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PII: S0040-4039(15)01146-6
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.07.016
Reference: TETL 46505

To appear in: *Tetrahedron Letters*

Received Date: 19 April 2015
Revised Date: 18 June 2015
Accepted Date: 4 July 2015

Please cite this article as: Iniyavan, P., Balaji, G.L., Sarveswari, S., Vijayakumar, V., CuO Nanoparticles: Synthesis and application as an efficient Reusable Catalyst for the preparation of xanthene substituted 1,2,3-triazoles via click chemistry, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.07.016

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Tetrahedron Letters
journal homepage: www.elsevier.com

CuO Nanoparticles: Synthesis and application as an efficient Reusable Catalyst for the preparation of xanthene substituted 1,2,3-triazoles via click chemistry

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Click chemistry
xanthenes
triazoles
CuO nanoparticles

ABSTRACT

Copper (II) oxide (CuO) nanoparticles have been found to be an efficient catalyst for 1,3-dipolar cycloaddition (CuAAC) of aromatic azides and acetylenic xanthenes furnishing the corresponding xanthene substituted triazoles in excellent yields. CuO nanoparticles have been synthesized from copper acetate by simple co-precipitation method and characterized by scanning electron microscope, energy dispersive X-ray analysis, transmission electron microscope and X-ray diffraction analysis. The salient features of the present protocol are mild reaction conditions, shorter reaction time, reusability of the catalyst, and applicable with a wide range of substrates.

Xanthenes are common natural products and an important motif in a variety of biologically active and useful compounds[1]. Compounds carrying the xanthene moiety exhibit promising biological activities such as anticancer[2], analgesic[3], anti-inflammatory[4] and antibacterial[5]. Some of the xanthene based compounds have found applications as antagonists for paralyzing the action of zoxalamine and in photodynamic therapy[6]. In addition, their derivatives can be used as pH sensitive fluorescent materials for the visualization of biomolecular assemblies[7], as bactericides in agriculture[8] and in laser technologies[9]. The combination of two heterocyclic skeletons having different biological functions to produce a new hybrid compound that is more medically effective than its parent molecules[10]. Several hybrid molecules having xanthene as one scaffold have been synthesized and applied in optical and medicinal studies[11]. In particular, xanthene-triazole based hybrid molecule has been reported as a new fluorophore with emission wavelengths from blue to yellow regions[12].

On the other hand, 1,2,3-triazoles possess a number of desirable features in the context of medicinal chemistry such as anti-bacterial[13], anti-viral[14], antibiotic[15], magnetic resonance imaging[16], anti-allergic[17] and trypanocidal activities[18]. Recently, 1,2,3-triazoles are synthesized by a process known as Cu-mediated 'click chemistry'[19] which has been explored in molecular hybridization system to synthesize the new analogs of quinolines[20], chalcones[21], peptides[22] and several other hybrid molecules[23].

Thus far, $CuSO_4$/sodium ascorbate[24], CuI/PEG-400[25] and Cu $(OAc)_2$ $3H_2O/H_2O$[26] are the most generalized and widely used catalytic systems for this pioneering work. However, the reusability of copper catalyst for these protocols is infrequently studied due to their homogeneous nature, which creating problem during separation of catalyst/product(s).

In order to overcome these drawbacks, recent research in this work has concentrated on heterogeneous catalytic systems, which have several advantages, such as good dispersion of active sites, easier and safer handling, easier separation from the reaction mixture and reusability. A large number of protocols have been developed for the azide-alkyne cycloaddition with the use of heterogeneous catalysts such as polymeric imidazole-Cu(II)[27], silica supported copper catalyst[28], hydroxyapatite supported copper (II)[29] and copper(I)-modified zeolites[30]. The susceptibility results obtained with these different techniques are, in general, excellent. But, since the discovery of nanostructured copper oxide has shown a general beneficial effect in the cycloaddition of alkynes and azides which has been used by many research groups[31].

Various groups have demonstrated the usefulness of nano-crystalline metal oxides as catalysts for organic transformations[32]. According to the factors mentioned and our continuous interest in synthesis of organic compounds[33], we report herein the first successful synthesis of xanthene substituted triazoles catalyzed by copper oxide nanoparticles.

