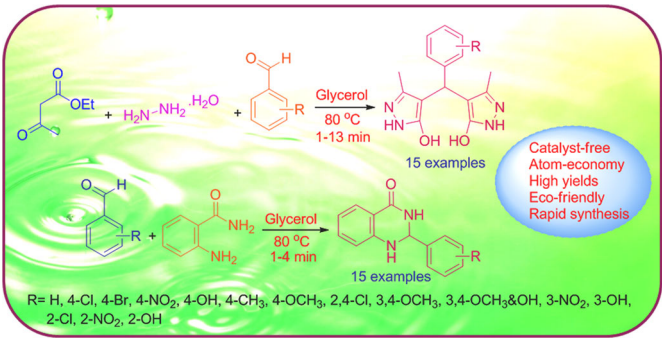
Abstract This article describes glycerol mediated eco-friendly approaches for the convenient access of structurally diverse 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) and 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one motifs under catalyst-free conditions. Prominent advantages include clean processes, atom-efficiency, simplicity of the work-up, neutral conditions, low-cost reaction medium, excellent product yield and solvent reusability, in addition to relatively shorter reaction times.

Graphical Abstract



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Keywords Glycerol · Catalyst-free · Bis(3-methyl-1*H*-pyrazol-5-ol) · 2,3-Dihydroquinazolin-4(1*H*)-one · Green synthesis

Introduction

The exploration of proficient and environmentally benevolent routes for the preparation of medicinally privileged organic molecules is a central goal of synthesis research. Generally, nitrogen containing heterocycles are omnipresent in several natural and biologically active synthetic molecules [1–3], and they have emerged as core components in drug development because N-rich heterocyclic compounds often improve dissolution and can facilitate salt formation [4]. Among the variety of nitrogen heterocyclics, pyrazole and quinazolinone compounds have received considerable interest, as they are present in natural as well as synthetic pharmacologically potent molecules [5–7]. Considering the many properties of glycerol, such as a long liquid range, unique solubility for polar organic compounds, non-flammability and direct usage as a solvent, it would fit perfectly the requirements of a green solvent [8]. Due to their unique behaviours, numerous glycerol mediated organic transformations have been reported to be successful for the synthesis of diverse heterocycles, such as hexahydro-9-aryl-xanthene-1,8-dione [8], tetrahydrobenzo-4*H*-pyran [9], benzimidazole [10], 2-arylbenzothiazole [11], triazolo[1,2-*a*]indazole-trione [12], 1*H*-tetrazole [13], 4,5-dihydropyrazoline [14] and triarylimidazole [15].

The 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) have attracted interest because they exhibit a wide range of approved biological activities, being used as anticancer [16], antipyretic [17], antidepressant [18], antiviral [19], antifungal [20], antitumor [21], anti-inflammatory agents [22] and inhibitors of mycobacterium tuberculosis [23]. Moreover, these compounds have been used as fungicides [24], pesticides and dyestuffs [25, 26] and also have been employed as the chelating and extracting reagents for different metal ions [27]. Some of the pyrazolone derivatives are applied in many commercialized drugs for brain ischemia [28] and myocardial ischemia [29]. Furthermore, a number of pyrazoles are used as intermediates in organic synthesis [30] and as bis-Schiff bases in complex chemistry [31].

Similarly, 2,3-dihydroquinazolin-4(1*H*)-ones are also being offered as effective antitumor [32, 33], anticancer [34], antidefibrillatory [35], antidepressant [36], analgesic [37], diuretic [38], antihistamine [39], vasodilating [40], anticonvulsant [41], antihypertensive [42], CNS stimulant [43], tranquilizer [44], antianxietic [45], antiparkinsonism [46] and bronchodilator agents [47] and, very interestingly, they have some plant growth regulating abilities [48]. Moreover, these compounds are also used as valuable synthons for the preparation of pharmacologically potent 4(3*H*)-quinazolinone motifs by oxidation [49].

Due to the broad spectrum of applications, numerous synthetic routes have been reported for the preparation of functionalized bis-3-methyl-1*H*-pyrazol-5-ol and 2,3-dihydroquinazolin-4(1*H*)-one compounds. However, inspite of their efficiencies, many of them suffer from limitations, such as use of expensive catalysts, prolonged reaction times, low yields and tedious operational procedures. Therefore, finding an

efficient, high yielding and greener methodology for the synthesis of these derivatives has attracted a great deal of attention. In continuation of our current research devoted to the development of greener routes for the synthesis of heterocyclic compounds [50–54], we wish to report herein the synthesis of potent N-rich molecules in glycerol as an effective reaction medium. To the best of our knowledge, this is the first report dealing with the glycerol assisted preparation of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) and 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones at benign conditions without the aid of any other catalysts.

Experimental

Reagents and equipments

A variety of substituted aromatic aldehydes, ethyl acetoacetate, hydrazine hydrate, anthranilamide, cyclic ketones and solvents were purchased from commercial sources (Sigma-Aldrich) and were used as received. Reactions were monitored by TLC using silica gel 60 F_{254} aluminium sheets with ethyl acetate/hexanes as the eluting medium. Melting points were determined with an electrothermal apparatus by the open capillary method and are uncorrected. IR spectra were recorded on a Bruker FT-IR27 spectrophotometer using KBr optics. NMR spectra were recorded on a BRUKER DRX-400 MHz spectrometer in DMSO-d_6 and δ values are expressed in ppm using TMS as an internal standard.

Typical procedure for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols)

In a 25 ml RB flask containing glycerol (1.0 ml), a mixture of ethyl acetoacetate (4.0 mmol) and hydrazine hydrate (4.0 mmol) was added and stirred at room temperature for about 2 min. To the solid obtained, aromatic aldehyde (2.0 mmol) was added and then the resulting mixture was stirred at 80 °C for the time specified in Table 3. After completion of the reaction (as evidenced by TLC), the solid obtained was treated with de-ionized water, well-stirred for a few minutes and filtered. The solid product was washed with water and then recrystallized from ethanol to afford a corresponding 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) in excellent purity for spectroscopic measurements. The glycerol present in the filtrate was extracted with diethyl ether (2 × 5 ml) to remove any organic compounds dissolved in the aqueous phase. The combined aqueous layer was evaporated under reduced pressure at 100 °C to afford a pure glycerol which was successfully reused for the next run with negligible loss in the product yields under similar reaction conditions.

