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Water-Mediated One-pot Three-Component Synthesis of Hydrazinyl-Thiazoles Catalyzed by Copper Oxide Nanoparticles Dispersed on Titanium Dioxide Support: A Green Catalytic Process

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Supporting information for this article (^{1}H & ^{13}C NMR, HRMS and MS spectra of all compounds and crystallographic data in CIF format (CCDC 1560154)) is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The present work describes the catalytic activity of copper oxide nanoparticles dispersed on titanium dioxide in water for one-pot synthesis of a library of hydrazinyl-thiazoles *via* a three-component reaction of various aldehydes/ketones with thiosemicarbazide and different phenacyl bromides. The structure of the synthesized compound, (*E*)-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene) hydrazinyl)thiazole is confirmed by single crystal X-ray diffraction studies. The catalyst prepared by a molten-salt method is characterized by X-ray diffraction, field emission scanning electron microscopy, transmission electron microscopy, energy dispersive X-ray spectroscopy, X-ray photoelectron spectroscopy, Auger electron spectroscopy and electron spin resonance spectroscopy. The noteworthy advantages of this method include its broad substrate scope, clean reaction profile, short reaction times and high yields at low catalyst loading. Further, the product does not require any chromatographic purification and the method has the potential for large-scale applications in pharmaceutical industries. In addition, the developed catalyst can be recovered and reused for 5 times without significant loss of activity. Mechanistic studies suggest that the reaction begins with the activation of the carbonyl group of both aldehyde/ketone and phenacyl bromide by copper oxide nanoparticles supported on titanium dioxide in water. These studies reveal that the reaction proceeds *via* the formation of thiosemicarbazone intermediate.

Keywords: copper oxide nanoparticles; titanium dioxide; water; multi-component reaction; hydrazinyl-thiazoles.

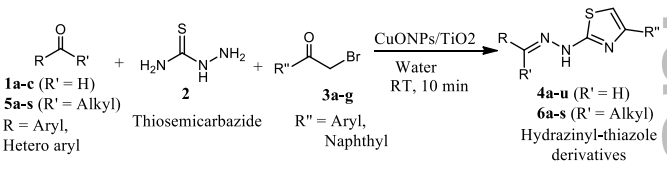
Introduction

Design and development of organic reactions in water is an excellent area of research that emphasizes the spirit of new and innovative green chemistry. Indeed, it is clear that water has many unique physical and chemical properties such as extensive hydrogen bonding, non-toxicity, high heat capacity, large dielectric constant, non-flammability, environmental compatibility etc. In addition, water is known to increase the rates and improve the selectivity of a wide variety of organic reactions.[1] Among the organic reactions, multi-component reactions (MCRs) are powerful tools for the sustainable and diversity-oriented synthesis of heterocycles[2] by the rapid construction of several multiple bonds in a single step operation with minimal waste and energy. MCRs performed with various heterogeneous catalysts have undergone remarkable progress in recent years. Among the heterocycles, thiazole and its derivatives are considered as 'privileged scaffolds' due to their potential biological activities like antimicrobial, anti-inflammatory, antihypertensive, anti-HIV and herbicidal activity.[3–7] They are important subunits in several pharmaceutical drugs, such as Ritonavir,[8] Bleomycin[9] and Tiazofurin,[10] Fanetizole and Meloxicam.[11] Some of these thiazoles and its metal complexes are also used as semiconducting materials,[12] fluorescent chemosensors [13] and organic light-emitting diodes.[14] Extensive literature study reveals that there are only two ways for the synthesis of hydrazinyl-thiazoles. First one is the homogeneous acid catalyzed conventional two-step process which involves the reaction of carbonyl compounds with thiosemicarbazide to produce thiosemicarbazones which subsequently undergo cyclization with α-halocarbonyl compounds.[15] But, this procedure suffered from disadvantages such as limited substrate scope, use of organic solvents, low yields, lengthy reaction times and complicated workup procedures. One-pot methods reported so far have been very limited. This method involves the reaction of carbonyl

compounds, thiosemicarbazide and α-halo carbonyl compounds in a single-step operation.[16] Though the reported one-pot methods are efficient to provide the desired hydrazinyl-thiazoles, there are still some drawbacks such as narrow substrate scope and use of expensive techniques; The method generates unwanted side products and the products require column chromatographic purification. Further, there is no mechanistic evidence for the reaction pathway and the method is unsuitable for large-scale applications.[16c,e]

Nowadays, nanocatalysis is an attractive and highly demanding area of research which involves the use of nanomaterials as catalysts in a variety of organic transformations.[17] This may be due to their unique characteristics like smaller size, high surface area, high density of defect sites, increased efficiency and selectivity and reusability.[18] The high surface energy of nano-size particles favors agglomeration. Therefore the nanocatalysis is considered as a sustainable and competitive alternative to conventional catalysis. Transition metal-based nanoparticles are employed as catalysts in many important organic conversions.[19] Among them, copper nanoparticles are considered as clean and abundant catalysts due to their low-cost, high stability, non-toxicity, recyclability, reusability and environmental friendly nature for several organic transformations.[20] Hence, several solid supported copper nanocatalysts such as silica, zeolites, metal oxides and carbon materials are utilized in a variety of organic reactions.[21] For example, copper nanoparticles supported on various solid supports such as TiO_2 (CuNPs/TiO_2),[21e-h] activated carbon (CuONPs/C),[21i,j] silica coated maghemite (CuNPs/MagSilica)[21k] zeolite (CuONPs/Zy),[21l] and graphene oxide (CuONPs/GO)[21m] are used for the catalytic activation of the C–H bond of terminal alkynes. Copper nanoparticles supported on silica CuNPs (CuNPs/Silica)[21n] and Hexagonal mesoporous silica (HMS) (CuO/HMS)[21o] are also utilized for the activation of aldehydes. Copper nanoparticles on silica (CuNPs/Silica)[21p] are used for the C–N cross-coupling reaction. Further, Copper nanoparticles supported on mesoporous titanium oxide and cobalt ferrite are successfully used in a variety of organic reactions like epoxidation, reduction, click reaction and Biginelli reaction.[21q] Among various catalysts supports, TiO_2 has been identified as an attractive support because of its unique physico-chemical properties such as high surface area, non- toxicity and high chemical and thermal stability in both acidic and oxidative environments. In addition, the surface of TiO_2 is highly hydrophilic which stabilizes the dispersion of the TiO_2 in water thus enabling the deposition of metal or metal oxide NPs on the TiO_2 surface.[22] Furthermore, the synergetic activity of TiO_2 support and the CuO nanoparticles increases the stability and catalytic activity of CuONPs on TiO_2. The TiO_2 supported CuNPs are widely used as heterogeneous catalysts in a variety of organic reactions.[21e-h,q] Inspired by the importance of CuNPs/TiO_2 in organic synthesis, we aimed to prepare economically viable and environmentally benign heterogeneous TiO_2 supported CuO nanocatalysts and explore their catalytic performance in organic transformations. To the best of our knowledge, there are no reports on CuONPs/TiO_2 catalyzed one-pot synthesis of a library of hydrazinyl-thiazoles in water.

