An environmentally benign synthesis of aryl-hydrazones with aqueous extract of *Acacia* pods as a natural surfactant type catalyst

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Abstract

An environmentally benign and clean synthesis of aryl-hydrazones by reacting variety of carbonyl compounds with thiosemicarbazide, semicarbazide, aminoguanidine, and phenyl hydrazine has been achieved using aqueous extract of *Acacia concinna* pods as a natural surfactant type catalyst. We found that the aqueous extract of *Acacia concinna* pods could be effectively used for the synthesis of aryl-hydrazones. This efficient process proceeds smoothly in aqueous medium at room temperature within a very short period of time. All the products were obtained by simple filtration. The low cost, easy availability of the catalyst and simple reaction conditions are the notable features of the present method.

Keywords: Thiosemicarbazones; semicarbazones; guanyl hydrazones; phenyl hydrazones; Acacia Concinna; aqueous medium.

Introduction

Aryl-hydrazones such as thiosemicarbazones (TSCZs), semicarbazones (SCZs), guanyl hydrazones (GHZs) and phenyl hydrazones (PHZs) are important

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classes of organic compounds which have long attracted attention, owing to their remarkable biological and pharmacological properties, such as antibacterial, antiviral, anticancer, anti-inflammatory, antineoplastic, antimalerial, analgesic, and antipyretic activity [1]. They can also be used as versatile building blocks for the synthesis of densely substituted heterocycles [2], as possible ligands for metal complexes [3]. The biological activity of TSCZs has been known for a considerable period of time, such as anticancer, antiviral drugs and antimicrobial [4-6], (Figure 1). Recently, GHZs are also the subject of intensive biological evaluation in the search of potential anticancer and antiviral drugs [7]. Moreover, some heterocyclic hydrazones have also been evaluated for anticancer, anti-HIV, antitubercular and antimicrobial activity [8].
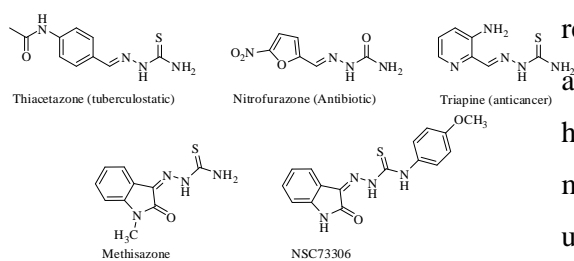

**Figure 1.** Biologically active aryl-hydrazones

Conventionally, aryl-hydrazones were prepared by the reaction of carbonyl compounds with semicarbazide, thiosemicarbazide and aminoguanidine in refluxing ethanol using acid catalysts [9]. Besides such conventional routes, the synthesis of these compounds using few chemical methods such as silica supported reagents, solvent free synthesis of heterocyclic hydrazones under microwave irradiation have also been attempted as alternative methods [10]. However, most of the methods suffer from drawbacks, which include the use of hazardous solvents, require expensive reagents, strong acid, high temperature and also the tedious work-up to afford the compounds of desired purity.

It is observed that very few simple, efficient and green methodologies have been reported for the synthesis of aryl hydrazones. Varma and Polshettiwar recently reported polystyrene sulfonic acid catalysed greener synthesis of hydrazones in aqueous medium using microwaves; elevated temperature and use of acid catalyst are the limitations of this method [11]. More recently, Leite and co-workers reported the ultrasound-accelerated synthesis of

aryl-hydrazones in aqueous medium. Use of noxious acids and requirement of huge ultrasonicator restrict the use of this method for the large scale preparations of aryl-hydrazones [12]. In an attempt to circumvent these disadvantages, in recent years, many efforts have been made to use intact plant systems as a potential biocatalysts for the synthesis of various organic compounds [13]. The synthetic transformations using these materials are more efficient and generate less waste than the conventional chemical methods. More recently, the plant cell culture of *Daucus Carota* root, soaked *Phaseolus Aureus* (green grams), and coconut juice (*Cocos Nucifera*) were used as biocatalyst for selective reduction of ketones [14].