Synthesis of Catalyst.

A 300 mL aliquot of 0.02 M copper acetate aqueous solution was mixed with 1 ml of glacial acetic acid in a round-bottomed flask equipped with refluxing device. Acetic acid was

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added to avoid hydrolyzation of Cu^{2+} ions. The solution was heated to 100 °C with vigorous stirring. Subsequently, 0.8 g of sodium hydroxide as reducing agent was added rapidly into the above boiling solution and stirred for 10 min until the value of the mixture reached the pH 6-7, where a large amount of black precipitate was formed instantly. After being cooled to room temperature, the resultant suspension was irradiated with ultrasonic horn (by using E-Chrom ultrasonic horn, 22 kHz frequency, 800 W) in ambient air for 1 h. Finally the precipitate was centrifuged, washed once with distilled water and three times with absolute ethanol, respectively, and dried in air at room temperature. The obtained dry black powder sample was used for further analysis.

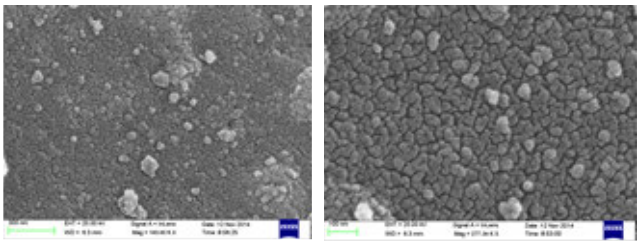


Fig. 1 SEM images of CuO nanoparticles

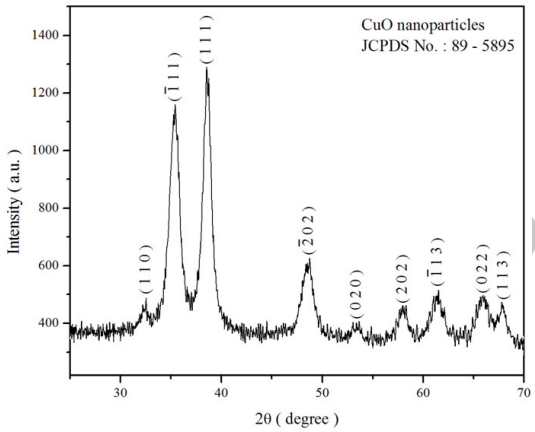


Fig. 2 XRD pattern of CuO nanoparticles

XRD patterns (Fig. **2**) of the products obtained are identical to the single-phase CuO with a monoclinic structure and the diffraction data were in good agreement with JCPDS card of CuO (JCPDS 80-1268). The peak broadening clearly indicates the small size of the products. The average size of the CuO nanoparticles is estimated to be 4-7 nm according to the Scherrer equation[34]. The EDX spectrum (Fig. **4**) of CuO nanoparticles indicates the presence of Copper and Oxygen. SEM and TEM observations were carried out and shown in Figs. **1** and **3**. From the SEM analysis, the shape of formed CuO nanoparticles was found to be spherical. From the TEM image it can be seen that the particles are nearly spherical with relatively uniform diameters and the particle size is found to be 3-6 nm which is in good agreement with the size which estimated by Scherrer's equation from the XRD pattern.

The outline for the preparation of various xanthene substituted triazoles is shown in Scheme **1**, **2** and **3**. For our present study, the key starting material, hydroxy substituted 9-aryl-1,8-dioxo-octahydroxanthenes (**6-9**) were synthesized through condensation reaction of dimedone (**4**) and hydroxy benzaldehydes (**1-3**) using ethanol as solvent in the presence of catalytic amount of BF_3:OEt_2[35]. Subsequently, substituted 3,3,6,6-tetramethyl-9-(4-(prop-2-ynyloxy)phenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene- 1,8(2*H*)-dione (**10-13**) was synthesized by *O*-alkylation of **6-9** with propargyl bromide using K_2CO_3 and DMF at room temperature. On the other hand, aromatic azides were synthesized from their corresponding aromatic amines by diazo-phenyl formation with sodium nitrite in acidic conditions followed by displacement with sodium azide