In this paper, we report a CuONPs/TiO_2 catalyzed one-pot three-component synthesis of a series of hydrazinyl-thiazoles (**4a-u & 6a-s**) from various aldehydes (**1a-c**)/ ketones (**5a-s**), thiosemicarbazide (**2**) and different phenacyl bromides (**3a-g**) in water under ambient reaction conditions (Scheme 1). Further, this study focuses on the explanation of reaction pathway; the intermediate (**I**) is isolated and confirmed by spectral studies.



Scheme 1. CuONPs/TiO_2 catalyzed multi-component synthesis of diversified hydrazinyl-thiazoles(**4a-u & 6a-s**) in water.

Results and Discussion

In the present study, we aimed to fulfill three major objectives: i) development of a new catalytic system ii) investigation of reaction mechanism and iii) establishing clean, economic and environmental friendly reaction conditions for the one-pot multi-component synthesis of hydrazinyl-thiazoles. Initially, a variety of TiO_2 supported copper catalysts were prepared by a molten-salt method using mixture-i (NaCl and commercial P-25 TiO_2) and mixture-ii (NaCl and Cu $(NO_3)_2.3H_2O$) as indicated in Table 1. Briefly, mixture-i and mixture-ii were mixed in an alumina crucible, calcined, washed with distilled water and dried. The obtained TiO_2 supported CuO nanoparticles were labelled as CT-1, CT-2, CT-3, CT-4, CT-5, CT-6 and CT-7 (Table 1).

Table 1. Chemical composition for the preparation of catalysts (CT-1 to CT-7).

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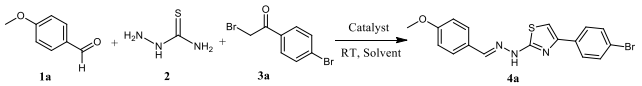
Entry	Catalyst Code	Mixture-i Wt. of NaCl (mg)	Mixture-i Wt. of TiO_2 (mg)	Mixture-ii Wt. of NaCl (mg)	Mixture-ii Wt. of $Cu(NO_3)_2.3H_2O$ (mg)	Wt.-% of Cu
1	CT-1	500	500	500	9.5	0.5
2	CT-2	500	500	500	19.0	1.0
3	CT-3	500	500	500	24.7	1.3
4	CT-4	500	500	500	28.5	1.5
5	CT-5	500	500	500	32.3	1.7
6	CT-6	500	500	500	38.0	2.0
7	CT-7	500	500	500	47.5	2.5

The prepared catalysts (CT-1 to CT-7) were examined for their potency along with commercially available CuO and TiO_2 catalysts for the one-pot synthesis of **(***E***)**-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene) hydrazinyl)thiazole (**4a**) from 4-methoxybenzaldehyde **(1a)**, thiosemicarbazide **(2)** and 2-bromo-1-(4-bromophenyl)ethanone **(3a)** as model substrates (Table 2). A control experiment was conducted in ethanol at RT in the absence of catalyst for 60 min; the yield obtained was 20 % only (Table 2, entry 1/C_2H_5OH). It was also observed that the reaction did not proceed in water (Table 2, entry 1/H_2O). To improve the yield, the same reaction was repeated with the aforementioned catalysts in different solvents at RT (Table 2). After examining these catalysts and solvents, it was found that the 25 mg of CT-4 catalyst in water was the best option to obtain better yield (85%) of product (**4a**) (Table 2, entry 7/H_2O) and other catalysts in different solvents afforded low to moderate yields of **4a** (Table 2, entries 2-6 and 8-10). From this study, it was observed that the of CT-4 catalyst in water was the most suitable medium for the synthesis of **4a**. The high catalytic activity of CuONPs/TiO_2 might be due to the high dispersity of TiO_2 supported CuO nanocatalyst in water followed by the interaction of organic substrates with CuONPs.[23]

Table 2 Screening of suitable catalyst and solvent for the one-pot three-component synthesis of (*E*)-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene)hydra zinyl)thiazole**(4a)**.[a]



Entry	Catalyst	Solvent	Time (min)	Product	Yield[b] (%)
1[c]	---	EtOH	60	**4a**	20
		Acetone	60		-
		Isopropanol	60		10
		H_2O	60		-
		Acetonitrile	60		-
2	CuO	EtOH	60	**4a**	25
		Acetone	60		-
		Isopropanol	60		15
		H_2O	60		20
		Acetonitrile	60		10
3	TiO_2	EtOH	60	**4a**	20
		Acetone	60		-
		Isopropanol	60		10
		H_2O	60		-
		Acetonitrile	60		-
4	CT-1	EtOH	60	**4a**	30
		Acetone	60		-
		Isopropanol	60		30
		H_2O	60		35
		Acetonitrile	60		10
5	CT-2	EtOH	20	**4a**	35
		Acetone	20		-
		Isopropanol	20		20
		H_2O	20		45
		Acetonitrile	20		10
6	CT-3	EtOH	20	**4a**	40
		Acetone	20		-
		Isopropanol	20		30
		H_2O	20		60
		Acetonitrile	20		10
7	CT-4	EtOH	20	**4a**	60
		Acetone	20		-
		Isopropanol	20		45
		H_2O	20		85
		Acetonitrile	20		10
8	CT-5	EtOH	20	**4a**	55
		Acetone	20		-
		Isopropanol	20		40
		H_2O	20		80
		Acetonitrile	20		15
9	CT-6	EtOH	20	**4a**	50
		Acetone	20		-
		Isopropanol	20		40
		H_2O	20		78
		Acetonitrile	20		25
10	CT-7	EtOH	20	**4a**	55
		Acetone	20		-
		Isopropanol	20		45
		H_2O	20		75
		Acetonitrile	20		30

[a]**Reagents and conditions:** 4-methoxy benzaldehyde (**1a**) (10.0 mmol), thiosemicarbazide (**2**) (10.0 mmol), 2-bromo-1-(4-bromophenyl)ethanone (**3a**) (10.0 mmol), catalyst (25 mg), solvent (25 mL), RT.
[b]Isolated yield.
[c]In the absence of catalyst.

