# RSC Advances

**Entry for the Table of Contents**

**Aqueous extract of *Balanites roxburghii* fruit: A green dispersant for C-C bond formation**

Madhuri Barge, and Rajashri Salunkhe*

Department of Chemistry, Shivaji University, Kolhapur, 416004, M. S., India

E-mail: rsschem1@gmail.com

*Corresponding author Tel.: +91 231 2609240; fax: +91 231 2692333.

A natural dispersant exhibiting recyclable buffer property is obtained from aqueous extract of *Balanites roxburghii* fruit and used as a highly efficient catalytic medium for C-C bond construction via Knoevenagel condensation and tandel Knoevenagel-Michael reaction.

**Graphical Abstract**

# Aqueous extract of *Balanites roxburghii* fruit: A green dispersant for C-C bond formation
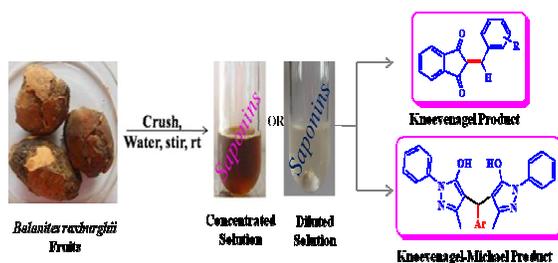
Madhuri Barge, and Rajashri Salunkhe*

Department of Chemistry, Shivaji University, Kolhapur, 416004, M. S., India

E-mail: rsschem1@gmail.com

*Corresponding author Tel.: +91 231 2609240; fax: +91 231 2692333.

## Abstract

The aqueous biosurfactant solution, a biobased green acidic catalyst for Knoevenagel condensation of 1,3-indanedione with aryl aldehydes and tandem Knoevenagel/ Michael reaction of 3-methyl-1-phenylpyrazole with aryl aldehydes has been reported for the first time. The synthetic pathway complies with several key requirements of green chemistry principles such as use of renewable feedstock, aqueous conditions, waste prevention, atom economy, biodegradable and recyclable catalyst. Thus the presented protocol offers an attractive option because of its versatility, ecological safety, environmental acceptance and sustainability.

**Keywords:** Green chemistry, *Balanites roxburghii*, Biosurfactant, 2-Arylideneindane-1,3-diones, Pyrazolones.

## Introduction

Recently energy efficient technologies eliminating waste production, toxic and hazardous solvents and reagents as well as employing renewable raw materials are experiencing a profound challenge to meet sustainability criteria.[1] In addition the

environmental risks posed by the volatile organic solvents have become a major concern. The reason is that the organic transformations employ high consumption of solvents than the reagents and employed solvents are difficult to recycle.[2] In process to be in line with the green chemistry principles, the first task is to replace the volatile organic solvents with the green one.

An ideal solvent that meets all the goals of function, performance, economy and greenness is water which has witnessed increasing popularity due to being inexpensive, readily available, non-inflammable, non-toxic, safe and environmentally benign.[3] However, organic reactions in water are often limited in scope due to the scarce solubility of the many organic compounds. A possible new way to improve the solubility of organic substrates is the use of amphiphiles such as surfactants,[4] hydrotropes[5] and phase transfer catalysts.[6]

Now a days biosynthetic processes involving biobased solvents or catalysts have received much attention as a viable alternative for the development of green methodologies for organic synthesis.[7] In this regard, biosurfactants or natural dispersants as a part of the chemical process offer an excellent alternative to volatile organic solvents in more environmental friendly technologies due to their low toxicity, easy biodegradability, ability to act as catalyst, non-inflammable and non-corrosive properties as compared to petroleum-based surfactants.[8] Also due to the high natural abundance their production is potentially less expensive.

Biosurfactants (**Surf**ace **Act**ive Ag**ents**) are microbial amphiphilic polymers obtained from plants, animals or microorganisms. It is an emergent tool with a great potential for industrial applications including the use in enhanced oil recovery, crude oil drilling, lubricants, health care and food processing industry.[9] Also full evaluations of the potential of these natural dispersants in cosmetic and soap formulations, foods and dermal or transdermal

drug delivery systems are developing at an incredible rate.[10] Notably, despite their diverse applications in industry and environmental biotechnology, their potential in accelerating the organic transformations has not been evolved till date. Therefore the aim of present work is to explore the synthetic utility of natural sugar-based surfactant in organic transformations. The catalytic medium is sourced from the aqueous extract of *Balanites roxburghii* fruit. From literature records it is well known that the *Balanites roxburghii* fruit locally known as Hingota in India is a wild plant species traditionally used as emetic, anthelmintic, anti-fungal, and purgative, in whooping cough, skin diseases and snake bite. Phytochemical study showed the presence of alkaloids, flavonoids, tannins, phenolic compounds and saponins.[11] In addition to this aqueous fruit extract exhibits acidic pH (*ca* 4.86). In view of this data and in continuation of our ongoing research in the development of green synthetic routes,[13] we thought this amazing medium may serve as be a better alternative to chemical surfactants and also to harmful corrosive acids.

**Results and discussion**

Initially, we focused our attention to prepare dispersant solution from *Balanites roxburghii* fruit. For this purpose mesocarp of a dried fruit was crushed to get powder which weighted about 3-4 g. The powder (1 g) was soaked in distilled water (100 mL) for 12 hours. The resultant material was then macerated and filtered to give wine red coloured solution.