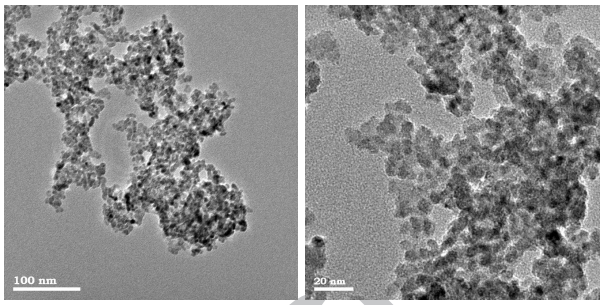


Fig. 3 TEM images of CuO nanoparticles

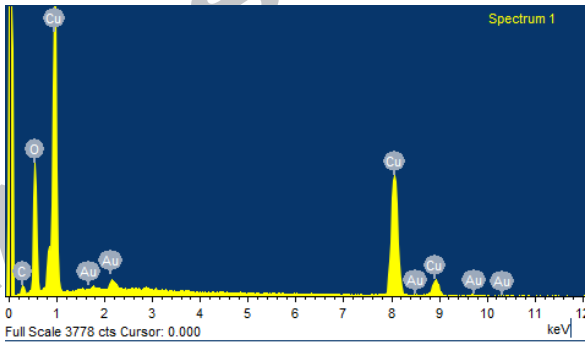
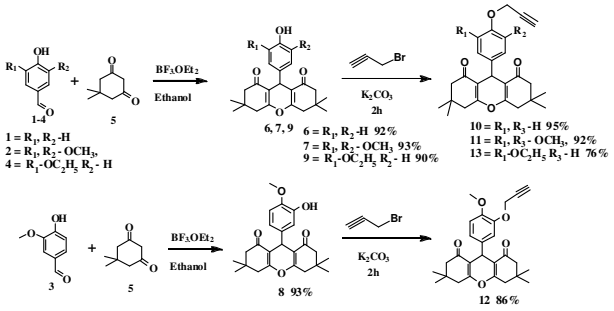
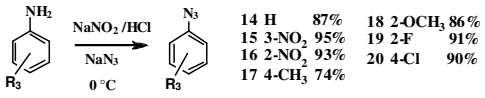


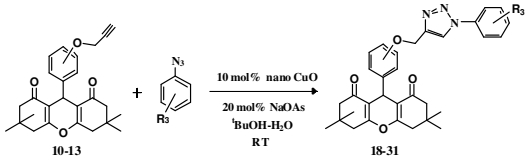
Fig. 4 EDS image of CuO nanoparticles



Scheme 1 Synthesis of acetylenic xanthenes (**10-13**)



Scheme 2 Synthesis of aromatic azides (**14-20**)



Scheme 3 Synthesis of xanthene substituted triazoles (**21-46**)

We have chosen 3,3,6,6-tetramethyl-9-(4-(prop-2-ynyloxy)phenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**10**) and phenyl azide (**14**) as the model substrates to find out the optimized reaction conditions for the synthesis of

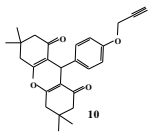
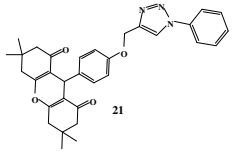
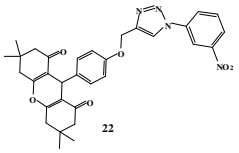
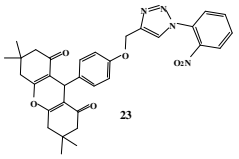
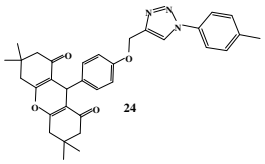
xanthene substituted 1,2,3-triazole derivatives (**21-46**). First, the model reaction was performed in the presence of various copper salt catalysts (Table **1**) along with either of D-glucose and sodium ascorbate (NaOAs) as reductant. Though all of the investigated copper sources were capable of catalyzing the synthesis to the desired product, yield was found be less and consuming more time. While we used CuO nanoparticles (Table **1**) along with sodium ascorbate, the yield improved remarkably in reasonable time. Several solvents were examined to set up a standard reaction condition, and results showed that the reaction proceeded with excellent yields when tertiary butanol-water (1:1) mixture was utilized. The next parameter catalyst loading was optimized and it was observed that 10 mol% CuO nanoparticles is sufficient to catalyze the reaction effectively. With these optimal conditions from the pilot study in-hand, we embarked on an investigation for the scope of the reaction with various xanthenes and azides. The reaction went along well with both electron-withdrawing and electron-donating substituted aromatic azides. The results are summarized in Table **2**.