Further, the amount of loading of CT-4 catalyst (5, 25, 50, 75, 100 and 125 mg) was varied to optimize the yield of product 4a (Table 3). From this study, it was found that 50 mg of CT-4 catalyst (1.12 mol.% of Cu) was the optimum amount to achieve maximum yield of product 4a (98%) for the stated quantity of substrates within a short period of time (10 min) (Table 3, entry 3); However, further increase in the amount of catalyst (i.e. 75, 100 and 125 mg), did

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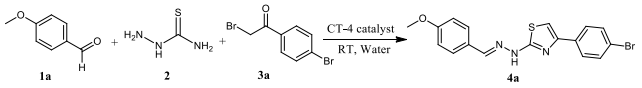
not show any significant effect on the product yields (Table 3, entries 4-6).

Table 3. Effect of amount of catalyst (CT-4) loading in the one-pot three-component synthesis of **4a**.[a]

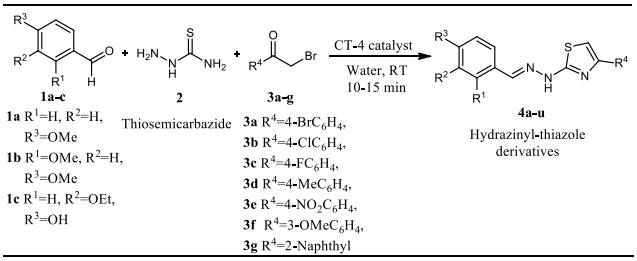


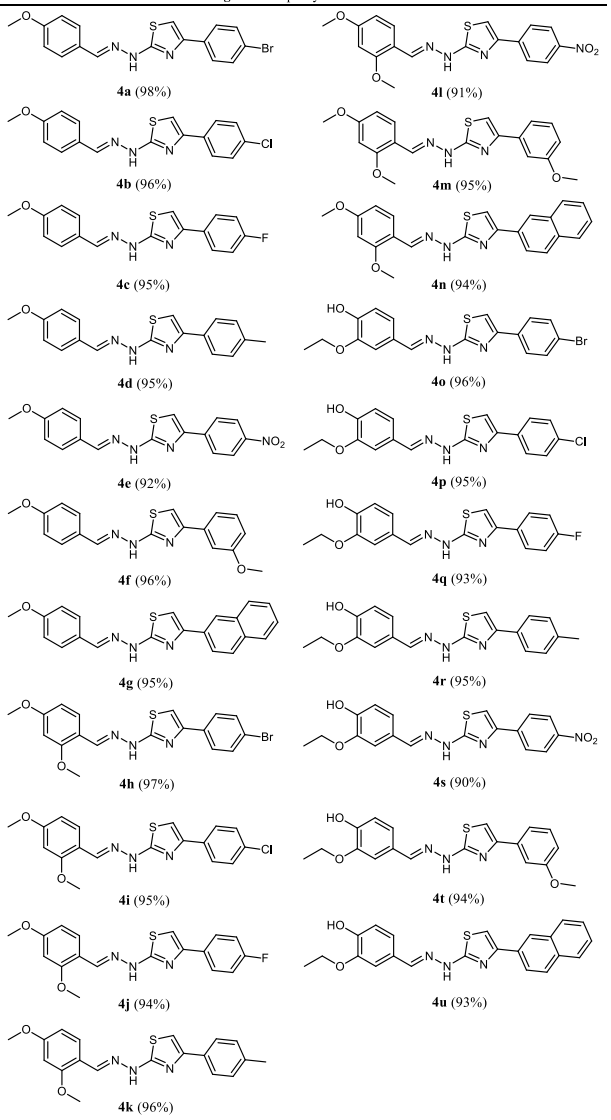
Entry	Amount of CT-4 catalyst (mg)	Copper content (mol-%)[b]	Solvent	Time (min)	Yield[c] (%)
1	5	0.11	H_2O	60	75
2	25	0.56	H_2O	20	85
3	50	1.12	H_2O	10	98
4	75	1.68	H_2O	10	97
5	100	2.23	H_2O	10	96
6	125	2.79	H_2O	10	96

[a]**Reagents and conditions:** 4-methoxy benzaldehyde (**1a**) (10.0 mmol), thiosemicarbazide (**2**) (10.0 mmol), 2-bromo-1-(4-bromophenyl)ethanone (**3a**) (10.0 mmol), CT-4 catalyst (5.0 to 125 mg), water (25 mL), RT.
[b] Referred to the substrates.
[c]Isolated yield.

To test the generality and scope of this MCR, various aromatic aldehydes **(1a-c)** and phenacyl bromides **(3a-g)** were employed in this reaction separately (Table **4)**. At first, 4-methoxy benzaldehyde **(1a)** underwent the reaction with thiosemicarbazide **(2)** and a variety of phenacyl bromides **(3a-g)** to afford the corresponding hydrazinyl-thiazoles **(4a-g)** in good yields that ranged from 92 to 98 %. Next, 2, 4-dimethoxy benzaldehyde **(1b)** also showed good reactivity towards thiosemicarbazide **(2)** and different phenacyl bromides **(3a-g)** to produce the corresponding hydrazinyl-thiazoles **(4h-n)** in good yields that ranged from 91 to 97 %. Further, 3-ethoxy-4-hydroxybenzaldehyde **(1c)** reacted with thiosemicarbazide **(2)** and a range of phenacyl bromides **(1a-g)** to yield the corresponding hydrazinyl-thiazoles **(4o-u)** in good yields that ranged from 90 to 96%. From this study, it was observed that the substrates with diverse functional groups on the aromatic ring proceeded well to provide the desired products in high yields under the optimized reaction conditions.

Table 4. Synthesis of hydrazinyl-thiazole derivatives (**4a-u**) using various aldehydes, thiosemicarbazide and phenacyl bromides.[a]





[a]**Reagents and conditions**: Aromatic aldehydes (**1a-c**) (10.0 mmol), thiosemicarbazide (**2**) (10.0 mmol), phenacyl bromides (**3a-g**) (10.0 mmol), CT-4 catalyst (50 mg; 1.12 mol-% of Cu), water, RT.
[b]Isolated yield.

The structure of **4a** was confirmed by a single crystal X-ray crystallography (Figure.1). The compound **4a** obtained was monoclinic with $P2_1/c$ space group and one molecule in the asymmetric unit ($Z = 4$, $Z' = 0$) (Figure 2). In the crystal packing (Figure. 2a), the molecules were linked by N(2)—H……N(1) with a significant bond length of 3.009 Å. The interactions propagated in a 3D network packing with respect to the *a* & *c* axes as

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shown in Figure S1 (See the Supporting Information).