Spectral data for selected compounds

4,4′-((4-Chlorophenyl)methylene)bis(3-methyl-1H-pyrazol-5-ol) (**4b**) White solid, mp 210–212 °C; IR (KBr) (υ_{max}/cm^{-1}): 3670, 3515, 3435, 2753, 1602, 1489, 1090,

852, 606; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.09 (s, 6H, 2CH_3), 3.37 (2OH exchanged with water of DMSO-d_6), 4.83 (s, 1H, CH), 7.13 (d, 2H, ArH, J = 8.0 Hz), 7.27 (d, 2H, ArH, J = 8.0 Hz), 11.33 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.3, 32.2, 103.8, 127.5, 129.3, 130.0, 139.6, 142.3, 160.9.

4,4′-((4-Bromophenyl)methylene)bis(3-methyl-1H-pyrazol-5-ol) (**4c**) Light orange solid, mp 216–218 °C; IR (KBr) (υ_{max}/cm^{-1}): 3742, 3105, 2945, 1600, 1530, 1209, 1004, 844, 604; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.07 (s, 6H, 2CH_3), 3.41 (2OH exchanged with water of DMSO-d_6), 4.79 (s, 1H, CH), 7.05 (d, 2H, ArH, J = 8.0 Hz), 7.38 (d, 2H, ArH, J = 8.4 Hz), 11.33 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.3, 18.5, 32.2, 56.0, 103.7, 118.4, 129.7, 130.4, 131.9, 139.6, 142.7, 160.9.

4,4′-((4-Nitrophenyl)methylene)bis(3-methyl-1H-pyrazol-5-ol) (**4d**) Yellow solid, mp 272–274 °C; IR (KBr) (υ_{max}/cm^{-1}): 3691, 3559, 3309, 2967, 1612, 1511, 1381, 834, 612; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.08 (s, 6H, 2CH_3), 3.39 (2OH exchanged with water of DMSO-d_6), 4.97 (s, 1H, CH), 7.36 (d, 2H, ArH, J = 8.4 Hz), 8.10 (d, 2H, ArH, J = 8.0 Hz), 11.36 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.3, 32.6, 103.6, 127.3, 129.3, 130.2, 139.6, 142.7, 160.6.

4,4′-((4-Hydroxyphenyl)methylene)bis(3-methyl-1H-pyrazol-5-ol) (**4e**) White solid, mp 260–262 °C; IR (KBr) (υ_{max}/cm^{-1}): 3267, 2937, 2714, 1561, 1464, 1233, 1116, 845, 659; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.06 (s, 6H, 2CH_3), 3.17 (2OH exchanged with water of DMSO-d_6), 3.68 (s, 3H, OCH_3), 4.71 (s, 1H, CH), 6.58 (d, 2H, ArH, J = 8.4 Hz), 6.90 (d, 2H, ArH, J = 8.0 Hz), 9.06 (s, IH, OH), 11.3 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.3, 31.9, 114.0, 114.4, 128.2, 133.4, 155.0.

4,4′-(p-Tolylmethylene)bis(3-methyl-1H-pyrazol-5-ol) (**4f**) White solid, mp 192–194 °C; IR (KBr) (υ_{max}/cm^{-1}): 3563, 3297, 2919, 1607, 1513, 1380, 1213, 925, 834, 612; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.08 (s, 6H, 2CH_3), 2.24 (s, 3H, CH_3), 3.36 (2OH exchanged with water of DMSO-d_6), 4.79 (s, 1H, CH), 7.02 (s, 4H, ArH), 10.7 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.4, 20.5, 32.4, 48.6, 104.4, 127.4, 128.3, 134.2, 139.7, 140.2, 161.1.

4,4′-((4-Methoxyphenyl)methylene)bis(3-methyl-1H-pyrazol-5-ol) (**4g**) Light orange solid, mp 200–202 °C; IR (KBr) (υ_{max}/cm^{-1}): 3778, 2732, 1599, 1508, 1452, 1248, 1034, 840, 747, 604; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.06 (s, 6H, 2CH_3), 3.43 (2OH exchanged with water of DMSO-d_6), 3.68 (s, 3H, OCH_3), 4.77 (s, 1H, CH), 6.76 (d, 2H, ArH, J = 8.4 Hz), 7.02 (d, 2H, ArH, J = 8.4 Hz), 11.31 (brs, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 10.3, 31.9, 54.9, 104.5, 113.1, 128.3, 135.2, 139.6, 157.1, 161.0.

Typical procedure for the synthesis of 2-aryl-2,3-dihydro-4(1*H*)-quinazolinone derivatives

A mixture of aromatic aldehyde or cyclic ketone (2.0 mmol) and anthranilamide (2.0 mmol) was added to a 25 ml RB flask containing 1.0 ml of glycerol. The resulting mixture was stirred at 80 °C for the time specified in Tables 6 and 7. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and treated with de-ionized water (10 ml), well-stirred for a few minutes, and the generated solid was filtered off. The crude products were recrystallized from ethanol. The glycerol present in the filtrate was extracted with diethyl ether (2 × 5 ml) to remove any organic compounds dissolved in the aqueous phase. The combined aqueous layer was evaporated under reduced pressure at 100 °C to afford a pure glycerol which was successfully reused for the next run with negligible loss in the product yields under similar reaction conditions.

Spectral data for selected compounds

2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one (**6b**) Colourless crystals; mp 202–204 °C; IR (KBr) (υ_{max}/cm^{-1}): 3306, 3188, 3063, 2936, 1659, 1609, 1486, 1384, 1091; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 5.77 (s, 1H, CH), 6.66 (t, 2H, ArH, $J = 7.6$ Hz), 6.74 (d, 2H, ArH, $J = 8.0$ Hz), 7.14 (s, 1H, NH), 7.23 (d, 1H, ArH, $J = 7.2$ Hz), 7.44 (2d, 4H, ArH, $J = 8.4$ Hz), 7.60 (d, 1H, ArH, $J = 7.6$ Hz), 8.33 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 65.7, 114.4, 114.9, 117.2, 127.3, 128.2, 128.7, 132.9, 133.3, 140.6, 147.6, 163.4.