Acacia is a medicinal plant (commonly known as Shikakai, Leguminosae family) grows in a tropical rainforests of southern Asia. The fruit is known as "fruit for hair" in its use as a traditional shampoo. Various properties of *Acacia* fruit are due to the presence of saponins in it, which are foaming agent. These saponins have surfactant properties similar to dodecyl benzene sulphonates [15]. Surfactants are best known to us as detergents which have ability to solubilize non-polar materials. This ability to solubilize non-polar materials has made aqueous surfactant systems increasingly popular alternatives to organic solvents in various applications. The fruit is known to contain 10-11.5 % saponins. The structures of different saponins present in the fruit have been recently established [16]. The pods of *Acacia* have been found to contain the saponin of acacic acid. Acacic acid was found to be a trihydroxy monocarboxylic triterpenic acid of either tetracyclic or -amyrin group [17]. The aqueous extract of these pods of *Acacia* shows acidic pH that is due to the presence of an acacic acid [18]. Thus, these interesting properties of aqueous extract of *Acacia* fruit inspired us to use it as an eco-friendly acidic surfactant type catalyst for the synthesis of various aryl-hydrazones (Scheme 1). Our approach reduces the use of hazardous organic solvents and uses simple and mild conditions, with inherently lower costs.
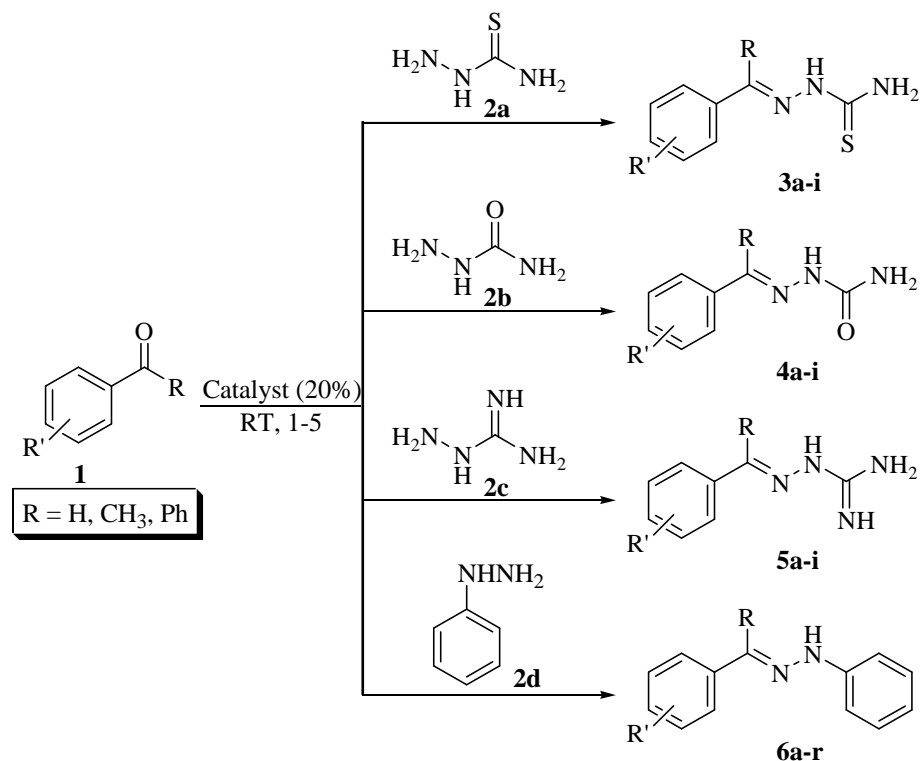
Scheme 1. Synthesis of aryl-hydrazones

Experimental

General procedure for the preparation of catalyst

Powdered pods of *Acacia* fruit (20 g) and water (100 mL) in a 250 mL conical flask was boiled for 15 min. The material was then filtered off and the aqueous extract was employed as a catalyst (20%, w/v) for the synthesis of aryl-hydrazones.

General procedure for the synthesis of aryl-hydrazones

A mixture of substituted aldehyde / ketone (2 mmol), semicarbazide / thiosemicarbazide / aminoguanidine / phenyl hydrazine (2 mmol) and catalyst (20%, 5 mL) were taken in a round-bottomed flask and stirred at room temperature for specified time period (Table 2). After completion of reaction (TLC), separated solid was filtered-off, washed well with water, dried to obtain the product in pure form.