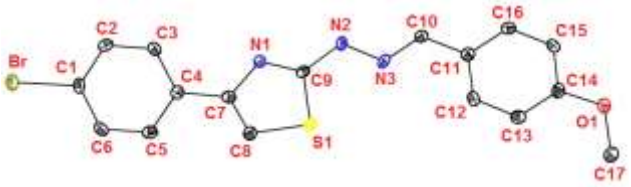


Figure 1. ORTEP diagram of (*E*)-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene)hydrazinyl)thiazole**(4a)**.

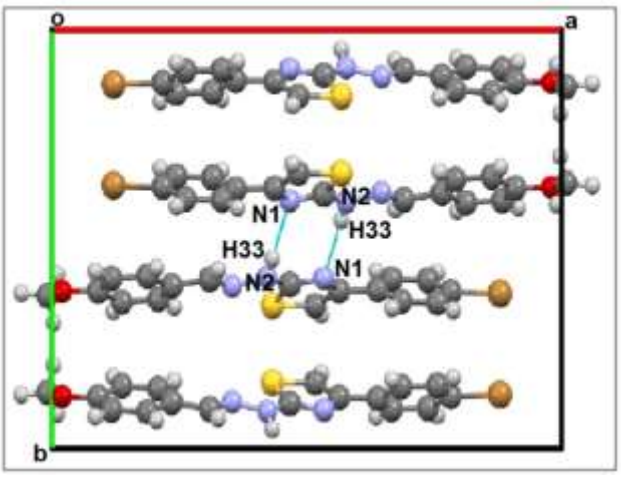
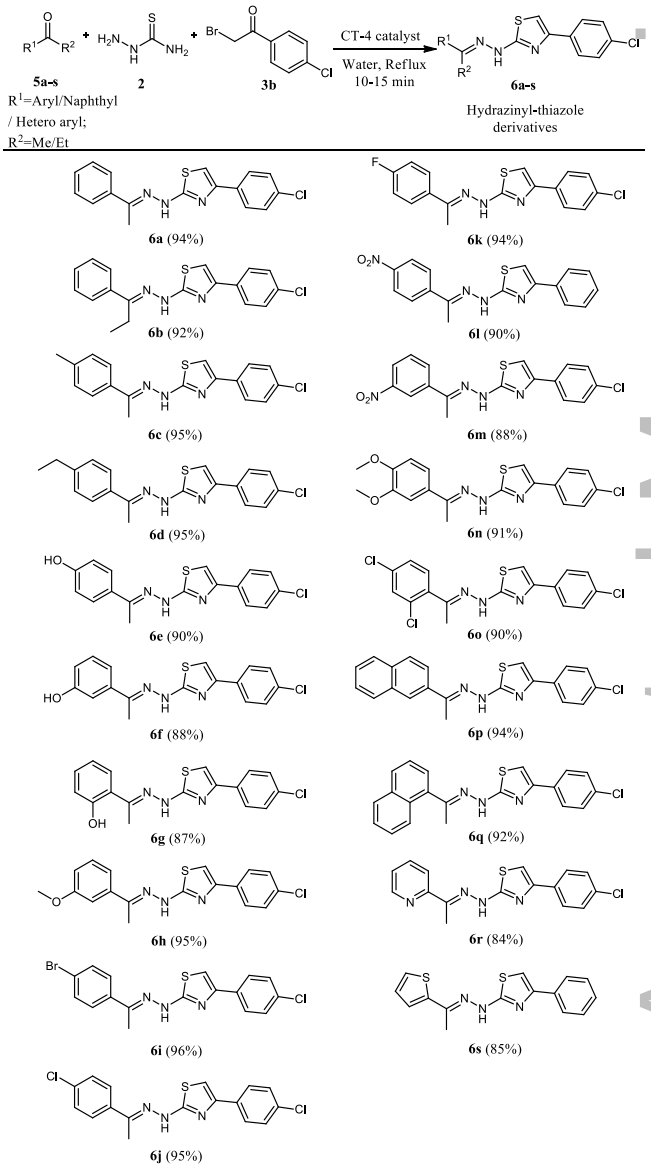


Figure 2. Hydrogen bonding pattern of molecule (*E*)-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene) hydrazinyl)thiazole **(4a)**.

Encouraged by these results, we proposed to extend this MCR for the synthesis of a library of structurally diverse hydrazinyl-thiazoles **(6)** from various ketones **(5a-s)**, thiosemicarbazide **(2)** and 4-chlorophenacyl bromide **(3b)**. For this purpose, initially, a reaction was carried out by using acetophenone (**5a**), thiosemicarbazide **(2)** and 4-chlorophenacyl bromide **(3b)** in the presence of CT-4 catalyst (50 mg) in H_2O at RT for 2h. It resulted in a 40 % yield of **6a**. The yield of the product was further increased to 94 % within 10 minutes by increasing the temperature from room temperature to reflux temperature. To demonstrate the generality and broad scope of the present protocol, a variety of ketones were employed under the optimized reaction conditions (Table **5)**. A range of functional groups such as electron-donating (Me, Et, OH and OMe) **(5c-5h)** and electron-withdrawing (Cl, Br, F and NO_2) **(5i-5m)** groups present at different positions on the aryl ring of ketones provided good to excellent isolated yields of the corresponding products **(6c-6h & 6i-6m)** that ranged from 88 to 96 %. Further, it was also observed that the presence of 3,4-dimethoxy **(5n)** and 2,4-dichloro **(5o)** substituents on the aryl ring of ketones gave good isolated yields of the corresponding products **6n** (91%) and **6o** (90%)**.** Acetonaphthones such as 2-acetyl and 1-acetyl naphthalenes **(5p & 5q)** afforded the products, **6p** and **6q** in good isolated yields of 94 and 92%, respectively. From the above study, it was observed that the reaction proceeded well, irrespective of the substituents present on the aryl ring of ketones. This MCR was also successfully applied to hetero aromatic ketones such as 2-acetyl pyridine and 2-acetylthiophene **(5r & 5s)** which afforded good yields of the corresponding products **6r** (84%) and **6s** (85%).

Table 5. Synthesis of hydrazinyl-thiazole derivatives **(6a-s)** using various ketones, Thiosemicarbazide and 4-Chlorophenacyl bromide.[a]



[a]**Reagents and conditions:** Aromatic ketones (**5a-s**) (10.0 mmol), thiosemicarbazide (**2**) (10.0 mmol), 2-bromo-1-(4-chlorophenyl)ethanone (**3b**) (10.0 mmol), CT-4 catalyst (50 mg; 1.12 mol-% of Cu) water, RT.
[b]Isolated yield.