2-(4-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one (**6d**) Yellow crystals; mp 200–202 °C; IR (KBr) (υ_{max}/cm^{-1}): 3304, 3189, 3061, 2934, 1659, 1608, 1484, 1383, 1069; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 5.94 (s, 1H, CH), 6.67 (t, 1H, ArH, $J = 7.6$ Hz), 6.78 (d, 1H, ArH, $J = 8.0$ Hz), 7.24 (t, 1H, ArH, $J = 7.2$ Hz), 7.33 (s, 1H, NH), 7.62 (d, 1H, ArH, $J = 7.2$ Hz), 7.75 (2d, 2H, ArH, $J = 8.4$ Hz), 8.24 (d, 2H, ArH, $J = 8.8$ Hz), 8.54 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 65.3, 114.5, 114.9, 117.4, 123.5, 127.4, 128.0, 133.5, 147.2, 147.4, 149.2, 163.3.

2-(4-Hydroxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**6e**) Colourless crystals; mp 272–274 °C; IR (KBr) (υ_{max}/cm^{-1}): 3311, 3194, 3060, 2937, 1663, 1609, 1438, 1385, 1157; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 5.67 (s, 1H, CH), 6.66 (t, 1H, ArH, $J = 7.2$ Hz), 6.74 (m, 3H, ArH, $J = 8.4$ Hz), 6.95 (s, 1H, NH), 7.22 (t, 1H, ArH, $J = 7.2$ Hz), 7.31 (d, 2H, ArH, $J = 8.8$ Hz), 7.64 (d, 1H, ArH, $J = 8.0$ Hz), 8.12 (s, 1H, NH), 9.52 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 66.7, 114.4, 114.9, 117.0, 127.3, 128.3, 131.6, 133.2, 148.1, 157.7, 163.8.

2-(3,4-Dimethoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**6i**) Colourless crystals; mp 212–214 °C; IR (KBr) (υ_{max}/cm^{-1}): 3309, 3195, 3065, 2939, 1668, 1611, 1437, 1386, 1099; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.34 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 5.69 (s, 1H, CH), 6.65–7.0 (m, 5H, ArH, $J = 7.6$ Hz), 7.12 (s, 1H, NH), 7.22 (t, 1H, ArH, $J = 8.0$ Hz), 7.60 (d, 1H, ArH, $J = 7.6$ Hz), 8.16 (s,

1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 55.2, 55.9, 66.4, 111.4, 114.6, 114.2, 115.4, 117.6, 119.3, 127.4, 132.5, 133.6, 147.2, 147.9, 148.6, 163.2.

2-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydroquinazolin-4(1H)-one (**6j**) White solid; mp 222–224 °C; IR (KBr) (υ_{max}/cm^{-1}): 3309, 3195, 3065, 2939, 1668, 1611, 1437, 1386, 1099; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.77 (s, 3H, OCH_3), 5.66 (s, 1H, CH), 6.66–6.95 (m, 5H, ArH, $J = 7.2$ Hz), 7.10 (s, 1H, NH), 7.23 (t, 1H, ArH, $J = 7.2$ Hz), 7.61 (d, 1H, ArH, $J = 7.2$ Hz), 8.11 (s, 1H, NH), 9.07 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 55.6, 66.8, 111.1, 114.4, 114.9, 115.0, 117.0, 119.6, 127.3, 131.9, 133.1, 146.9, 147.4, 148.1, 163.7.

1′H-Spiro[cyclohexane-1,2′-quinazolin]-4(3′H)-one (**8b**) Colourless crystals; mp 220–222 °C; IR (KBr) (υ_{max}/cm^{-1}): 3364, 3269, 3173, 3029, 2929, 1644, 1487, 1380, 1093; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.23 (m, 2H, CH_2), 1.61 (m, 8H, CH_2) 6.60 (t, 1H, ArH), 6.63 (s, 1H, NH), 6.80 (d, 1H, ArH, $J = 8.0$ Hz), 7.18 (t, 1H, ArH, $J = 6.8$ Hz), 7.57 (d, 1H, ArH, $J = 7.2$ Hz), 7.95 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.8, 24.6, 37.1, 67.8, 114.4, 114.5, 116.4, 127.1, 133.1, 146.7, 163.2.

1′H-Spiro[cyclopentane-1,2′-quinazolin]-4(3′H)-one (**8c**) Colourless crystals; mp 258–260 °C; IR (KBr) (υ_{max}/cm^{-1}): 3289, 3165, 3010, 2940, 1640, 1484, 1384, 1144; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.65 (m, 4H, CH_2, $J = 3.6$ Hz), 1.77 (t, 4H, CH_2, $J = 5.2$ Hz) 6.60 (t, 1H, ArH, $J = 7.2$ Hz), 6.68 (d, 1H, ArH, $J = 8.0$ Hz), 6.73 (s, 1H, NH), 7.18 (t, 1H, ArH, $J = 7.2$ Hz), 7.56 (d, 1H, ArH, $J = 6.8$ Hz), 8.09 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.9, 77.0, 114.3, 114.5, 116.5, 127.2, 132.9, 147.4, 163.4.

Results and discussion

To test our hypothesis, we began by examining the pseudo five-component reaction of ethyl acetoacetate (**1**), hydrazine hydrate (**2**) and benzaldehyde (**3a**) as a model for the synthesis of 4,4′-(phenylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) (**4a**) in neat conditions at room temperature. The reaction under neat conditions resulted in the formation of **4a** with a poor yield (27 %) even after 90 min.

Then, we studied the same reaction in different polar solvents such as ethanol, methanol, acetonitrile and water, which also provided lower yields of product **4a**, whereas glycerol and PEG-400 on the model reaction resulted in much better yields (59 and 51 % respectively) at ambient conditions. From the results outlined in Table 1, we selected glycerol as an effective promoting medium due to the increased yield in shorter reaction time for this multi-component reaction.