The next task was to optimise different reaction parameters for Knoevenagel reaction. Knoevenagel products i.e. 2-arylideneindane-1,3-dione scaffolds obtained from 1,3-indanedione and aryl aldehydes are industrially important precursors because they are used as intermediates for the synthesis of different bio-active molecules.[14] As well as they own propitious pharmacological activities such as anticoagulants[15] and cytotoxics.[16] Only sporadic reports are available for the synthesis of these derivatives. A detailed literature survey about the synthesis of these derivatives revealed that most of the methods employed operated under

reflux conditions using various catalysts including acids or bases such as acetic acid, concentrated $H_2SO_4$,[15] gaseous HCl and *p*-TSA,[17] piperidine.[18] Ren *et al*. reported solvent-free route by grinding method in presence of silica gel and MgO as catalysts at ambient temperature.[19] Recently, Yang *et al*. reported catalyst-free synthesis of 2-arylideneindane-1,3-diones in refluxing water but the process is very tedious and lengthy.[20] Thus, the generality of the existing reports is somewhat visited by the severe reaction conditions and the catalysts and solvents used are not acceptable in the context of green synthesis. To defeat these circumstances we employed a simple and efficient micellar approach which led to the development of new, rapid and robust route towards focused libraries.

To optimize the reaction conditions, a round bottom flask was charged with 1,3-indanedione **1** (1 mmol) and 2-nitrobenzaldehyde **2h** (1 mmol). To this, aqueous fruit extract (5 mL) was added and stirred the mixture at room temperature. On the completion of reaction as monitored by TLC, the product separated out by simple filtration which on sufficient washing with water and ethanol afforded the corresponding product of high purity.

To check the effect of dilution on the yield of product, the model reaction was carried out with various concentrations of dispersant solution. Initially prepared wine coloured solution was diluted with distilled water till to get a clear solution. It was surprising to note that there was no effect on the yield of product even with the much diluted clear solution **(Table 1, Entry 1 and 2)**.

**Table 1.** Optimization of reaction parameters[a].

| Entry | Catalyst | Time (min) | Yield (%)[b] |
|:---:|:---:|:---:|:---:|
| 1 | Wine red coloured surfactant solution (5 mL) | 5 | 94 |
| 2 | Diluted colourless surfactant solution (5 mL) | 5 | 94 |
| 3 | SDS (10 mol %) | 18 | 86 |
| 4 | Sodium Stearate (10 mol %) | 25 | 79 |
| 5 | Diluted colourless surfactant solution (fifth run) | 5 | 94 |
| 6 | Distilled water (5 mL) | 6 h | - |

[a]Reaction Conditions: 1,3-indanedione (1 mmol), 2-nitrobenzaldehyde (1mmol), rt.

[b]Isolated Yields.

To understand this effect, pH of each solution was measured and amazingly it was observed that pH remained constant for each diluted solution which indicated that the aqueous extract of *Balanites roxburghii* fruit worked like buffer. Furthermore, addition of acid or base could not change the pH of catalytic medium confirming the buffering property of medium. Buffering action of the catalytic solution is accounted on the basis of structure of one of the saponins[12] **(Fig. 1)** present in fruit extract. Saponin is an amphiphilic molecule in which sugar is linked to sterol non-polar group. As we know sugar part acts as a buffer and thus change in concentration by dilution with water or by addition of acid or base didn't affect the catalytic property of biosurfactant solution.
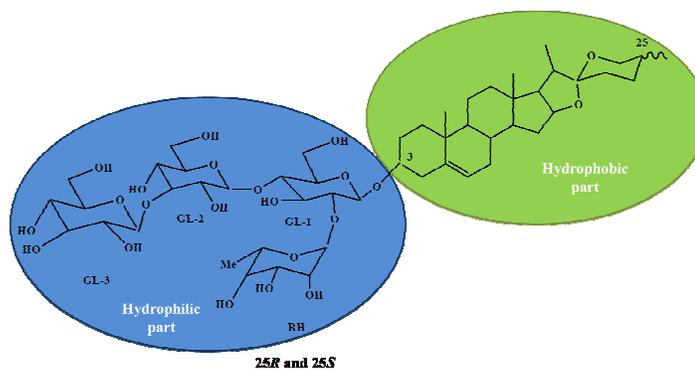


**Figure 1.** Structure of saponin.

Thus acidic nature of aqueous extract as well as surface activity due to saponins offered synergistic effect and reaction proceeded rapidly within short time. To compare the catalytic activity of natural surfactant with chemical surfactant, we also carried out the model reaction using synthetic surfactants **(Table 1, Entry 3 and 4)**. Natural surfactant was found to be excellent alternative to the chemical surfactants with respect to time as well as yield of the product. In addition biosurfactant is a recyclable buffer system which furnished the constant yield of product for several runs **(Table 1, Entry 5)** indicating its versatile reusability which is seldom possible for chemical surfactants. A controlled reaction conducted under identical conditions and devoid of biosurfactant only in water could not furnish the corresponding product, despite the prolonged reaction times indicates role of biosurfactant is decisive **(Table 1, Entry 6)**.

After the optimization of concentration, a series of structurally diverse aryl aldehydes were treated with 1,3-indanedione in diluted dispersant solution at ambient temperature **(Table 2)**. The reactions proceeded at room temperature within 5 to 20 minutes affording the desired products in excellent yields. The aryl aldehydes bearing electron-donating as well as electron-withdrawing groups underwent reactions successfully. The method is also suitable for the sterically hindered 1-naphthaldehyde **(Table 2, Entries 10)**. In addition, heteroaromatic aldehydes such as furfuraldehyde and thiophene-2-aldehyde **(Table 2, Entries 14 and 15)** reacted efficiently furnishing anticipated products in good yields. In all the cases 2-arylideneindane-1,3-diones were the sole products and no anomalies were noted. Pure products obtained by washing with water and hot ethanol were characterised by their physical constants and spectral techniques.