Spectral data of selected compounds:

(E)-2-benzylidenehydrazinecarbothioamide (3a)

MS (ESI): 180 (M+1), IR (KBr, cm^{-1}): 3400, 3286, 2910, 1612, 1585, 1144, 1091, 945; ^{1}H NMR (DMSO-d$_6$) δ =

6.79 (m, 1H, Ar*H*), 6.90 (m, 2H, Ar*H*), 7.15 (d, 2H, *J* = 8Hz, Ar*H*), 7.60 (s, 1H, N=*CH*), 8.92 (s, 1H, *NH*), 10.85 (s, 2H, *NH₂*).

$2H$, *J* = 8Hz, Ar*H*), 7.66 (s, 1H, N=*CH*), 8.94 (s, 1H, *NH*), 10.78 (s, 2H, *NH₂*).

(E)-2-(4-chlorobenzylidene)hydrazinecarbothioamide (3b)

MS (ESI): 214 (M+1), IR (KBr, cm^{-1}): 3402, 3280, 2918, 1610, 1575, 1145, 1096, 948; ^{1}H NMR (DMSO-d₆) δ = 7.41 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.56 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.68 (s, 1H, N=*CH*), 8.95 (s, 1H, *NH*), 10.87 (s, 2H, *NH₂*).

(E)-2-(3-nitrobenzylidene)hydrazinecarbothioamide (3c)

MS (ESI): 225 (M+1), IR (KBr, cm^{-1}): 3411, 3283, 2915, 1611, 1530, 1450, 1146, 1095, 947; ^{1}H NMR (DMSO-d₆) δ = 7.43 (m, 1H, Ar*H*), 7.52 (d, 1H, *J* = 8.6 Hz, Ar*H*), 7.65 (d, 1H, *J* = 8.4 Hz, Ar*H*), 7.75 (s, 1H, Ar*H*), 7.79 (s, 1H, N=*CH*), 8.98 (s, 1H, *NH*), 10.90 (s, 2H, *NH₂*).

(E)-2-(4-methoxybenzylidene)hydrazinecarbothioamide (3d)

MS (ESI): 210 (M+1), IR (KBr, cm^{-1}): 3401, 3285, 2915, 1610, 1573, 1148, 1095, 946; ^{1}H NMR (DMSO-d₆) δ = 7.11 (d, 2H, *J* = 8 Hz, Ar*H*), 7.32 (d,

(E)-2-benzylidenehydrazinecarboxamide (4a)

MS (ESI): 164 (M+1), IR (KBr, cm^{-1}): 3412, 3320, 2934, 1620, 1580, 1149, 947; ^{1}H NMR (DMSO-d₆) δ = 6.87 (m, 1H, Ar*H*), 6.98 (m, 2H, Ar*H*), 7.20 (d, 2H, *J* = 8Hz, Ar*H*), 7.74 (s, 1H, N=*CH*), 8.98 (s, 1H, *NH*), 10.90 (s, 2H, *NH₂*).

(E)-2-(4-chlorobenzylidene)hydrazinecarboxamide (4b)

MS (ESI): 198 (M+1), IR (KBr, cm^{-1}): 3405, 3325, 2913, 1610, 1571, 1146, 1093, 946; ^{1}H NMR (DMSO-d₆) δ = 7.49 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.62 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.80 (s, 1H, N=*CH*), 8.94 (s, 1H, *NH*), 10.85 (s, 2H, *NH₂*).

(E)-2-(3-nitrobenzylidene)hydrazinecarboxamide (4c)

MS (ESI): 209 (M+1), IR (KBr, cm^{-1}): 3410, 3315, 2912, 1615, 1533, 1450, 1147, 1097, 945; ^{1}H NMR (DMSO-d₆) δ = 7.56 (m, 1H, Ar*H*), 7.63 (d, 1H, *J* = 8.4 Hz, Ar*H*), 7.71 (d, 2H, *J* = 8 Hz, Ar*H*), 7.82 (s, 1H, Ar*H*), 7.90 (s, 1H,

N=*CH*), 8.97 (s, 1H, *NH*), 10.88 (s, 2H, *NH₂*).

(E)-2-(4-methoxybenzylidene)hydrazinecarboxamide (4d)

MS (ESI): 194 (M+1), IR (KBr, cm^{-1}): 3401, 3295, 2915, 1610, 1583, 1148, 1095, 946; ^{1}H NMR (DMSO-d₆) δ = 7.12 (d, 2H, *J* = 8 Hz, Ar*H*), 7.35 (d, 2H, *J* = 8 Hz, Ar*H*), 7.71 (s, 1H, N=*CH*), 8.98 (s, 1H, *NH*), 10.88 (s, 2H, *NH₂*).