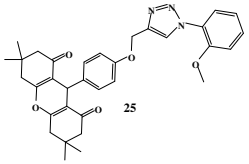
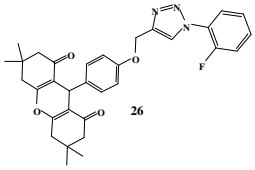
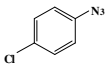
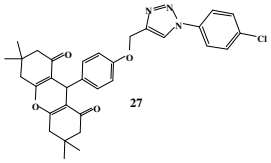
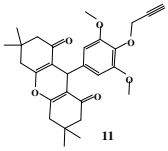
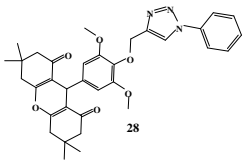
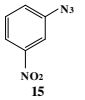
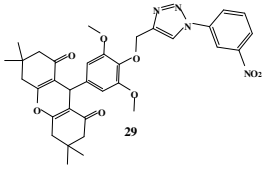
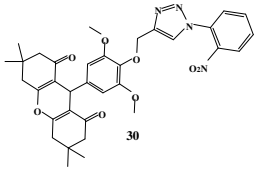
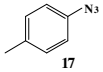
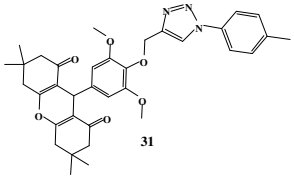
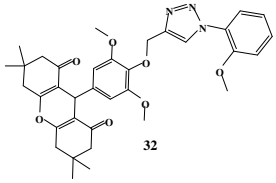
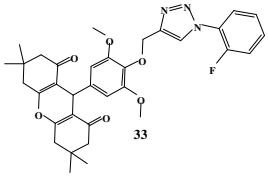
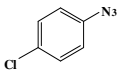
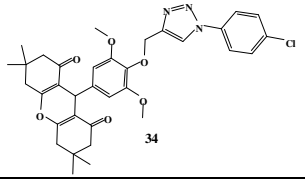
Table 1 Synthesis of derivative **21** in different conditions.