**Table 2.** Synthesis of 2-arylideneindane-1,3-diones catalysed by natural dispersant.
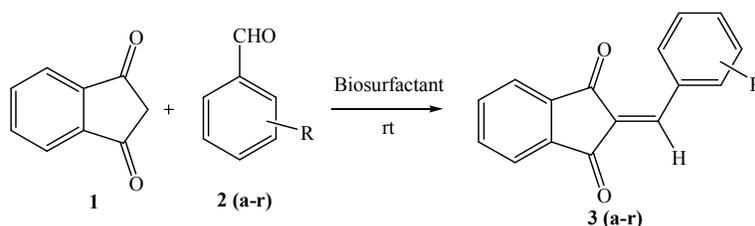


| Sr. No. | Aldehyde 2 (a-r) | Product[a] 3 (a-r) | Time (min) | Yield[b] (%) | M. P. [Lit.][c] ($^{o}$C) |
|---|---|---|---|---|---|
| 1 | Ph | 3a | 5 | 93 | 150 [152-153][15] |
| 2 | 4-Me-C$_6$H$_4$ | 3b | 15 | 92 | 150 [150-151][19] |
| 3 | 4-OMe-C$_6$H$_4$ | 3c | 20 | 89 | 155 [156-157][19] |
| 4 | 4-Cl-C$_6$H$_4$ | 3d | 5 | 92 | 180 [180-182][20] |
| 5 | 4-F-C$_6$H$_4$ | 3e | 5 | 90 | 170 [170][18] |
| 6 | 2-OH-C$_6$H$_4$ | 3f | 12 | 88 | 194 [193-195][20] |
| 7 | 4-OH-C$_6$H$_4$ | 3g | 10 | 90 | 241 [241-243][20] |
| 8 | 2-NO$_2$-C$_6$H$_4$ | 3h | 5 | 94 | 190 [192-194][20] |
| 9 | 4-NO$_2$-C$_6$H$_4$ | 3i | 17 | 94 | 232 [234-236][20] |
| 10 | 1-naphthyl | 3J | 10 | 83 | 172 [174-176][15] |
| 11 | 4-N(Me)$_2$-C$_6$H$_4$ | 3k | 20 | 88 | 178 [180][18] |
| 12 | 4-OH, 3-OMe-C$_6$H$_3$ | 3l | 15 | 93 | 218-220 |
| 13 | 3,4,5-(OMe)$_3$-C$_6$H$_2$ | 3m | 18 | 92 | 185 [185][18] |
| 14 | Furyl-2-yl | 3n | 5 | 90 | 210 [209-211][20] |
| 15 | Thiophene-2-yl | 3o | 5 | 94 | 178-180 |
| 16 | 2-CHO-C$_6$H$_4$ | 3p | 5 | 92 | 218-220 |
| 17 | 4-Br-C$_6$H$_4$ | 3q | 5 | 90 | 173-175 |
| 18 | 4-CN-C$_6$H$_4$ | 3r | 5 | 93 | 238-240 |

[a]Representative products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy as well as elemental analysis technique.
[b]Isolated yields.
[c]Literature values in parenthesis.

Inspired by these tempting results obtained for Knoevenagel condensation at ambient temperature, we extended same protocol for Knoevenagel/ Michael reaction of aryl aldehydes and 3-methyl-1-phenyl-5-pyrazolone to yield 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols). This is because pyrazolone nucleus is one of the most omnipresent heterocyclic structures found in numerous bioactive molecules with predominant properties such as antitumor,[21] selective COX-2 inhibitory[22] and cytokine inhibitors.[23] They found many

applications as extractant for metal ions and ligands.[24] 2,4-Dihydro-3*H*-pyrazol-3-one derivatives including 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) also display a wide range of pharmacological activities such as gastric secretion stimulatory,[25] antidepressant,[26] antibacterial[27] and antifilarial agents.[28] Also, they are extensively applied as fungicides, pesticides, insecticides and dyestuffs.[29]

Synthetic route to prepare 4,4'-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) generally involves the tandem Knoevenagel-Michael reaction of aryl aldehydes with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one. Several methods and catalysts have been reported in literature to synthesize these derivatives including microwave irradiation,[30] triethylbenzylammonium chloride (TEBA),[31] sodium dodecyl sulphate,[32] electrolysis,[33] cerium (IV) ammonium nitrate,[34] silica bonded S-sulfonic acid,[35] cellulose sulphuric acid,[36] silica sulfuric acid,[37] silica bonded ionic liquid[38] and 1,3-disulfonic acid imidazolium tetrachloroaluminate {[Dsim]AlCl$_4$}.[39] Although diverse approaches towards the synthesis of these derivatives have been developed, use of biosurfactant is the most elegant strategy.

The condensation reactions were carried out in 5 mL aqueous extract of fruit at at 60 °C in a preheated oil bath using a series of structurally diverse aryl aldehydes with 3-methyl-1-phenyl-5-pyrazolone **(Table 3)**. Initially Knoevenagel condensation proceeded rapidly within 2 minutes to furnish 1:1 products i.e. orange coloured arylidenepyrazolones which were converted to final white products through Michael step within 15-60 minutes. On the completion of reactions as monitored by TLC, the reaction mixtures were filtered to isolate products and purified by washing with water and hot ethanol. In IR spectrum of all the compounds characteristic broad absorption in the region 2500-2600 cm$^{-1}$ was noticed for the H-bonded enolic -OH and carbonyl absorption was absent indicating that the pyrazolonyl group in all compounds exists in enol form.[40]