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The scalability of the optimized procedure was then studied by the reaction of 4-methoxybenzaldehyde **(1a)**, thiosemicarbazide **(2)** and 2-bromo-1-(4-bromophenyl)ethanone **(3a)** in the presence of CT-4 catalyst in water in different gram scale reactions, 1.0, 5.0, 10.0, 15.0, 20.0 and 25.0 grams. The yields of product **4a** were 98%, 98%, 98%, 97%, 97% and 96%, respectively (Figure. 3). In this investigation, it is found that the developed catalytic system is a promising greener alternative for the gram-scale production of hydrazinyl-thiazoles.

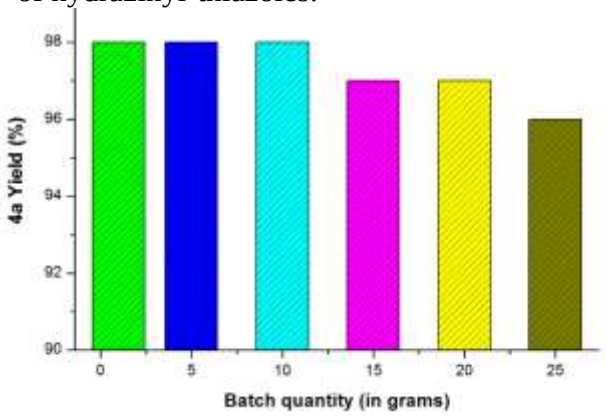


Figure 3 Gram-scale synthesis of (*E*)-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene)hydrazinyl) thiazole **(4a).**

The reusability of the catalyst was also examined by using the model reaction for the preparation of **4a** from 4-methoxybenzaldehyde **(1a)**, thiosemicarbazide **(2)** and 2-bromo-1-(4-bromophenyl) ethanone **(3a)** in water. After completion of the first cycle, the catalyst was recovered by filtration, dried under vacuum and was reused in the next cycle. The yields obtained for product **4a** were 98, 98, 98, 97 and 97 % for first, second, third, fourth and fifth cycles, respectively (Figure 4). It is noteworthy to mention that there is no significant loss of catalytic activity of CuONPs/TiO_2 in water up to five cycles.

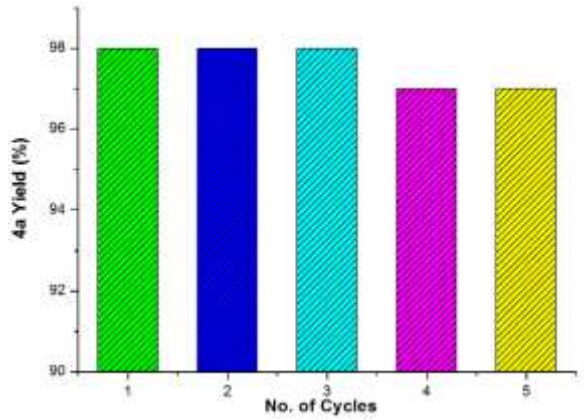
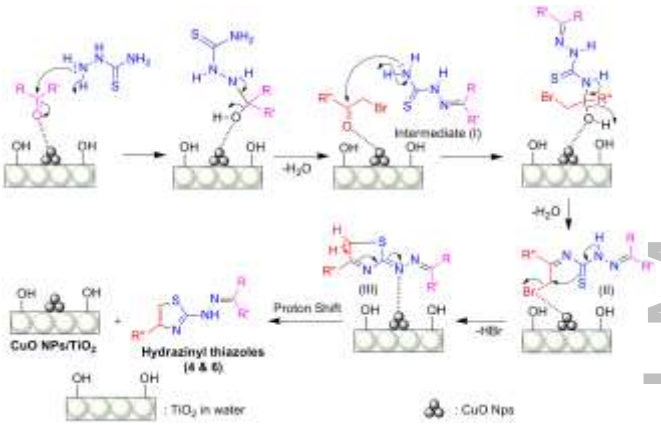


Figure 4 Efficiency of a CT-4 catalyst.

A plausible mechanism for the one-pot three-component synthesis of hydrazinyl-thiazoles in the presence of CuONPs/TiO_2 as the catalyst is depicted in Scheme **2**. The mechanism begins with the activation of a carbonyl carbon of aldehyde/ketone by CuONPs on a hydrophilic TiO_2 surface in water followed by condensation with NH_2 group of thiosemicarbazide to give a thiosemicarbazone intermediate **(I)**. To investigate the reaction mechanism, the obtained intermediate **(I)** was isolated and confirmed by ^1H & ^{13}C NMR and HRMS spectral studies. The NH_2-group of intermediate (I) reacts with the carbonyl carbon of phenacyl bromide that was activated by CuONps/TiO_2 in the same pot to form diimine (II). The obtained diimine **(II)** undergoes intramolecular cyclization to give dihydro hydrazinyl-thiazole (**III**) *via* intra molecular S_N2 displacement of bromide ion followed by proton transfer (aromatization) to yield hydrazinyl-thiazoles (**4 & 6**).



Scheme 2. A plausible mechanism for the synthesis of hydrazinyl-thiazoles **(4 & 6)** in the presence of CuONPs/TiO_2 in water.

Isolation and characterization of Intermediate ((*E*)-2-(3-ethoxy-4-droxybenzylidene) hydrazinecarbothioamide)(I):

A mixture of 3-ethoxy-4-hydroxybenzaldehyde **(1c)** (10.0 mmol), thiosemicarbazide **(2)** (10.0 mmol), 2-bromo-1-(4-bromophenyl)ethanone **(3a)** (10.0 mmol) in 25.0 mL H_2O was stirred in the presence of CT-4 catalyst (50 mg) at 25-30 °C for 3-5 min. The progress of the reaction was monitored by TLC. As per TLC, we noticed that there was a formation of an intermediate (I) along with starting materials and product. In order to identify the reaction pathway, the pure intermediate was isolated by preparative TLC and it was characterized by ^1H & ^{13}C NMR and HRMS data.

Further, the degradation of the intermediate (I) was also examined by mass spectral fragmentations (Figure **5**). The presence of molecular ion 240.0804

$[M+H]^+$ $C_{10}H_{14}N_3O_2S$ of intermediate (**I**) and a series of daughter ions i.e., 223.0774 $[M+H-OH]^+$, 164.0697$[M+H-CH_2NS]^+$ and 149.0835 $[M+H-CH_3N_2S]^+$ in the mass spectrum of intermediate (**I**) revealed that the reaction proceeded *via* a thiosemicarbazone intermediate (**I**).