(E)-2-benzylidenehydrazinecarboximidamide (5a)

MS (ESI): 163 (M=1); IR (KBr, cm^{-1}): 3324, 3289, 3160, 2813, 1673, 1626, 1597, 1546. ^{1}H NMR (300 MHz, DMSO-d₆): δ = 7.38 (m, 3H, Ar*H*), 7.81 (m, 2H, Ar*H*), 7.85 (s broad, =*NH, NH₂*), 8.20 (s, 1H, N=*CH*), 12.11 (s, 1H, =N-*NH*).

(E)-2-(4-chlorobenzylidene)hydrazinecarboximidamide (5b)

MS (ESI): 197 (M+1), IR (KBr, cm^{-1}): 3398, 3245, 2975, 2916, 1673, 1620. ^{1}H NMR (300 MHz, DMSO-d₆): δ = 7.49 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.89 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.91 (s broad, =*NH, NH₂*), 8.18 (s, 1H, N=*CH*), 12.22 (s, 1H, =N-*NH*).

(E)-2-(4-methoxybenzylidene)hydrazinecarboximidamide (5d)

MS (ESI): 193 (M+1), IR (KBr, cm^{-1}): 3386, 3270, 3176, 2964, 1670, 1628, 1597, 1577, 1490, 1023. ^{1}H NMR (300 MHz, DMSO-d₆): δ = 3.77 (s, 3H, O*CH₃*), 6.97 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.79 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.80 (s broad, =*NH, NH₂*), 8.12 (s, 1H), 12.03 (s, 1H, =N-*NH*).

(E)-1-benzylidene-2-phenylhydrazine (6a)

MS (ESI): 197 (M+1), IR (KBr, cm^{-1}): 3312, 1602, 1592, 1521, 1261, 750, 691; ^{1}H NMR (400MHz, CDCl₃): = 6.81 (m, 1H, Ar*H*), 6.97 (m, 2H, ArH), 7.12 (d, 2H, J = 8Hz, Ar*H*), 7.22-7.25 (m, 3H, Ar*H*), 7.51 (s, 1H, NH), 7.57 (d, 2H, J = 8Hz, ArH), 7.62 (s, 1H, N=*CH*).

(E)-1-(4-methoxybenzylidene)-2-phenylhydrazine (6b)

MS (ESI): 227 (M+1), IR (KBr, cm^{-1}): 3314, 3022, 2954, 2836, 1596, 1507, 1296, 1246, 748, 693; ^{1}H NMR (400MHz, CDCl₃): = 3.83 (s, 3H, O*CH₃*), 6.85 (m, 1H, Ar*H*), 6.90 (d, 2H, J = 8Hz, Ar*H*), 7.10 (d, 2H, J = 8Hz, Ar*H*), 7.28 (m, 2H, Ar*H*,), 7.50 (s, 1H, NH), 7.60 (d, 2H, J = 8Hz, ArH), 7.66 (s, 1H, N=*CH*).

(E)-1-phenyl-2-((E)-3-phenylallylidene)hydrazine (6C)

MS (ESI): 223 (M+1), IR (KBr, cm^{-1}): 3313, 3029, 1603, 1518, 1487, 1293, 1260, 748, 698; ^{1}H NMR (400MHz, CDCl$_3$): = 6.71-6.80 (m, 2H, Ar*H*), 6.93-7.10 (m, 3H, Ar*H*), 7.18-7.22 (m, 3H, Ar*H*, =*CH*), 7.35 (d, 2H, J = 8Hz, Ar*H*,), 7.52 (d, 2H, J = 8Hz, Ar*H*), 7.71 (d, 1H, J = 16Hz, N=*CH*), 10.26 (s, 1H, *NH*).

(E)-2-((2-phenylhydrazono)methyl)phenol (6d)

MS (ESI): 213 (M+1), IR (KBr, cm^{-1}): 3317, 3294, 3054, 1602, 1567, 1524, 1495, 1273, 742, 688; ^{1}H NMR (400MHz, CDCl$_3$): = 6.80 (m, 1H, Ar*H*), 6.88-7.01 (m, 4H, Ar*H*), 7.15 (d, 2H, J = 8Hz, Ar*H*), 7.31 (m, 1H, Ar*H*,), 7.56 (d, 1H, *J* = 8Hz, Ar*H*), 7.70 (s, 1H, N=*CH*), 9.45 (s, 1H, *OH*), 10.21 (s, 1H, *NH*).