Next, to determine the optimal thermal conditions, we checked the above reaction at different temperatures ranging from ambient to 100 °C. It was found that 80 °C would be a suitable temperature by providing 91 % of **4a** in 3 min (Table 2). However, further elevation in the temperature did not cause any significant improvements in the yield of the product. Overall, this non-catalytic and straightforward synthetic route turned out to be more efficient for the synthesis of

Table 1 Optimization of suitable solvent

Entry	Solvent	Time (min)	Yield[b] (%)
1	–	90	27
2	EtOH	120	34
3	MeOH	120	31
4	CH_3CN	120	26
5	Water	150	29
6[a]	**Glycerol**	**75**	**59**
7[a]	PEG-400	75	51

Reaction conditions: ethyl acetoacetate (4.0 mmol), hydrazine hydrate (4.0 mmol) and benzaldehyde (2.0 mmol) in different solvents (10 ml) stirred at room temperature

The suitable conditions for the synthesis of compound **4a** was indicated by bold letters

[a] Reaction conditions: ethyl acetoacetate (4.0 mmol), hydrazine hydrate (4.0 mmol) and benzaldehyde (2.0 mmol) in solvent (1.0 ml) stirred at room temperature

[b] Isolated yields

diverse 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) in a practical manner (Scheme 1).

With these encouraging optimized results in hand, we investigated the generality and effectiveness of this protocol with a variety of aromatic aldehydes **3(b–o)**. Aldehydes bearing both electron-donating (*methyl, methoxy* or *hydroxy*) and electron-withdrawing (*nitro, chloro* or *bromo*) substituents gave the corresponding 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) in good yields within shorter reaction times (Table 3). As can be seen from the same table, we can state that the aldehydes containing *ortho* substituents also provided comparably good yields, indicating that this method is not responsive to *steric* effects.

It is worth noting that the present green procedure was very simple and found to be more efficient than conventional procedures (Table 4). After the reaction was completed, the obtained residue was treated with water and was isolated by simple filtration. All the synthesized compounds are known and were well characterized by IR, ^{1}H NMR and ^{13}C NMR spectral analyses which were compared with the literature. In the ^{1}H NMR spectrum of compound **4b**, a singlet appeared at δ 11.33 ppm corresponding to the two NH protons in addition to a couple of doublets at δ 7.27 and 7.13 ppm for the aromatic protons. The benzylic methine (–CH) proton appeared at δ 4.83 ppm and also the two methyl ($-CH_3$) protons appeared at δ 2.09 ppm as a singlet. The hydroxyl (–OH) protons are merged with the water of DMSO-d_6. In the ^{13}C NMR, a signal at δ 10.3 ppm indicates the presence of methyl carbon and a peak at δ 32.2 ppm denotes the existence of benzylic methine carbon (–CH). Meanwhile, the IR spectrum shows two dissimilar bands at 3670 and 3435 cm^{-1} corresponding to –OH and –NH stretching.

A mechanism that tentatively accounts for the synthesis of **4(a–o)** is shown in Scheme 2. Initially, the condensation of ethyl acetoacetate (**1**) with hydrazine hydrate (**2**) occurs to give the intermediate, 3-methyl-5-pyrazolone (**II**) which is converted into **III** by tautomerisation. Then, **III** attacks the carbonyl carbon of the

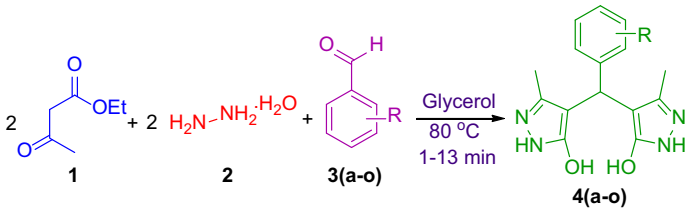
Table 2 Optimization of suitable temperature

Entry	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
1	Glycerol	RT	75	59
2	Glycerol	50	35	76
3	Glycerol	60	20	84
4	Glycerol	70	10	89
5	**Glycerol**	**80**	**3**	**91**
6	Glycerol	90	3	91
7	Glycerol	100	3	92

Reaction conditions: ethyl acetoacetate (4.0 mmol), hydrazine hydrate (4.0 mmol) and benzaldehyde (2.0 mmol) in glycerol (1.0 ml) stirred at different temperature

The suitable conditions for the synthesis of compound **4a** was indicated by bold letters

[a] Isolated yields



Scheme 1 Glycerol assisted pseudo five-component synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols)

aromatic aldehyde (**3a**) that is activated by the glycerol through the hydrogen bonding and affords the intermediate **IV**, which on removal of a molecule of water furnishes the Knoevenagel adduct **V**. Compound **V** acts as a Michael acceptor and is activated by glycerol. In this step, another molecule of 3-methyl-5-pyrazolone **II** in its tautomeric form (**III**) attacks the **V** to give intermediate **VI**. Finally, **VI** gets converted to target product molecule (**4a**) by the tautomerisation step, which is facilitated by the glycerol as an effective and greener solvent.

We were delighted by the non-catalytic results obtained in the above case and wanted to further check the optimized protocol with another two-component system through the reaction of benzaldehyde (**3a**) with anthranilamide (**5**) as starting substrates. In this case, the expected 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**6a**) was obtained in good yield (92 %) and the results were compared with that of reported literature (Table 5). Next, we probed the generality of this methodology with a variety of aromatic aldehydes **3(b-n)** as shown in Scheme 3. Apparently, the substituents in the aromatic ring do not affect the outcome significantly, furnishing the desired 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one derivatives **6(b-n)** in much shorter reaction times with excellent yields (Table 6). Similarly, the thiophene-2-carboxaldehyde as hetero aryl aldehyde (**3p**) underwent cyclization very smoothly with anthranilamide (**5**), which also provided the targeted 2-(thiophen-2-yl)-2,3-dihydro-4(1*H*)-quinazoline (**6p**) in good yield (93 %, Table 6, Entry 15).