Characterization of (*E*)-2-(3-ethoxy-4-hydroxybenzylidene) hydrazinecarbothioamide: Pale yellow solid; ^{1}H NMR (500MHz, DMSO-d_6): δ (ppm) 11.24 (s, 1H, NH), 9.39 (s, 1H, OH), 8.09 (s, 1H, NH), 7.94 (s,1H, NH), 7.92 (s, 1H, H-C=N-), 7.45 (d, J = 1.5 Hz, 1H, arom H), 7.02 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, arom H), 6.78 (d, J = 8.0 Hz, 1H, arom H), 4.08 (q, J = 7.0 Hz, 2H, $=CH_2$), 1.34 (t, J = 7.0 Hz, 3H, $-CH_3$). ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 177.82 (1C), 149.48 (1C), 147.68 (1C), 143.42 (1C), 126.02 (1C), 122.77 (1C), 115.70 (1C), 110.94 (1C), 64.36 (1C), 15.14 (1C). HRMS: *m/z* calcd for $C_{10}H_{14}N_3O_2S$ $[M+H]^+$ 240.0806, found: 240.0804.

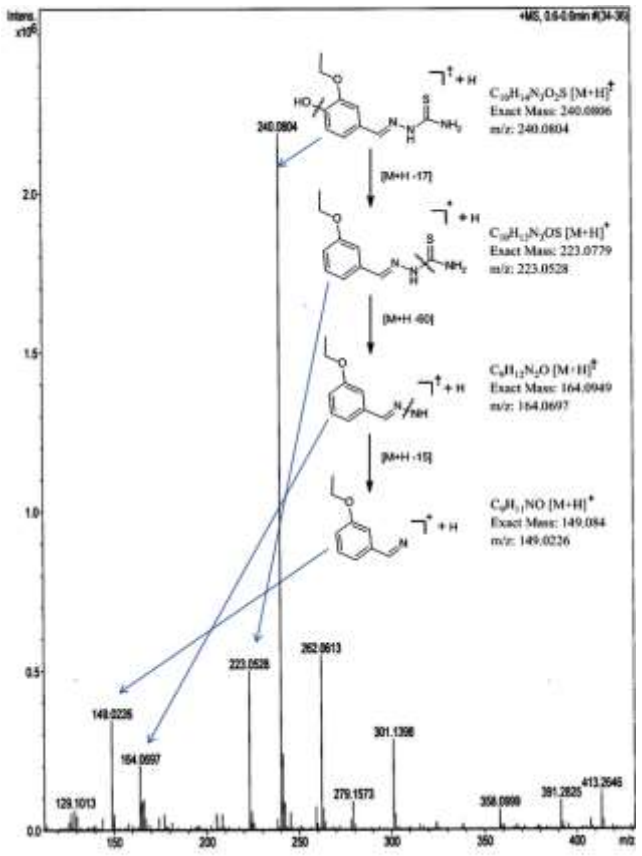


Figure 5. HRMS of (*E*)-2-(3-ethoxy-4-hydroxy benzylidene)hydrazinecarbothioamide(I).

Characterization of CT-4 catalyst:

The chosen catalyst was characterized by XRD, FESEM with EDS, TEM with EDS, XPS, AES and ESR.

Powder XRD pattern of catalyst was shown in Figure **6**. The diffraction peaks at 2θ = 25.57, 38.09, 48.30, 54.18, 55.29, 62.99, 69.11 and 70.49° were attributed to the (101), (004), (200), (105), (221), (204), (116) and (220) planes of anatase TiO_2 (JCPDS 21-1272). The diffraction peaks at 2θ = 27.71, 36.35, 41.49 and 56.88° were assigned to the (110), (101), (111) and (220) planes of rutile TiO_2 (JCPDS 21-1276). The XRD data revealed the presence of highly crystalline biphasic TiO_2. No characteristic peaks owing to copper species were found in XRD pattern; this could be ascribed to fine dispersion of CuO nanoparticles below the detectable limit of X-rays.[24] FESEM images and EDS analysis of catalyst showed that the CuO nanoparticles were distributed on the TiO_2 surface (Figures S2 and S3. see the Supporting Information). TEM and HRTEM images further confirmed the particle size of TiO_2 and CuO and dispersion CuO on TiO_2 in CT-4 catalyst (*vide infra*).

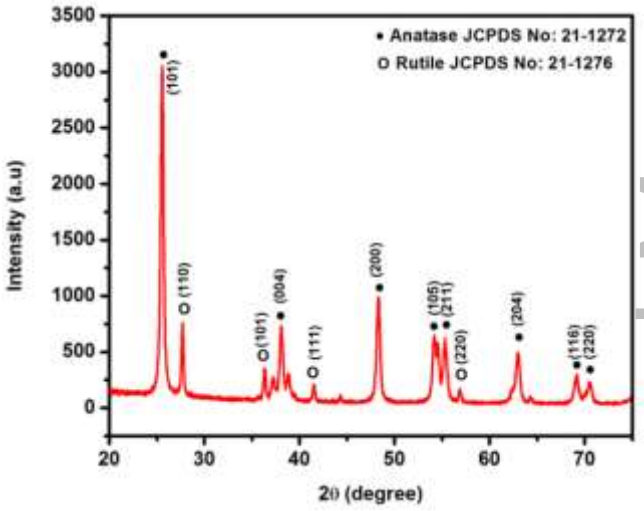
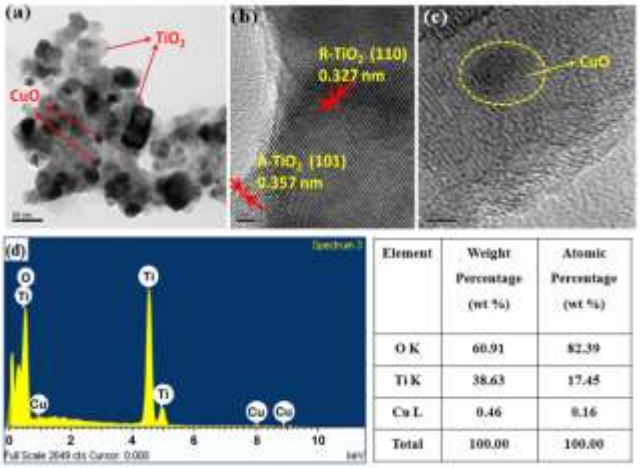


Figure 6. XRD pattern of CT-4 catalyst.

TEM micrograph revealed that the CuO nanoparticles were randomly dispersed on the surface of TiO_2 (Figure **7a**). The particle size of TiO_2 was 40 ± 5 nm (Figure **7a**) and CuO was 5 ± 2 nm (Figure **7c**). The lattice fringes with d-spacing values of 0.357 nm and 0.327 nm confirmed anatase (101) and rutile (110) phases of TiO_2, respectively as shown in high resolution TEM image (Figure 7b). Further, Figure **7c** provides evidence for CuO nanoparticles dispersed over a TiO_2 support. EDS analysis on various areas revealed that the presence of copper oxide on TiO_2 support as evidenced by the energy bands at 8.01, 8.92 (*K* lines) and 0.91 keV (*L* line) (Figure 7d).