(E)-N-(4-((2-carbamothioylhydrazono)methyl)phenyl)acetamide (8)

MS (ESI): 237 (M+1), IR (KBr, cm^{-1}): 3310, 3250, 3220, 3140, 1680, 1115, 815; ^{1}H NMR (DMSO-d$_6$) δ = 2.15 (s, 3H, *CH$_3$*), 6.82 (d, 2H, *J* = 8.3 Hz, Ar*H*), 7.08 (d, 2H, *J* = 8.3 Hz, Ar*H*),

7.60 (s, 1H, N=*CH*), 9.04 (s, 1H, *NH*), 9.10 (s, 1H, *NH*), 10.78 (s, 2H, *NH$_2$*).

1,4-bis((E)-(2-phenylhydrazono)methyl)benzene (10)

MS (ESI): 315 (M+1); IR (KBr, cm^{-1}): 3301, 3053, 1601, 1580, 1494, 1257, 749, 691; ^{1}H NMR (400MHz, CDCl$_3$): = 6.84 (m, 2H, Ar*H*), 7.12 (d, 4H, *J* = 8Hz, Ar*H*), 7.25-7.30 (m, 4H, Ar*H*), 7.54 (s, 2H, *NH*), 7.68 (s, 2H, N=*CH*), 7.86 (s, 4H, Ar*H*)

Results and discussion

In our initial studies, a test reaction using benzaldehyde (2 mmol) and thiosemicarbazide **2a** (2 mmol) in 5 mL 10% (W/V) aqueous extract of *Acacia* pods at room temperature was performed in order to establish the real effectiveness of the catalyst, and we are fortunate to get the excellent yield of the product **3a** in very short reaction time (90%, 10 min). In order to optimize the reaction conditions, the same reaction was carried out using different concentrations of catalyst. It was found that 20% of catalyst shows maximum yield in very short reaction time (98%, 1 min). Higher concentration of the catalyst (30%, 50%) neither increases the yield nor lowers the conversion time (Table 1).

Thus, 20% (W/V), 5 mL aqueous extract was found to be the optimal quantity and sufficient to push the reaction forward. The purity of product obtained was high enough for spectroscopic analysis without any further purification. In the identical reaction when performed in water without any catalyst, starting material was recovered.

Table 1. Optimization of the concentration of catalyst

Sr. No.	% conc. of aqueous extract (W/V)	Time (min)	Yield (%)[a]
1	5	10	--
2	10	10	90
3	20	1	98
4	30	1	98
5	50	2	94

[a]Isolated yield, "--" starting materials recovered

In addition, we have also studied the reactions of semicarbazide (**2b**), aminoguanidine (**2c**) and phenyl hydrazine (**2d**) with benzaldehyde under optimized reaction conditions and the products (**4a**, **5a**, **6a**) were obtained with excellent yields. The efficiency and applicability of this aqueous approach was studied for the synthesis of wide variety of aryl-hydrazones by the condensation of various aldehydes and ketones with hydrazides (**2a-d**) using the similar reaction conditions and the results are summarized in tables given below (Table 2,3 and 4). All the reactions were preceded smoothly for various substituted and unsubstituted aromatic aldehydes / ketones and furnished excellent yields of the corresponding hydrazones in a very short period of time.

The rate enhancement in aqueous extract of *Acacia concinna* pods might be attributed due to its surfactant property and acidic pH. The probability of enzyme catalysed reaction is ruled out because the plant extraction is carried out at 100 °C. The saponins which are highly acidic solubilize the reactant species strongly by hydrogen bond formation in aqueous medium. This increases number of favourable collisions between the reactant species. Further encapsulation of reactants in micellar cages may drive the equilibrium towards product side by expelling the water molecule out of its

hydrophobic interior which increases the speed as well as yields of products [19] (Figure 2). This remarkable enhancement in reaction rate, prompted us to explore the potential of this protocol for the synthesis of aryl hydrazones.