Table 3 Non-catalytic approach for the synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ols) in glycerol

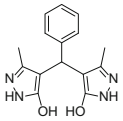
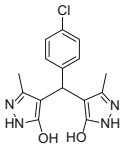
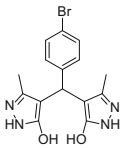
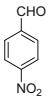
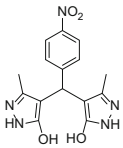
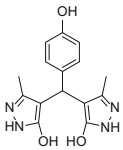
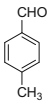
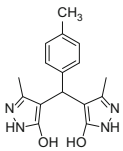
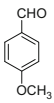
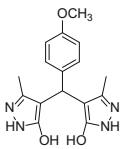
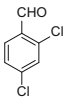
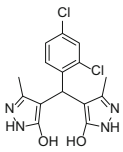
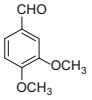
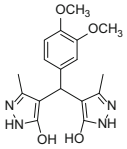
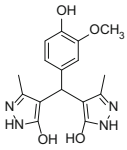
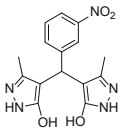
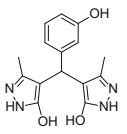
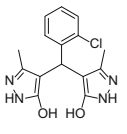
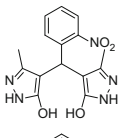
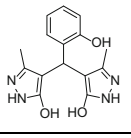
Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Mp (°C) [ref]
1			3	91	206–208 [57]
2			3	94	210–212 [57]
3			2	91	216–218 [55]
4			1	94	272–274 [57]
5			4	88	260–262 [60]
6			2	90	192–194 [55]
7			1	89	200–202 [60]
8			13	90	262–264 [57]

Table 3 continued

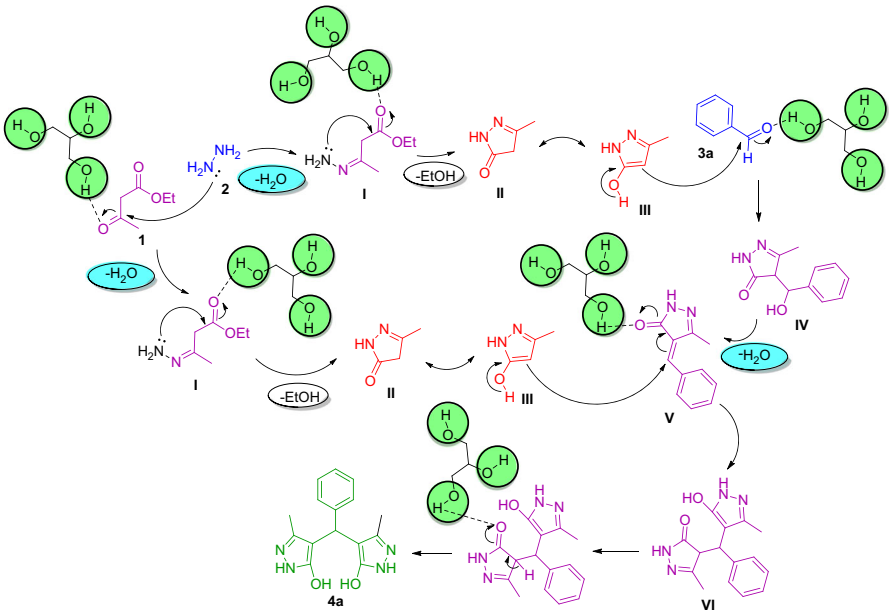
Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Mp (°C) [ref]
9			10	86	218–220
10			3	85	240–242
11			6	90	280–282 [57]
12			9	86	210–212 [57]
13			1	92	264–266 [57]
14			1	91	236–238 [60]
15			2	89	242–244 [60]

Reaction conditions: ethyl acetoacetate (4.0 mmol), hydrazine hydrate (4.0 mmol) and aromatic aldehyde (2.0 mmol) in glycerol (1.0 ml) stirred at 80 °C

[a] Isolated yields

Table 4 Comparison of efficiency of glycerol with some reported catalysts for the synthesis of **4a**

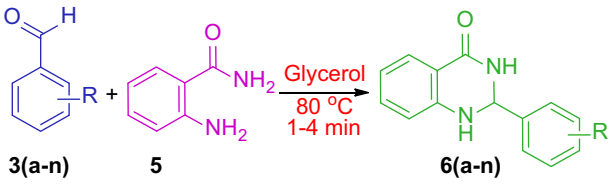
Entry	Catalyst	Condition	Time (min)	Yield (%)
1	$H_3PW_{12}O_{14}$	EtOH/Reflux	15	91 [55]
2	2-HEAP	Solvent-free, 90 °C	20	92 [56]
3	$ZnAl_2O_4$ NPs	H_2O/60 °C	23	87 [57]
4	SDS	H_2O/Reflux	60	87 [58]
5	HAP@AEPH$_2$-SO_3H	Solvent-free, 80 °C	10	98 [59]
6	–	Glycerol/80 °C	3	91 This work



Scheme 2 Plausible mechanistic approach in the formation of **4a**

Table 5 Comparison of efficiency of glycerol with some reported catalysts for the synthesis of **6a**

Entry	Catalyst	Condition	Time (min)	Yield (%)
1	Boehmite-SSA	EtOH/Reflux	50	96 [63]
2	Graphine oxide	H_2O/RT	20	94 [65]
3	$Ce(MS)_3$	H_2O/60 °C	20	93 [66]
4	Cyanuric chloride	CH_3CN/RT	10	96 [67]
5	$[Bmim]PF_6$	Solvent-free, 75 °C	35	89 [68]
6	Co-CNT	Solvent-free, MW	10	98 [62]
7	$H_3PW_{12}O_{40}$	H_2O/RT	8	94 [69]
8	*p*-SAC	H_2O/RT	18	94 [64]
9	MES	Aq.EtOH/60 °C	150	93 [70]
10	α-Chymotrypsin	EtOH/60 °C	30	91 [71]
11	–	Glycerol/80 °C	1	93 This work



Scheme 3 Glycerol assisted two-component synthesis of 2,3-dihydro-4(1*H*)-quinazolinones