Further, the elemental composition of catalyst was determined by EDS analysis (Figure 7d).



Element	Weight Percentage (wt %)	Atomic Percentage (wt %)
O K	60.91	82.39
Ti K	38.63	17.45
Cu L	0.46	0.16
Total	100.00	100.00

Figure 7. TEM image **(7a)** and HRTEM Images (7b & 7c) and **(7d)** EDS analysis of CT-4 catalyst.

The CT-4 catalyst surface composition was determined by XPS. From this study, it was found that the weight percentages of Ti, O and Cu were 53.95%, 44.63% and 1.42% respectively. The copper content of 1.42 wt.-% in the catalyst corresponds to 1.12 mol-% of copper with respect to the reactants i.e. aldehyde, thiosemicarbazide and phenacyl bromide. The Ti 2p XPS spectrum of CT-4 catalyst (Figure 8b) clearly showed two well-resolved peaks at 458.6 and 464.6 eV. These were assigned to Ti $2p_{3/2}$ and Ti $2p_{1/2}$ spin-orbital components of TiO_2, respectively. A peak at 529.9 eV in the O1s XPS spectrum (Figure 8c) was attributed to O 1s in the CT-4 catalyst. The Cu 2p XPS spectrum of CT-4 catalyst (Figure 8d) showed two peaks at 932.8 and 951.8 eV. These were assigned to Cu $2p_{3/2}$ and Cu $2p_{1/2}$; However, no corresponding satellite peaks (941-944 eV) were found. The lower binding energy values (i.e. slightly higher than that of Cu_2O) and the absence of satellite peaks in the XPS spectra of Cu 2p might be due to the presence of CuO in a highly dispersed amorphous state at lower amount of Cu loadings (1.0-2.6 wt.-% of Cu).[24] From the above study, it was clear that the copper was present in the form of Cu(II) in the CT-4 catalyst. Further, the formation of CuO was also supported by Auger and ESR spectral analysis. A peak at 917.5 eV in the Auger spectrum revealed that the presence of Cu(II) in the CT-4 catalyst This is in good agreement with the reported data.[25] Finally, the ESR spectrum of the CT-4 catalyst showed a broad band centered at g = 2.11 [g (2.11) > g_e (2.0036)] without resolved hyperfine structure (Figure 10). The observed *g*-value corresponds to the presence of Cu(II) in an octahedral geometry.[26]

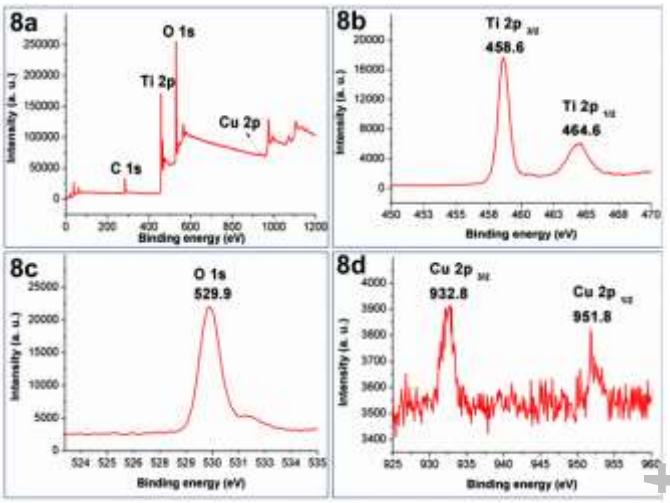


Figure 8. XPS spectra of CT-4 catalyst

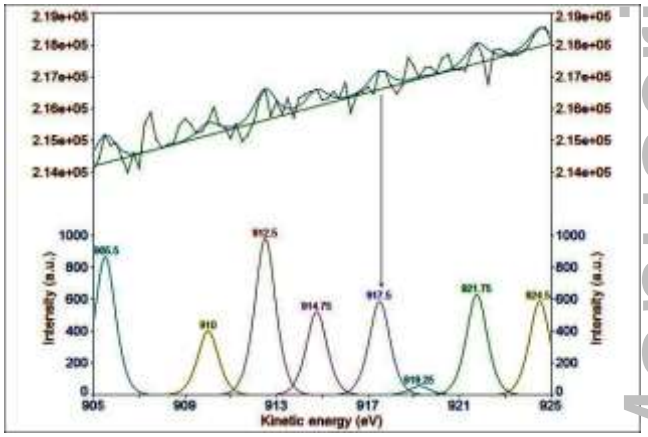


Figure 9. Auger spectrum of CT-4 catalyst

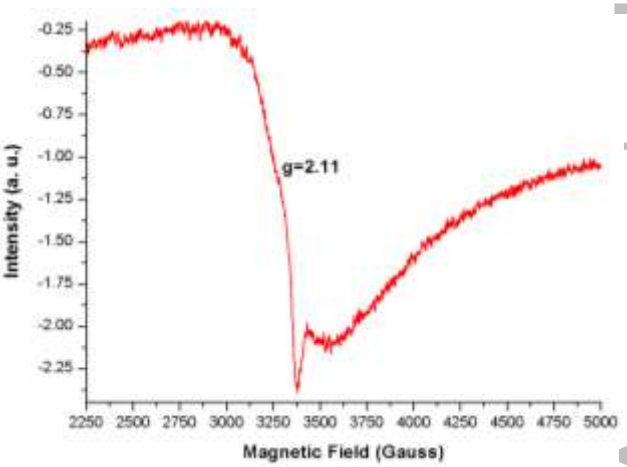


Figure 10. ESR spectrum of a CT-4 catalyst

Conclusions

A new catalytic system i.e. CuO nanoparticles dispersed on TiO_2 has been developed for the synthesis of a series of medicinally privileged hydrazinyl-thiazoles from the reaction of carbonyl compounds, thiosemicarbazide and α-bromo

carbonyl compounds in water *via* a one-pot multi-component reaction. The mechanistic study revealed that the reaction proceeds *via* a thiosemicarbazone intermediate formation. The present method has several advantages, such as its ease of operation, wide substrate scope, clean reaction profile, scalability, short reaction times and high yields at ambient conditions. In addition, all the reactions are performed in water and the product does not require any chromatographic purification. The catalyst used at lower amount of copper loading and could be reutilized for up to five cycles without significant loss of activity. Further, the high catalytic performance of CuONPs/TiO_2 might be due to the high dispersity of the catalyst in water followed by interaction of organic substrates with CuONPs. The developed catalyst is superior to other commercially available heterogeneous copper catalysts and outwardly operates under heterogeneous conditions.