**Table 3.** Tandem Knoevenagel-Michael synthesis catalysed by biosurfactant.
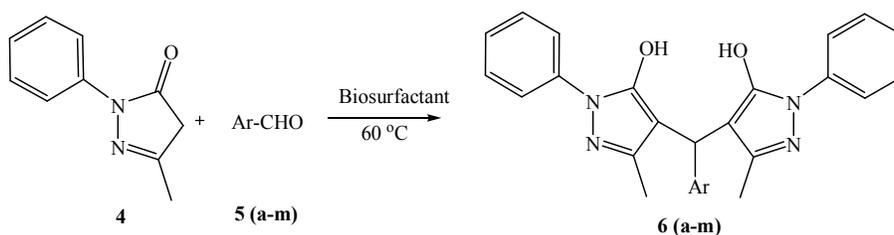


| Sr. No. | Aldehyde 5 (a-m) | Product[a] 6 (a-m) | Time (min) | Yield[b] (%) | M. P. [Lit.][c] ($^{o}$C) |
|---|---|---|---|---|---|
| 1 | Ph | 6a | 15 | 90 | 170-171 [169-171][32] |
| 2 | 4-Me-$C_6H_4$ | 6b | 20 | 93 | 200-202 [203][32] |
| 3 | 4-OMe-$C_6H_4$ | 6c | 30 | 90 | 148-150 [148][40b] |
| 4 | 2-Cl-$C_6H_4$ | 6d | 20 | 92 | 235-236 [235-237][32] |
| 5 | 4-Cl-$C_6H_4$ | 6e | 20 | 90 | 215-217 [214-217][39] |
| 6 | 4-Br-$C_6H_4$ | 6f | 25 | 88 | 215-217 [215][40b] |
| 7 | 4-F-$C_6H_4$ | 6g | 25 | 85 | 180-182 [182][40b] |
| 8 | 4-$NO_2$-$C_6H_4$ | 6h | 25 | 83 | 218-220 [218-220][32] |
| 9 | 2-$NO_2$-$C_6H_4$ | 6i | 30 | 89 | 220-222 [221-222][32] |
| 10 | 3-$NO_2$-$C_6H_4$ | 6j | 50 | 86 | 151-153 [151-153][32] |
| 11 | Thiophene-2-yl | 6k | 25 | 89 | 187-189 [189-190][39] |
| 12 | 2-CHO-$C_6H_4$ | 6l | 35 | 90 | 247-250 |
| 13 | 1-naphthyl | 6m | 60 | 87 | 208-210 |

[a]Representative products were characterized by IR, $^1$H NMR, $^{13}$C NMR spectroscopy and
  elemental analysis technique.
[b]Isolated yields.
[c]Literature values in parenthesis.

Since the blank reaction only in water could not give the corresponding products even after the long reaction time, the exceptionally higher catalytic activity of biosurfactant can be related to its ability to form micelles in water. The role of micelle to catalyse the reaction can be explained as shown in **Fig. 2 (a)**. As the impact of micellar solution, hydrophobic reactants i.e. pyrazolone **4** and aldehyde **5** get pushed away from water molecules towards the hydrophobic core of micelle leading to the effective collisions and water formed by condensations is repelled out to give corresponding Knoevenagel product **7** which was further reacted with another molecule of pyrazolone with shifting of equilibrium towards formation of desired product **6** with excellent yield. As the impact of micellar solution reaction mixture

turned turbid due to the formation of colloidal aggregates which was confirmed on the basis
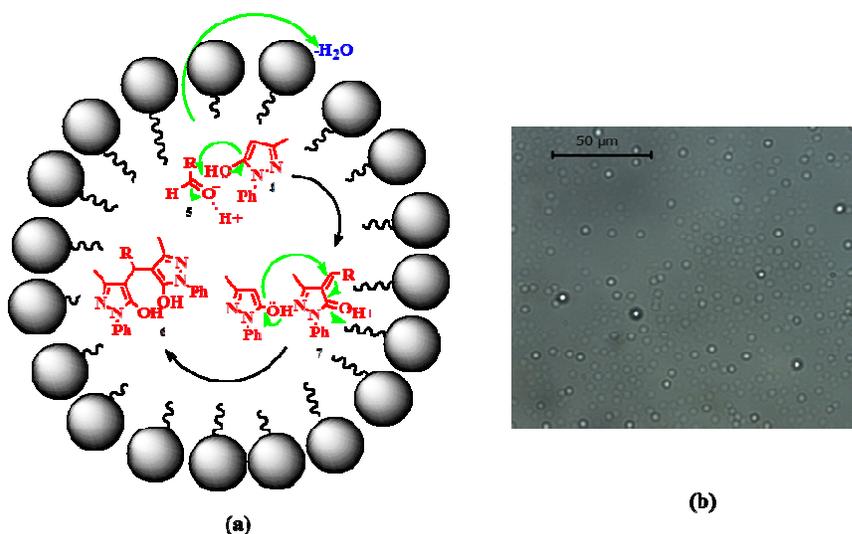
of optical microscopy **(Fig. 2 (b))**.



**Figure 2.** (a) Mechanistic picture of bispyrazolone formation. (b) Optical micrograph of

reaction mixture.

## Conclusion

In summary, we report a straightforward bioorganic approach for C-C bond

construction via Knoevenagel condensation and tandem Knoevenagel/ Michael reaction

which represents a highly efficient and environmental benign system. Apart from this

simplicity of product separation and effortless reusability of catalyst are the significant

advantages of this protocol. This new acidic dispersant should thereby provide attractive

alternative to the harmful corrosive acids. However in true sense, we think that biosurfactant

doesn't offer only a synergistic effect of acidic nature and surface activity but might be

combination of many other factors. Hence to have a good contribution in innovation of green

chemistry, we will lengthen our research to have more exposure to natural dispersant

mediated organic transformations.