Table 6 Non-catalytic approach for synthesis of 2-aryl-2,3-dihydro-4(1*H*)-quinazolinones in glycerol

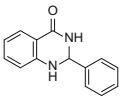
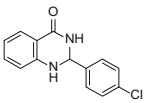
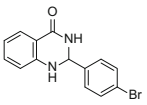
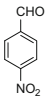
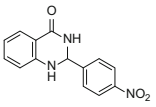
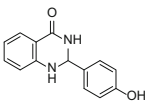
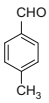
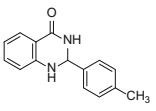
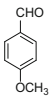
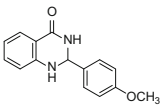
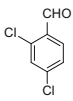
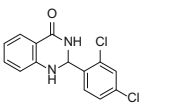
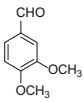
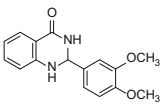
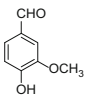
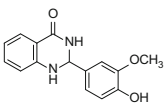
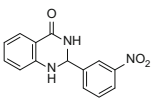
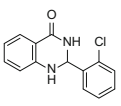
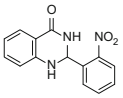
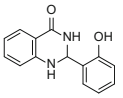
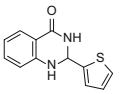
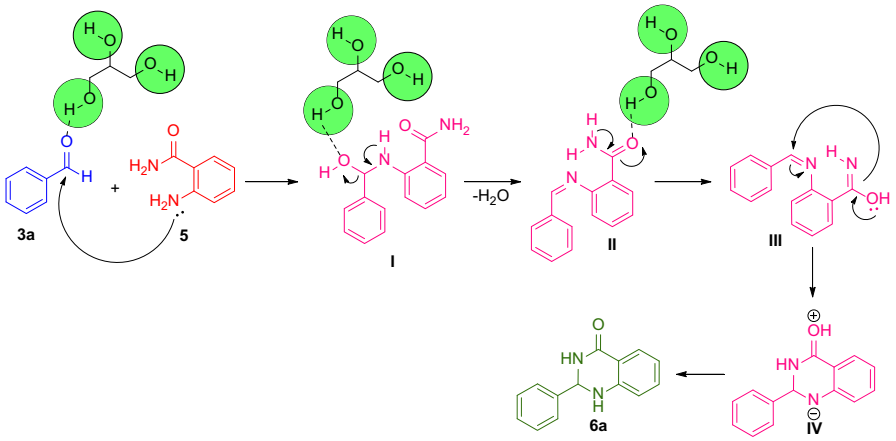
Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Mp (°C) [ref]
1			3	92	218–220 [61]
2			1	93	202–204 [61]
3			4	95	194–196 [62]
4			3	91	200–202 [61]
5			1	89	272–274 [61]
6			2	90	228–230 [62]
7			2	90	186–188 [61]
8			1	92	168–170 [62]
9			3	89	212–214 [63]
10			1	87	222–224 [61]
11			3	93	184–186 [61]
12			3	91	204–206 [61]

Table 6 continued

Entry	Aldehyde	Product	Time (min)	Yield[a] (%)	Mp (°C) [ref]
13			1	90	190–192 [62]
14			1	88	208–210 [61]
15			2	93	216–218 [64]

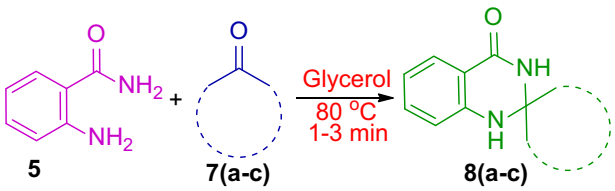
Reaction conditions: anthranilamide (2.0 mmol) and aromatic aldehyde (2.0 mmol) in glycerol (1.0 ml) stirred at 80 °C

[a] Isolated yields



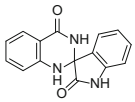
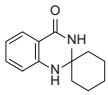
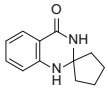
Scheme 4 Plausible mechanistic approach in the formation of **6a**

In the ^{1}H NMR spectrum of compound **6b**, the cyclic amide (–CONH) and amine (–NH) protons appeared as singlets at δ 8.33 and d 7.14 ppm respectively. The benzylic methine (–CH) proton appeared at δ 5.77 ppm as a singlet. The aromatic protons appeared in the range of δ 6.66–7.60 ppm. In ^{13}C NMR spectrum, the cyclic amide carbonyl carbon (–CONH) appeared at δ 163.4 ppm. The benzylic carbon (–CH) appeared at δ 65.7 ppm and the aromatic carbon atoms appeared in the range of δ 114.4–147.6 ppm. The IR spectrum showed the bands at 3306 and 3188 cm^{-1} corresponding to the two NH stretchings. In addition to that, the NH bending vibrations appeared at 1609 cm^{-1}. Aromatic and aliphatic C–H stretching vibrations appeared at 3063 and 2936 cm^{-1}. A stretching corresponding to the carbonyl group (–CO) appeared at 1659 cm^{-1}.



Scheme 5 Glycerol assisted synthesis 1*H*-spiro-quinazolin-4-one derivatives

Table 7 Un-catalyzed synthesis of 1*H*-spiro-quinazolin-4-ones in glycerol

Entry	Ketone	Product	Time (min)	Yield[a] (%)	Mp (°C) [ref]
1			3	90	262–264 [72]
2			1	91	220–222 [72]
3			3	88	258–260 [72]

Reaction conditions: anthranilamide (2.0 mmol), cyclic ketone (2.0 mmol) in glycerol (1.0 ml) stirred at 80 °C

[a] Isolated yields

A mechanism that accounts for the synthesis of **6(a–n)** is shown in Scheme 4. Initially, the glycerol might activate the carbonyl carbon of **3a**, which would be simultaneously attacked by the amino group of the anthranilamide (**5**) resulting in the formation of hydroxyl intermediate **I**. Next, glycerol promotes the formation of Schiff base (**II**) from **I** by the removal a water molecule. Finally, the imine undergoes intramolecular cyclization through the tautomerization of ketoamide (**II**) to enaminol (**III**) to furnish the corresponding product **6a** in quantitative yields.