Experimental Section

General Material and Methods

Aldehydes, ketones, thiosemicarbazide, sodium chloride and copper nitrate tri-hydrate and solvents were purchased from Sigma Aldrich, Acros Organics Ltd., and Merck and were used as received. Photocatalyst grade titanium dioxide nanoparticles (TiO_2 P-25) composed of anatase 80%, rutile 20%, was procured from Degussa Corporation, Germany. Melting points were determined by MR-Vis+ instrument (Labindia) and are uncorrected. The ^1H (500 and 400 MHz) and ^{13}C (125 and 100 MHz) NMR spectra were recorded on Bruker NMR spectrometer (500 and 400 MHz). Chemical shifts are reported in (δ) parts per million and coupling constant(s) (J) in Hertz. Mass Spectra were recorded on Shimadzu-LCMS-2010 A mass spectrometer. High-Resolution Mass Spectra were recorded on a Bruker micrOTOF-QII mass spectrometer. XRD pattern was recorded using a Rigaku Miniflex 600 diffractometer. Field Emission Scanning Electron Microscopy (FESEM) images were recorded using Ultra 55 Carl Zeiss instrument with an operating voltage of 10 kV. Transmission electron microscopy (TEM) and HRTEM measurements were carried out by using a JEOL JEM 2100 electron microscope at 200 keV. X-ray photoelectron spectra and Auger electron spectra were recorded on Kratos Analytical (AXIS Supra), UK (SHIMADZU group). ESR spectrum of the powdered sample was recorded at room temperature (RT) on Bruker EMX ESR spectrometer operating at X-band frequencies (ν = 9.66322 GHz), having a 100 kHz field modulation to obtain a first derivative ESR spectrum. DPPH with a g-value of 2.0036 is used for g factor calculations. Thin layer chromatography was performed on 0.25 mm silica gel plates (Merck). Millipore double distilled water was used for the workup process. All phenacyl bromides are prepared according to the reported methods.[27]

Preparation of TiO_2 supported CuONPs by molten salt method: A mixture of NaCl (0.5 g) and TiO_2 P-25 (0.5 g) (1:1 ratio) was taken in a mortar and ground together with a pestle for 10 min. Then the mixed powder was transferred into a petridish and baked at 150 °C for 12 h. This was labelled as mixture (**i**). Another mixture of NaCl (0.5 g) and different amounts of Cu $(NO_3)_2.3H_2O$ (to get various amounts i.e. 0.5, 1.0, 1.3, 1.5, 1.7, 2.0 and 2.5 wt.-% of Cu on TiO_2) as indicated in Table 1 was taken in a mortar and ground together with a pestle for 10 min. This was labelled as mixture (**ii**). These two mixtures were then transferred into an alumina crucible in such a way as mixture (**i**) as bottom layer and mixture (**ii**) as top layer and calcined at 500 °C for 4 h. Finally, the calcined powder was washed with distilled water and dried at 80 °C for 12 h. The obtained TiO_2 supported CuO nanoparticles labelled as CT-1, CT-2, CT-3, CT-4, CT-5, CT-6, and CT-7.

General procedure for synthesis of Hydrazinyl thiazoles (4): A mixture of aldehydes **(1)** (10.0 mmol), thiosemicarbazide **(2)** (10.0 mmol), phenacyl bromides **(3)** (10.0 mmol) in H_2O (25.0 mL) was stirred in the presence of CT-4 catalyst (50 mg, 1.12 mol-% of Cu) at 25-30°C for 10-15 min. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the crude mass was washed with ethyl acetate (25.0 mL) and the catalyst was recovered by filtration under vacuum. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude product **(4)** was purified by recrystallization (ethanol). The spectroscopic data of the synthesized compounds (**4a**–**4u**) are in accordance with their proposed structures.

General procedure for synthesis of Hydrazinyl-thiazoles (6): A mixture of ketones **(5)** (10.0 mmol), thiosemicarbazide **(2)** (10.0 mmol), 2-bromo-1-(4-chlorophenyl) ethanone **(3b)** (10.0 mmol) in H_2O (25.0 mL) was stirred in the presence of CT-4 catalyst (50 mg, 1.12 mol-% of

Cu) at reflux temperature for 10-15 min. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the crude mass was washed with ethyl acetate (25.0 mL) and the catalyst was recovered by filtration under vacuum. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude product (**6**) was purified by recrystallization (ethanol). The spectroscopic data of the synthesized compounds (**6a**–**6s**) are in accordance with their proposed structures.

General procedure for gram scale (25 g scale) synthesis of (*E*)-4-(4-bromophenyl)-2-(2-(4-methoxybenzylidene)hydrazinyl) thiazole (4a): A mixture of 4-methoxybenzaldehyde **(1a)** (0.1835 moles), thiosemicarbazide **(2)** (0.1835 moles) and 2-bromo-1-(4-bromophenyl)ethanone **(3a)** (0.1835 moles) in H_2O (500 mL) was stirred in the presence of CT-4 catalyst (915 mg, 1.12 mol-% of Cu) at 25-30 °C for 20–30 min. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the crude mass was washed with ethyl acetate (500 mL) and the catalyst was recovered by filtration under vacuum. The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude product (**4a**) was purified by recrystallization (ethanol).

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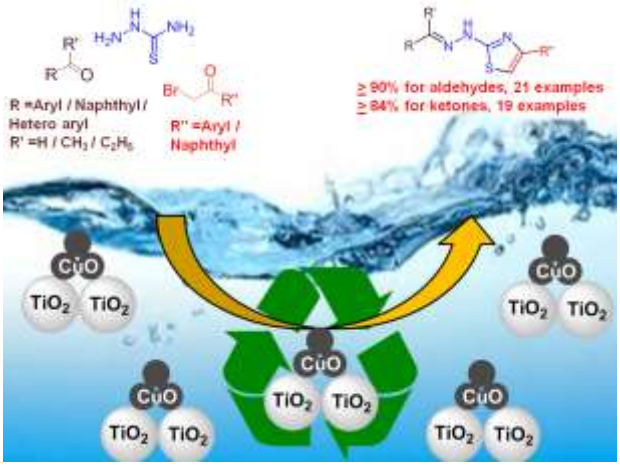
FULL PAPER

Water-Mediated One-pot Three-Component Synthesis of Hydrazinyl-Thiazoles Catalyzed by Copper Oxide Nanoparticles Dispersed on Titanium Dioxide Support: A Green Catalytic Process



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