**Experimental**

Solvents and reagents were commercially sourced from Sigma Aldrich and used without further purification. Melting points were determined in an open capillary and are uncorrected. Infrared spectra were measured with a Perkin Elmer FT-IR spectrophotometer. The samples were examined as KBr discs ~ 5 % *w/w*. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) spectrometer using CDCl$_3$ and DMSO-d$_6$ as solvents. Chemical shifts are expressed in δ parts per million (ppm) values with tetramethylsilane (TMS) as the internal reference and coupling constants are expressed in hertz (Hz). Mass spectra were recorded on Shimadzu QP2010 GCMS. Elemental analysis was carried out using Uro EA 3000 Vectro model. Optical micrograph was taken using ordinary light microscope (Leica DM 2000) under 100 × magnifications.

**Preparation of aqueous extract from plant material**

Dried fruits of *Balanites roxburghii* plant were purchased from local market and authenticated by the Department of Botany, Shivaji University, Kolhapur, India. The mesocarp of a fruit was crushed to get powder weighted about 3-4 g. 1 g powder was soaked in 100 mL of distilled water for 12 hours and filtered to get wine red coloured solution. This concentrated solution was diluted by distilled water till to get colourless solution. Dispersant solution was stored below 5$^o$ C and found to be stable for several months.

**General procedure for synthesis of 2-arylideneindane-1,3-diones**

A mixture of 1,3-indanedione (1 mmol) and aldehyde (1 mmol) in biosurfactant (5 mL) was stirred at ambient temperature till the completion of reaction as indicated by TLC (pet ether: ethyl acetate, 7:3). The solid products were separated by adding 50 mL water followed by simple filtration. The pure products were obtained by washing with water and hot ethanol. The identity of representative compounds was ascertained on the basis of IR, $^1$H

NMR, ^{13}C NMR spectroscopy and mass spectrometry as well as by elemental analysis. The physical and spectroscopic data are in consistent with the proposed structures and are in harmony with the literature values.

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

In a 100 mL round bottom flask 3-methyl-l-phenyl-5-pyrazolone (2 mmol) and aldehyde (1 mmol) were placed in biosurfactant solution (5 mL ) and stirred at 60 $^o$C temperature in preheated oil bath till the completion of reaction as indicated by TLC (pet ether: ethyl acetate, 8:2). The solid products were separated by simple filtration and purified by washing with water and hot ethanol. Representative compounds were confirmed by physical constants and characterized by spectral analysis.

**Spectral data of representative compounds**

2-(4-chlorobenzylidene)-2*H*-indene-1,3-dione (Table 2, Entry 3d): White solid; mp 180 $^o$C; IR (KBr): $\upsilon_{max}$/cm$^{-1}$ = 1726 and 1690 (CO), 1580, 831, 736 ; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.49-7.52 (d, 2H), 7.84-7.88 (m, 3H), 8.02-8.06 (m, 2H), 8.44-8.46 (d, 2H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ = 123.4, 123.4, 129.1, 129.5, 131.7, 135.3, 135.5, 139.5, 140.5, 143.0, 145.1, 189.1 (CO), 190.3 (CO) ppm; Elemental analysis: requires: C, 71.52; H, 3.38; O, 11.91 % (C$_{16}$H$_9$O$_2$Cl) found: C, 71.49; H, 3.40; O, 11.97 %.

2-(4-hydroxy, 3-methoxybenzylidene)-2*H*-indene-1,3-dione (Table 2, Entry 3l): Yellow solid; mp 218-220 $^o$C; IR (KBr): $\upsilon_{max}$/cm$^{-1}$ = 3453 (OH), 1715 and 1672 (CO), 998, 740 cm$^{-1}$; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.15 (s, 3H), 6.27 (s, 1H), 7.00-7.03 (d, 1H), 7.60-7.64 (dd, 1H), 7.78-7.83 (m, 3H), 7.97-8.01 (m, 2H), 9.04 (d, 1H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$): δ = 56.1, 114.5, 115.1, 122.9, 123.1, 126.1, 126.6, 132.2, 134.6, 134.8, 140.0, 142.4, 146.3,

147.7, 151.2, 189.6 (CO), 190.3 (CO) ppm; Elemental analysis: requires: C, 72.85; H, 4.32; O, 22.83 % ($C_{16}H_{10}O_3$) found: C, 72.80; H, 4.38; O, 22.84 %.

2-(thiophen-2-yl)methylene)-2*H*-indane-1,3-dione (Table 2, Entry 3o): Yellow solid; mp 178-180 °C; IR (KBr): $\upsilon_{max}$/cm$^{-1}$ = 1724 and 1684 (CO), 1585, 811, 726 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.25-7.27 (m, 1H), 7.79-7.83 (m, 1H), 7.87-7.88 (d, 1H), 7.98-8.06 (m, 3H), 8.10-8.11 (d, 1H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 123.0, 123.1, 124.9, 128.5, 134.7, 134.9, 136.0, 137.5, 137.9, 140.4, 141.3, 142.1, 188.9 (CO), 189.7 (CO) ppm; Elemental analysis: requires: C, 69.98; H, 3.36; O, 13.32 % ($C_{14}H_8O_2S$) found : C, 69.96; H, 3.40; O, 13.35 %.