Aromatic ketones were found to be less reactive as compared to aldehydes and require more time for the completion of reaction. It may happen because of the reduced electrophilicity of the carbonyl group due to electron donating methyl group. Similarly, benzophenone reacted more slowly than acetophenones because of the strong resonance of two aromatic rings (Table 5, Entry 18). The nature (electron withdrawing or electron donating) and position of the substituent on the aromatic ring *viz, p*-chloro, *m*-nitro and *p*-methoxy did not show any marked differences in the yield of hydrazones.
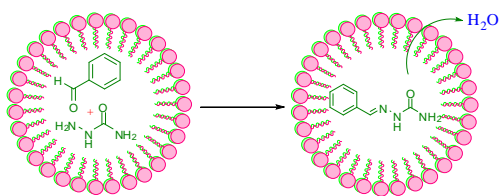
Figure 2. Micelle-promoted synthesis of aryl hydrazones

In the next attempt, we carried out the synthesis of (*E*)-*N*-{4-

[(ethanethioamidoimino)methyl]phenyl }acetamide (Thiacetazone) **8**, a well known antitubercular drug, by the condensation of *p*-acetamidobenzaldehyde **7** with thiosemicarbazide **2a** under the identical reaction conditions and obtained the excellent yield of product in very short period of time (Scheme 2).
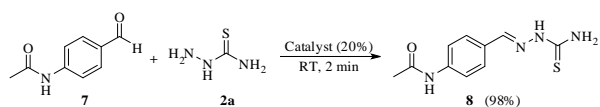
Scheme 2. Synthesis of Thiacetazone

In many conventional methods, solvent extraction is of great need for product isolation, but this aqueous approach overcomes this drawback and simple filtration afforded the products in excellent yield. In another variation, dialdehyde such as 1,4-benzenedicarboxaldehyde **9** underwent condensation with phenyl hydrazine **2d** in the presence of aqueous extract (20%) afforded bis-hydrazone **10** in 96% yield (Scheme 3). Particularly noteworthy is that the highly sterically crowded carbonyl compounds were also undergoes hydrazone formation with the usual rate and with excellent yield at room temperature (Table 5, Entries 8, 17).
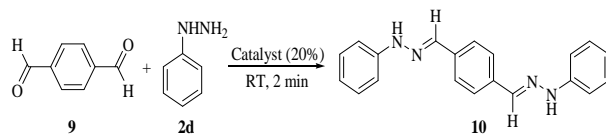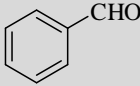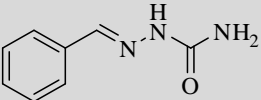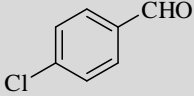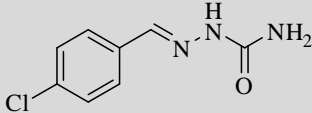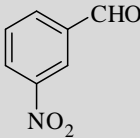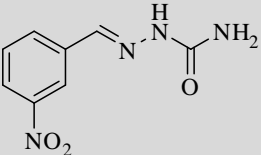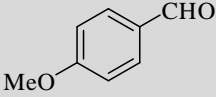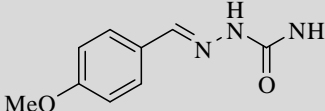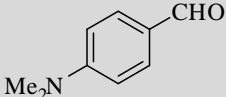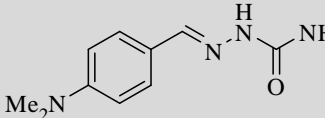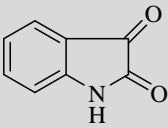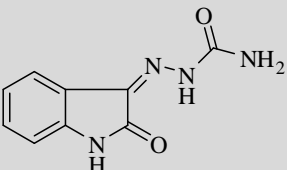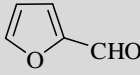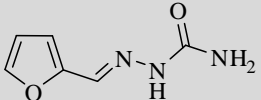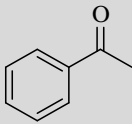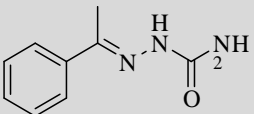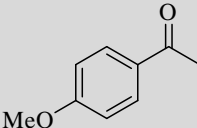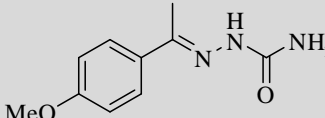
Scheme 3. Synthesis of bis-hydrazone