We also applied our protocol to the synthesis of some spiro-quinazolinones by using various cyclic ketones **7(a–c)** in place of aromatic aldehydes as represented in Scheme 5. We were pleased to observe that the reaction of cyclic ketones with **5** under optimized thermal conditions furnished the desired 1*H*-spiro-1,2-quinazolin-4(3*H*)-ones **8(a–c)** in excellent yields in reasonably shorter times (Table 7).

Conclusion

We have established a glycerol mediated, benign, facile, mild and rapid protocol for the efficient synthesis of 4,4′-(arylmethylene)bis(3-methyl-1*H*-pyrazol-5-ol) and 2-aryl-2,3-dihydroquinazolin-4(1*H*)-one derivatives under catalyst-free conditions.

The prominent merits of this route are the availability of starting materials, broad substrate scope, much simpler work-up, economic viability and excellent yields of desired products. This new chemistry is complementary to existing synthetic procedures and suggests a powerful route for the progress of N-heterocyclic scaffolds with more sensitive functionalities.

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References

1. Y. Zhuang, X. Teng, Y. Wang, P. Liu, G. Li, W. Zhu, Org. Lett. **13**, 1130 (2011)
2. R. Bouley, M. Kumarasiri, Z. Peng, L.H. Otero, W. Song, M.A. Suckow, V.A. Schroeder, W.R. Wolter, E. Lastochkin, N.T. Antunes, H. Pi, S. Vakulenko, J.A. Hermoso, M. Chang, S. Mobashery, J. Am. Chem. Soc. **137**, 1738 (2015)
3. I. Khan, A. Ibrar, W. Ahmed, A. Saeed, Eur. J. Med. Chem. **90**, 124 (2015)
4. P.D. Leeson, B. Springthorpe, Nat. Rev. Drug Discovery **6**, 881 (2007)
5. B.N. Borse, S.R. Shukla, Y.A. Sonawane, Synth. Commun. **42**, 412 (2012)
6. J.F. Wolfe, T.L. Rathman, M.C. Sleevi, J.A. Campbell, T.D. Greenwood, J. Med. Chem. **33**, 161 (1990)
7. J.K. Padia, M. Field, J. Hinton, K. Meecham, J. Pablo, R. Pinnock, B.D. Roth, L. Singh, N.S. Chauhan, B.K. Trivedi, L. Webdale, J. Med. Chem. **41**, 1042 (1998)
8. F. He, P. Li, Y. Gu, G. Li, Green Chem. **11**, 1767 (2009)
9. H.R. Safaei, M. Shekouhy, S. Rahmanpur, A. Shirinfeshan, Green Chem. **14**, 1696 (2012)
10. C.S. Radatz, R.B. Silva, G. Perin, E.J. Lenardão, R.G. Jacob, D. Alves, Tetrahedron Lett. **52**, 4132 (2011)
11. K.U. Sadek, R.A. Mekheimed, A.M.A. Hameed, F. Elnahas, M.H. Elnagdi, Molecules **17**, 6011 (2012)
12. M. Shekouhya, A.M. Sarvestania, S. Khajeha, A.K. Nezhad, RSC Adv. **5**, 63705 (2015)
13. K.P. Nandre, J.K. Salunke, J.P. Nandre, V.S. Patil, A.U. Borse, S.V. Bhosale, Chin. Chem. Lett. **23**, 161 (2012)
14. V.B. Jagrut, D.L. Lingampalle, P.D. Netankar, W.N. Jadhav, Der Pharma Chemica **5**, 8 (2013)
15. F. Nemati, M.M. Hosseini, H.Kiani, J. Saudi Chem. Soc. (2013). doi:10.1016/j.jscs.2013.02.004
16. M.F. Brana, A. Gradillas, A.G. Ovalles, Bioorg. Med. Chem. **14**, 9 (2006)
17. N. Uramaru, H. Shigematsu, A. Toda, R. Eyanagi, S. Kitamura, S. Ohta, J. Med. Chem. **53**, 8727 (2010)
18. D.M. Bailey, P.E. Hansen, A.G. Hlavac, E.R. Baizman, J. Pearl, A.F. Defelice, M.E. Feigenson, J. Med. Chem. **28**, 256 (1985)
19. K. Sujatha, G. Shanthi, N.P. Selvam, S. Manoharan, P.T. Perumal, M. Rajendran, Bioorg. Med. Chem. Lett. **19**, 4501 (2009)
20. D. Singh, D. Singh, J. Indian Chem. Soc. **68**, 165 (1991)
21. J.J. Liu, M.Y. Zhao, X. Zhang, X. Zhao, H.L. Zhu, Mini Rev. Med. Chem. **13**, 1957 (2013)
22. S. Sugiura, S. Ohno, O. Ohtani, K. Izumi, T. Kitamikado, H. Asai, K. Kato, M. Hori, H. Fujimura, J. Med. Chem. **20**, 80 (1977)
23. D. Castagnolo, A.D. Logu, M. Radi, Bioorg. Med. Chem. **16**, 8587 (2008)
24. Y. Liu, G. He, C. Kai, Y. Li, H. Zhu, J. Heterocycl. Chem. **49**, 1370 (2012)
25. M. Londershausen, Pestic. Sci. **48**, 269 (1996)
26. R.C. Maurya, R. Verma, Indian J. Chem., Sect A **36**, 596 (1997)
27. A.D. Garnovskii, A.I. Uraev, V.I. Minkin, Arkivoc **3**, 29 (2004)
28. H. Nakagawa, R. Ohyama, A. Kimata, T. Suzuki, N. Miyata, Bioorg. Med. Chem. Lett. **16**, 5939 (2006)
29. P. Kessler, T. Aybek, G. Neidhart, S. Dogan, D.H. Bremerich, V. Lischke, C. Byhahan, J. Cardiothorac. Vasc. Anesth. **19**, 32 (2005)
30. W.S. Hamama, Synth. Commun. **31**, 133 (2001)