2-(1,3-dioxo-1*H*-inden-2(3*H*)-ylidene)methyl)benzaldehyde (Table 2, Entry 3p): White solid; mp 218-220 °C; IR (KBr): $\upsilon_{max}$/cm$^{-1}$ = 1723, 1710 and 1691 (CO), 1589, 805, 733 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.69-7.74 (t, 1H), 7.85-7.90 (m, 2H), 7.94-7.98 (m, 1H), 8.03-8.11 (m, 3H), 8.67-8.69 (d, 1H), 9.03 (s, 1H), 10.16 (s,1H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 123.5, 123.6, 129.4, 130.6, 132.2, 133.8, 135.3, 135.4, 135.8, 136.9, 139.0, 140.2, 142.6, 144.5, 188.4 (CO), 189.1 (CO), 190.8 (CO) ppm; Mass (EI): m/z = 262; Elemental analysis: requires: C, 77.85; H, 3.84; O, 18.30 % ($C_{17}H_{10}O_3$) found: C, 77.88; H, 3.80; O, 18.31 %.

2-(4-bromobenzylidene)-2*H*-indene-1, 3-dione (Table 2, Entry 3q): Yellow solid; mp 173-175 °C; IR (KBr): $\upsilon_{max}$/cm$^{-1}$ = 1725 and 1689 (CO), 1578, 991, 736 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.66-7.88 (d, 2H), 7.82-7.88 (m, 3H), 8.02-8.05 (m, 2H), 8.35-8.38 (d, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 123.4, 123.5, 128.3, 129.6, 131.9, 132.1, 135.2, 135.3, 135.4, 140.1, 142.6, 145.1, 188.7 (CO), 189.6 (CO) ppm; Elemental analysis: require:  C, 61.37; H, 2.90; O, 10.22 % ($C_{16}H_9O_2Br$) found:  C, 61.41; H, 2.91; O, 10.19 %.

2-(4-cyanobenzylidene)-2*H*-indene-1, 3-dione (Table 2, Entry 3r): Yellow solid; mp 238-240 °C; IR (KBr): $\upsilon_{max}$/cm$^{-1}$ = 2227 (CN), 1727 and 1689 (CO), 1589, 989, 733 cm$^{-1}$; $^1$H NMR

(300 MHz, CDCl$_3$): δ = 7.80-7.92 (m, 5H), 8.05-8.08 (q, 2H), 8.51-8.54 (d, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 115.5, 117.9, 123.6, 123.7, 131.8, 132.2, 133.7, 135.6, 135.7, 136.6, 140.2, 142.6, 143.2, 188.2 (CO), 188.9 (CO) ppm; Mass (EI): m/z = 282; Elemental analysis: requires: C, 78.76; H, 3.50; O, 12.34 % (C$_{17}$H$_9$NO$_2$) found: C, 78.80; H, 3.52; O, 12.32 %.

4,4′-(phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, Entry 6a): Pale yellow solid; mp 170-172 °C; IR (KBr): υ$_{max}$/cm$^{-1}$ = 2620 (OH), 1615, 1489, 780 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 2.30 (s, 6H, CH$_3$), 4.98 (s, 1H, CH), 7.12-7.16 (m, 1H, ArH), 7.21-7.25 (m, 6H, ArH), 7.38-7.42 (t, 4H, ArH), 7.58-7.62 (d, 4H, ArH) ppm; $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ = 12.0, 33.5, 121.3, 126.4, 126.5, 127.7, 128.7, 129.5, 137.4, 142.5, 146.8 ppm; Elemental analysis requires: C, 74.29; H, 5.54; O, 7.33 % (C$_{27}$H$_{24}$N$_4$O$_2$) found: C, 74.31; H, 5.50; O, 7.38 %.

4,4'-[(4-chlorophenyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, Entry 6e): White solid; mp 215-217 °C; IR (KBr): υ$_{max}$/cm$^{-1}$ = 2553 (OH), 1598 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 2.31 (s, 6H, CH$_3$), 4.86 (s, 1H, CH), 7.18-7.21 (d, 6H, ArH), 7.34-7.39 (t, 4H, ArH), 7.69-7.02 (d, 4H, ArH), 13.69 (brs, 1H, OH) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 11.8, 3 3.1, 120.9, 125.6, 128.2, 128.8, 129.1, 131.5, 137.6, 140.7, 145.9 ppm; Elemental analysis: requires: C, 68.86; H, 4.92; O, 6.79 % (C$_{27}$H$_{23}$N$_4$O$_2$Cl) found: C, 68.80; H, 4.94; O, 6.75 %.

4,4'-[(2-thienyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, Entry 6k): Off White solid; mp 190-193 °C; IR (KBr): υ$_{max}$/cm$^{-1}$ = 2600, 1525 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 2.32 (s, 6H, CH$_3$), 5.04 (s, 1H, CH), 6.74-6.75 (d, 4H, ArH), 6.84 (s, 1H, ArH), 7.17-7.22 (t, 3H, ArH), 7.37-7.41 (t, 3H, ArH), 13.88 (brs, 1H, OH) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ =11.8, 30.7, 120.8, 124.0, 124.9, 125.7, 126.9, 128.9, 145.7, 147.6 ppm;

Elemental analysis: requires: C, 67.85; H, 5.01; O, 7.23 % ($C_{25}H_{22}N_4O_2S$) found: C, 67.80; H, 5.05; O, 7.27 %.

4,4'-[(2-formyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, Entry 6l): White solid; mp 247-250 °C; IR (KBr): $\upsilon_{max}/cm^{-1}$= 2552 (OH), 1688 (CO), 1598, $cm^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$): δ =2.34 (s, 6H, CH$_3$), 4.96 (s, 1H, CH), 7.15-7.20 (m, 2H, ArH), 7.34-7.47 (m, 4H, ArH), 7.57-7.59 (d, 2H, ArH), 7.70-7.73 (m, 6H), 9.92 (s, 1H), 13.80 (brs, 1H, OH) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 11.9, 33.5, 104.7, 120.9, 125.7, 127.8, 128.5, 128.9, 129.1, 133.8, 136.5, 137.6, 143.4, 146.1, 157.6, 192.6 ppm; Elemental analysis: requires: C, 72.40; H, 5.21; O, 10.33 % ($C_{28}H_{24}N_4O_3$) found: C, 72.44; H, 5.18; O, 10.37 %.