Table 2. Synthesis of thiosemicarbazones

Entry	Aldehyde / Ketone	Product [a,b]		Time (min)	Yield (%)[c]
1			3a	1	98
2			3b	2	97
3			3c	2	95
4			3d	1	96
5			3e	2	95
6			3f	2	92
7			3g	1	98
8			3h	5	92
9			3i	5	90

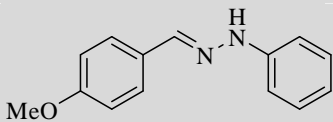[a] Reaction performed at rt
[b] All the compounds are reported in literature
[c] Isolated yields

Table 3. Synthesis of semicarbazones
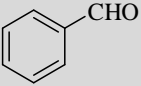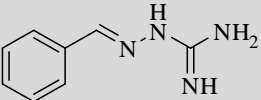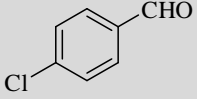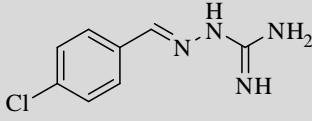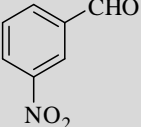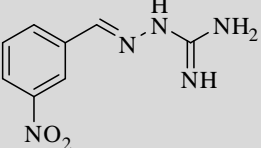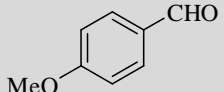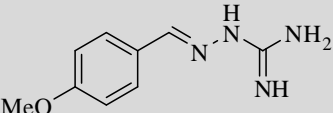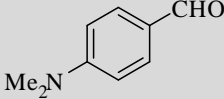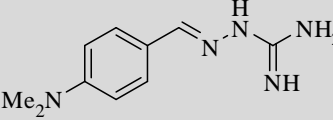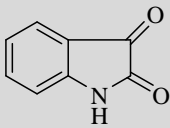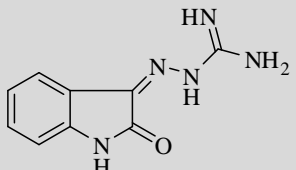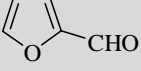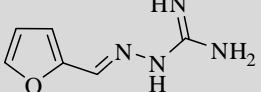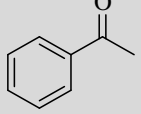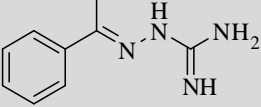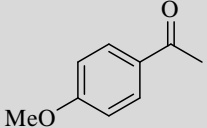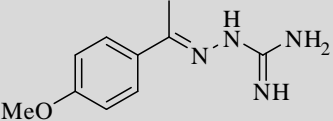
Entry	Aldehyde / Ketone	Product [a,b]		Time (min)	Yield (%)[c]
1			4a	1	97
2			4b	2	96
3			4c	2	94
4			4d	1	95
5			4e	2	92
6			4f	2	91
7			4g	1	98
8			4h	5	90
9			4i	5	90
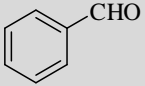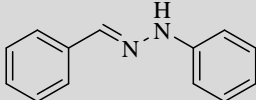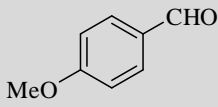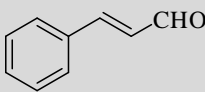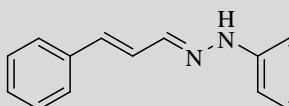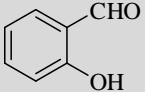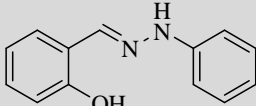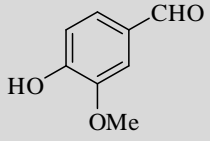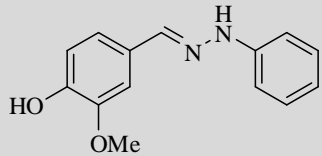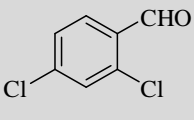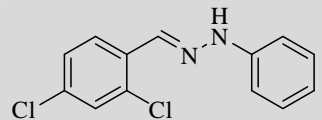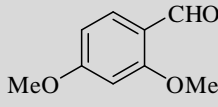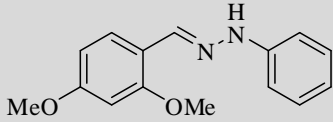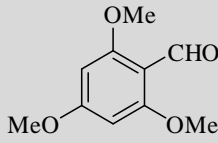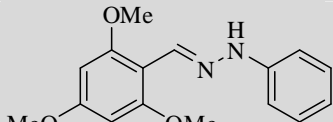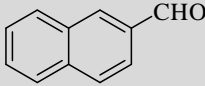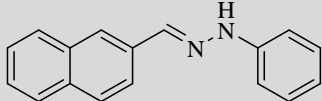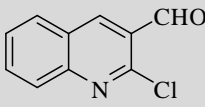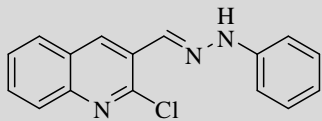
[a] Reaction performed at rt
[b] All the compounds are reported in literature
[c] Isolated yields
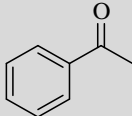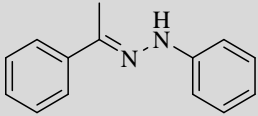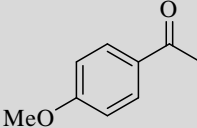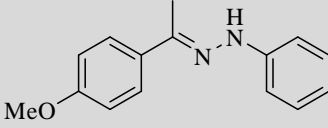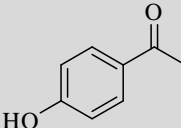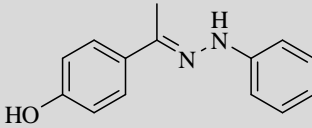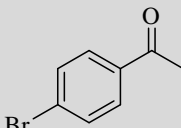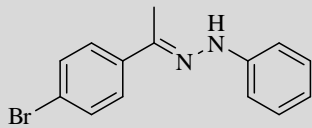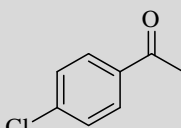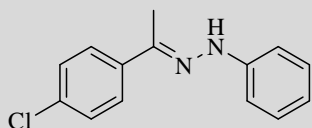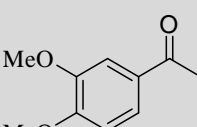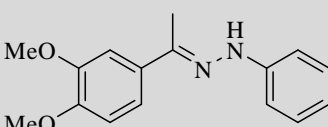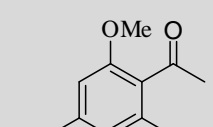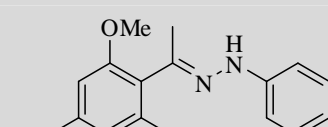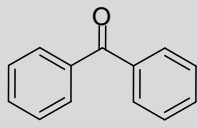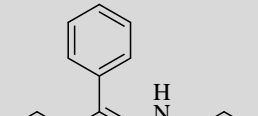
Table 4. Synthesis of guanyl hydrazones