31. T. Ren, S. Liu, G. Li, J. Zhang, J. Guo, W. Li, L. Yang, Spectrochim. Acta, Part A **97**, 167 (2012)
32. M.J. Hour, L.J. Huang, S.C. Kuo, Y. Xia, K. Bastow, Y. Nakanishi, E. Hamel, K.H. Lee, J. Med. Chem. **43**, 4479 (2000)
33. V. Murugan, M. Kulkami, R.M. Anand, E.P. Kumar, B. Suresh, V.M. Reddy, Asian J. Chem. **18**, 900 (2006)
34. H.L. Birch, G.M. Buckley, N. Davies, H.J. Dyke, E.J. Frost, P.J. Gilbert, D.R. Hannah, A.F. Haughan, M.J. Madigan, T. Morgan, W.R. Pitt, A.J. Ratcliffe, N.C. Ray, M.D. Richard, A. Sharpe, A.J. Taylor, J.M. Whitworth, S.C. Williams, Bioorg. Med. Chem. Lett. **15**, 5335 (2005)
35. G. Bonola, R.P. Da, M.J. Magistretti, E. Massarani, I. Setnikar, J. Med. Chem. **11**, 1136 (1968)
36. Rexall Drug Co., U.S. Patent 3257397, 1966
37. K. Okumura, T. Oine, Y. Yamada, G. Hayashi, M. Nakama, J. Med. Chem. **11**, 348 (1968)
38. E. Cohen, B. Klarberg, J.R. Vaughan, J. Am. Chem. Soc. **81**, 5508 (1959)
39. V. Alagarsamy, V.R. Solomon, M. Murugan, Bioorg. Med. Chem. **15**, 4009 (2007)
40. J. Obniska, K. Shi, Acta Pol. Pharm. **63**, 101 (2006)
41. J.I. Levin, P.I. Chan, T. Bailey, A.S. Katocs, A.M. Venkatesan, Bioorg. Med. Chem. Lett. **4**, 1141 (1994)
42. Instituto De Angeli S.p.A. French Patent M 1893, 1963
43. Shulton Inc. U.S. Patent 3265697, 1966
44. N. Hirose, S. Kuriyama, S. Sohda, K. Sakaguchi, H. Yamamoto, Chem. Pharm. Bull. **21**, 1005 (1973)
45. C. Mustazza, A. Borioni, I. Sestili, M. Sbraccia, A. Rodomonte, R. Ferretti, M.R. Giudice, Chem. Pharm. Bull. **54**, 611 (2006)
46. A.N. Gangwal, U.R. Kothawade, A.D. Galande, D.S. Pharande, A.S. Dhake, Indian. J. Heterocycl. Chem. **10**, 291 (2001)
47. A.R. Raghu Ram, R.H. Bahekar, Indian J. Chem **38**(B), 434 (1999)
48. S. Schramm, E. Schmitz, E. Grundemann, J. Prakt. Chem. **326**, 279 (1984)
49. L. He, H. Li, H. Chen, X.F. Wu, RSC Adv. **4**, 12065 (2014)
50. R. Ramesh, A. Lalitha, RSC Adv. **5**, 51188 (2015)
51. R. Ramesh, A. Lalitha, Res. Chem. Intermed. **41**, 8009 (2015)
52. R. Ramesh, S. Maheswari, S. Murugesan, R. Sandhiya, A. Lalitha, Res. Chem. Intermed. **41**, 8233 (2015)
53. R. Ramesh, P. Vadivel, S. Maheswari, A. Lalitha, Res. Chem. Intermed. **42**, 7625 (2016)
54. R. Ramesh, A. Lalitha, ChemistrySelect **1**, 2085 (2016)
55. A. Vafaee, A. Davoodnia, M. Pordel, Res. Chem. Intermed. **41**, 8343 (2015)
56. Z. Zhou, Y. Zhang, Green Chem. Lett. Rev. **7**, 18 (2014)
57. J.S. Ghomi, B.K. Koopaei, H.S. Alavi, RSC Adv. **4**, 46106 (2014)
58. W. Wang, S.X. Wang, X.Y. Qin, J.T. Li, Synth. Commun. **35**, 1263 (2005)
59. M. Zarghani, B. Akhlaghinia, RSC Adv. **5**, 87769 (2015)
60. E. Soleimani, S. Ghorbani, M. Taran, A. Sarvary, C. R. Chimie **15**, 955 (2012)
61. P. Sivaguru, K. Parameswaran, M. Kiruthiga, P. Vadivel, A. Lalitha, J. Iran. Chem. Soc. **12**, 95 (2015)
62. J. Safari, S.G. Ravandi, J. Mol. Catal. A: Chem. **390**, 1 (2014)
63. A.G. Choghamarani, B. Tahmasbi, New J. Chem. **40**, 1205 (2016)
64. M. Rahman, I. Ling, N. Abdulah, R. Hashim, A. Hajra, RSC Adv. **5**, 7755 (2015)
65. N. Kausar, I. Roy, D. Chattopadhyay, A.R. Das, RSC Adv. **2016**(6), 22320 (2016)
66. M. Wang, J. Gao, Z. Song, L. Wang, J. Heterocyclic Chem. **49**, 1250 (2012)
67. M. Sharma, S. Pandey, K. Chauhan, D. Sharma, B. Kumar, M.S. Chauhan, J. Org. Chem. **77**, 929 (2012)
68. J. Chen, W. Su, H. Wu, M. Liub, C. Jin, Green Chem. **9**, 972 (2007)
69. Y.X. Zong, Y. Zhao, W.C. Luo, X.H. Yu, J.K. Wang, Y. Pan, Chin. Chem. Lett. **21**, 778 (2010)
70. V.B. Labade, P.V. Shinde, M.S. Shingare, Tetrahedron Lett. **54**, 5778 (2013)
71. S.G. Zhang, Z.B. Xie, L.S. Liu, M. Liang, Z.G. Le, Chin. Chem. Lett. (2016). doi:10.1016/j.cclet.2016.06.001
72. K. Revathy, A. Lalitha, J. Iran. Chem. Soc. **12**, 2045 (2015)