4,4'-[(1-naphthyl)methylene]bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (Table 3, Entry 6m): White solid; mp 208-210 °C; IR (KBr): $\upsilon_{max}/cm^{-1}$ = 2585 (OH), 1608, 1544, 1497, 1402, 784 $cm^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ = 2.32 (s, 6H, CH$_3$), 5.52 (s, 1H, CH), 7.33-7.42 (m, 17H, ArH) ppm; $^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.2, 31.4, 106.0, 120.5, 123.7, 125.4, 125.5, 126.1, 126.2, 127.4, 129.0, 129.1, 129.1, 131.2, 134.1, 137.0, 137.7, 146.1, 158.8 ppm; Elemental analysis: requires: C, 76.52; H, 5.39; O, 6.58 % ($C_{31}H_{26}N_4O_2$) found: C, 76.55; H, 5.32; O, 6.60 %.

**Acknowledgements**

**References**

1.      (a) P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford
        University Press, New York, 1998. 3; (b) J. H. Clarke, *Green Chem.*, 1999, **1**, 1.

2.      R. A. Sheldon, *Green Chem.*, 2005, **7**, 267.

3.      (a) S. Kobayashi, *Pure Appl. Chem.*, 2007, **79**, 235; (b) A. Chanda and V. V.

        Fokin, *Chem. Rev.*, 2009, **109**, 725; (c) R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159.

4.      (a) S. Kobayashi and K. Manabe, *Pure Appl. Chem*., 2000, **72**, 1373; (b) S. Kobayashi
        and K. Manabe, *Acc. Chem. Res*., 2002, **35**, 209; (c) M. Shiri and M. A. Zolfigol,
        *Tetrahedron*, 2009, **65**, 587.

5.      (a) Y. Zhu, M. Durand, V. Molinier and J. M. Aubry, *Green Chem.*, 2008, **10**, 532; (b)
        S. Kamble, A. Kumbhar, M. Barge, G. Rashinkar and R. Salunkhe, *Ultrason.
        Sonochem.*, 2012, **19**, 812.

6.      (a) S. Shirakawa, K. Liu, H. Ito and K. Maruoka, *Chem. Commun.*, 2011, **47**, 1515;
        (b)Y. Liu, B. A. Provencher, K. J. Bartelsona and Li. Deng, *Chem. Sci*., 2011, **2**,
        1301.

7.      (a) F. He, P. Li, Y. Gu and G. Li, *Green Chem*., 2009, **11**, 1768; (b) M. Li, C. Chen,
        F. He and Y. Gu, *Adv. Synth. Catal*., 2010, **352**, 519; (c) D. M. Alonso, J. Q. Bond
        and J. A. Dumesic, *Green Chem*., 2010, **12**, 1493; (d) B. Zhou, J. Yang, M. Li and
        Y. Gu, *Green Chem.*, 2011, **13**, 2204; (e) Y. Gu and F. Jérôme, *Chem. Soc.
        Rev.*, 2013, **42**, 9550; (f) S. Sun, R. Bai and Y. Gu, *Chem. Eur. J*., 2014, **20**, 549.

8.      R. S. Makkar and K. J. Rockne, *Environmental Toxicol. Chem.*, 2003, **22**, 2280.

9.  (a) J. Desai and I. Banat, *Microbiol. Mol. Rev.*, 1997, **61**, 47; (b) A. Fiechter, *Trends Biotechnol.*, 1992, **10**, 208; (c) W. Finnerty, *Curr. Opin. Biotechnol.*, 1994, **5**, 291; (d) S. J. Lin, *Chem. Technol. Biotechnol.*, 1996, **66**, 109; (e) S. Cameotra and R. Makkar, *Appl. Microbiol. Biotechnol.*, 1998, **50**, 520.

10. (a) R, Makkar and S. Cameotra, *Appl. Microbiol. Biotechnol.*, 2002, **58**, 428; (b) S. Itoh, *Fat. Sci. Technol.*, 1987, **89**, 470; (c) M. Brown, *Int. J. Cosmet. Sci.*, 1991, **13**, 61.

11. V. Singh, P. Tripathi, J. R. Patel, M. L. Kori and V. K. Dixit, *Int. J. Pharm. Clin. Res.*, 2009, **1**, 40.

12. D. C. Jain, *Phytochemistry*, 1987, **26**, 2223.

13. (a) A. Kumbhar, S. Kamble, M. Barge, G. Rashinkar and R. Salunkhe, *Tetrahedron Lett.*, 2012, **53**, 2756; (b) M. Barge, S. Kamble, A. Kumbhar, G. Rashinkar and R. Salunkhe, *Monatsh Chem.*, 2013, **144**, 1213.

14. (a) U. M. Shanmugavel, B. Kamaraj, P. Subbu, Y. Perumal and S. Dharmarajan, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 7278; (b) B. F. Dai, L. P. Song, P. Y. Wang, H. Yi, W. G. Cao, G. F. Jin, S. Z. Zhu and M. Shao, *Synlett*, 2009, **11**, 1842; (c) B. A. R. Suresh and R. Raghunathan, *Synth. Commun.*, 2009, **39**, 347.