Entry	Aldehyde / Ketone	Product [a,b]		Time (min)	Yield (%)[c]
1			5a	2	94
2			5b	3	92
3			5c	3	92
4			5d	2	90
5			5e	3	91
6			5f	3	88
7			5g	2	95
8			5h	5	88
9			5i	5	85

[a] Reaction performed at rt
[b] All the compounds are reported in literature
[c] Isolated yields

Table 5. Synthesis of phenyl hydrazones

Entry	Aldehyde / Ketone	Product[a,b]		Time (min)	Yield (%)[c]
1			6a	2	97
2			6b	2	95
3			6c	3	96
4			6d	3	95
5			6e	2	94
6			6f	2	95
7			6g	3	92
8			6h	3	90
9			6i	2	94
10			6j	3	92

11			6k	3	92
12			6l	5	90
13			6m	5	87
14			6n	3	90
15			6o	3	92
16			6p	5	88
17			6q	5	86
18			6r	10	85

[a] Reaction performed at rt;
[b] All the compounds are reported in literature;
[c] Isolated yields

Conclusion

In summary, the aqueous extract of *Acacia* pods was successfully employed as a natural surfactant type catalyst for the synthesis of wide variety of aryl-hydrazones by condensing variety of carbonyl compounds with thiosemicarbazide, semicarbazide, aminoguanidine and phenyl hydrazone at room temperature. Simple and mild reaction conditions, cheap, readily available and biodegradable catalyst

and short reaction time are the important features of this protocol.

Acknowledgements

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