15. M. Katarzyna, K. Piot, P. Dariusz and M. Zbigniew, *Croat. Chem. Acta*, 2009, **82**, 613.

16.  H. N. Pati, D. Umashankar, D. C. Erik, J. Balzarini and J. R. Dimmock, *Enzyme Inhibit. Med. Chem.*, 2007, **22**, 37.

17. J. L. Bullington, J. C. Cameron, J. E. Davis, J. H. Dodd, C. A. Harris, J. R. Henry, L. P. Gensey, K. C. Rupert and J. Siekierka, *J. Bioorg. Med. Chem. Lett.*, 1998, **8**, 2489.

18.    R. Karthik, S. R. Jasmin, S. Sasikumar, S. B. Kalyan, A. J. M. Christina, A. Jagan and S. K. Sundara, *Pharmacologyonline*, 2008, **2**, 176.

19.    D. Y. Wu, Z. J. Ren, W. G. Cao and W. Q. Tong, *Synth. Commun.*, 2005, **35**, 3157.

20.    P. H. Yang, Q. Z. Zhang and W. Sun, *Res. Chem. Intermed.*, 2012, **38**, 1063.

21.    (a) H. J. Park, K. Lee, S. J. Park, B. Ahn, J. C. Lee, H. Y. Cho and K. I. Lee, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3307; (b) M. P. Clark, S. K. Laughlin, M. J. Laufersweiler, R. G. Bookland, T. A. Brugel, A. Golebiowski, M. P. Sabat, J. A. Townes, J. C. VanRens, J. F. Djung, M. G. Natchus, B. De, L. C. Hsieh, S. C. Xu R. L. Walter, M. J. Mekel, S. A. Heitmeyer, K. K. Brown, K. Juergens, Y. O. Taiwo and M. J. Janusz, *J. Med. Chem*., 2004, **11**, 2724.

22.    I. H. Cho, J. Y. Noh, S. W. Park, H. C. Ryu, J. W. Lim, J. H. Kim, M. Y. Chae, D. H. Kim, S. H. Jung, H. J. Park, Y. H. Kim and I. K. Min, US Patent.2, 004, 002, 532, (2004).

23.    M. P. Clark, S. K. Laughlin, A. Golebiowski, T. A. Brugel and M. Sabat, WO Patent. 2, 005, 047, 287, (2005).

24.    (a) H. Takeishi, Y. Kitatsuji, T. Kimura, Y. Meguro, Z. Yoshida and S. Kihara, *Anal. Chim. Acta*, 2001, **431**, 69; (b) S. A. Abdel-Latif, *Synth. React. Inorg. Met. Org. Chem.*, 2001, **31**, 1355.

25.    C. E. Rosiere and M. I. Grossman, *Science*, 1951, **113**, 651.

26.    D. M. Bailey, P. E. Hansen, A. G. Hlavac, E. R. Baizman, J. Pearl, A. F. Defelice and M. E. Feigenson, *J. Med. Chem*., 1985, **28**, 256.

27.    R. N. Mahajan, F. H. Havaldar and P. S. Fernandes, *J. Indian Chem. Soc*., 1991, **68**, 245.

28.    P. M. S. Chauhan, S. Singh and R. K. Chatterjee, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem*., 1993, **32**, 858.

29.    (a) D. Singh and D. Singh, *J. Indian Chem. Soc*. 1991, **68**, 165; (b) M. Londershausen, *Pestic. Sci*. 1996, **48**, 269; (c) H. A. Lubs, The Chemistry of Synthetic Dyes and Pigments; Eds. American Chemical Society, Washington D. C., 1970; (d) A. B. Uzoukwu, *Polyhedron*. 1993, **12**, 2719; (e) R. C.; Maurya and R. Verma, *Indian J. Chem., Sect. A* 1997, **36**, 596; (f) A. D. Garnovskii, A. I. Uraev and V. I. Minkin, *Arkivoc.*, 2004, **3**, 29.

30.    Y. J. Bai, J. Lu, Z. J. Wang, H. Y. Gan and H. R. Ma, *Chin. J. Org. Chem*., 2004, **6**, 616.

31.    D. Q. Shi, J. Chen, N. Wu, Q. Y. Zhuang and X. S. Wang, *Chin. J. Org.Chem*., 2005, **4**, 405.

32.    W. Wang, S. X. Wang, X. Y. Qin and J. T. Li, *Synth. Commun*., 2005, **35**, 1263.

33.    M. N. Elinson, A. S. Dorofeev, R. F. Nasybullin and G. I. Nikishin, *Synthesis*, 2008, **12**, 1933.

34.    K. Sujatha, G. Shanthi, N. P. Selvam, S. Manoharan, P. T. Perumal and M. Rajendran, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4501.

35.    D. Niknam, D. Saberi, M. Sadegheyan and A. Deris, *Tetrahedron Lett*., 2010, **51**, 692.

36.    E. Mosaddegh, A. Hassankhani and A. Baghizadehb, *J. Chil. Chem. Soc*., 2010, **55**, 419.

37.    K. Niknam and S. Mirzaee, *Synth. Commun.*, 2011, **41**, 2403.

38.    M. Baghernejad and K. Niknam*, Int. J. Chem*., 2012, **4**, 52.

39.    A. Khazaei, M. A. Zolfigol, A. R. M. Zare, Z. Asgari, M. Shekouhy, A. Zare and A. Hasaninejad, *RSC Adv*., 2012, **2**, 8010.

40.      (a) L. Xiaoliu, D. Daming, W. Yongmei and M. Jiben, *Science In China (Series B)*, 1997, **40**, 205; (b) L. Xiao, W. Yong, T. Bing, M. Teruo and M. Ji, *J. Heterocycl. Chem.*, 1998, **35**, 129.