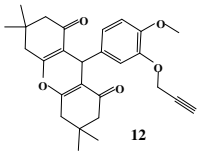
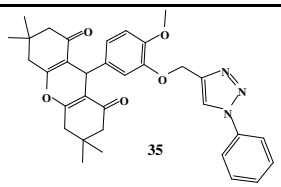
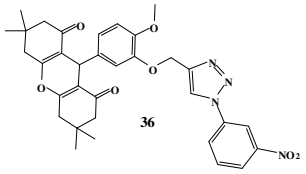
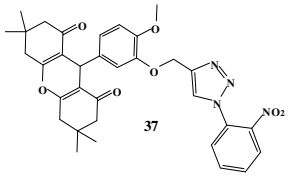
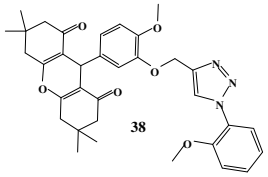
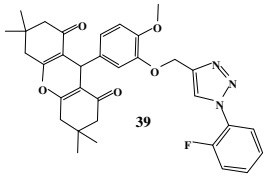
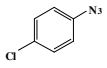
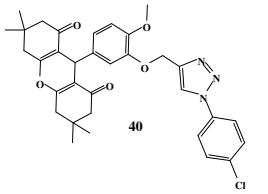
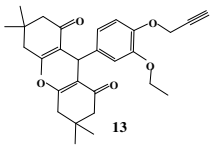
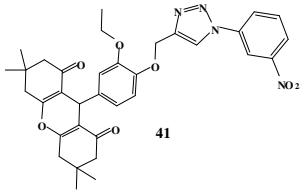
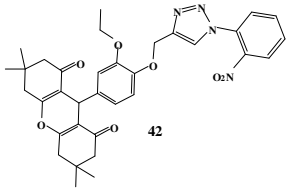
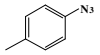
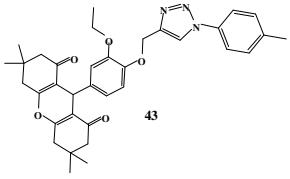
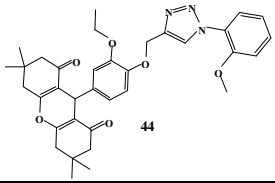
Entry	Catalyst (mol %)	Reductant	Solvent	Time (min)	Yield (%)[a]
1	**CuO NPs (10)**	**NaOAs**	**^{t}BuOH-H_2O**	**60**	**87**
2	CuO NPs (5)	NaOAs	^{t}BuOH -H_2O	60	64
3	CuO NPs (15)	NaOAs	^{t}BuOH -H_2O	60	83
4	CuO NPs (10)	D-Glucose	^{t}BuOH -H_2O	60	43
5	CuO NPs (10)	-	^{t}BuOH -H_2O	60	12
6	CuO NPs (10)	NaOAs	Ethanol	60	65
7	CuO NPs (10)	NaOAs	^{t}BuOH	60	76
8	CuO NPs (10)	NaOAs	^{t}BuOH -H_2O	30	42
9	CuO NPs (10)	NaOAs	^{t}BuOH -H_2O	90	87
10	$CuSO_4.5H_2O$ (10)	NaOAs	^{t}BuOH -H_2O	60	74
11	$CuSO_4.5H_2O$ (10)	D-Glucose	^{t}BuOH -H_2O	60	34
12	$Cu(OAc)_2.2H_2O$ (10)	NaOAs	^{t}BuOH -H_2O	60	51
13	$Cu(OAc)_2.2H_2O$ (10)	D-Glucose	^{t}BuOH -H_2O	60	32

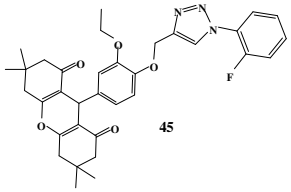
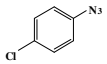
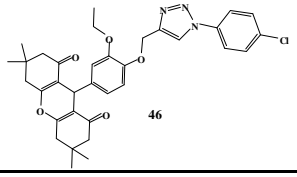
xanthene **10** (1 mmol), azide **14** (1.2 mmol) in room temperature under the above conditions.

Table 2 Synthesis of xanthenes substituted triazoles (**21-46**).

Entry	xanthenes	azides	Product	Yield (%)
1	 **10**	 **14**	 **21**	87
2		 **15**	 **22**	85
3		 **16**	 **23**	91
4		 **17**	 **24**	78

5		18	 25	85
6		19	 26	87
7		20	 27	74
8		11	 14	 28	85
9			 15	 29	82
10			 16	 30	86
11			 17	 31	75
12			 18	 32	82
13			 19	 33	84
14			 20	 34	78

15	 **12**	 **14**	 **35**	81
16		 **15**	 **36**	79
17		 **16**	 **37**	85
18		 **18**	 **38**	86
19		 **19**	 **39**	84
20		 **20**	 **40**	85
21	 **13**	 **15**	 **41**	76
22		 **16**	 **42**	79
23		 **17**	 **43**	72
24		 **18**	 **44**	74

25	 **19**	 **45**	79
26	 **20**	 **46**	68

a – isolated yields

Reusability

The reusability of CuO NPs was also examined. After the reaction, the catalyst was separated by centrifugation, washed three times with 5 mL of methanol, dried at 100 °C overnight and subjected to the subsequent run. The catalyst can be used for four times without dramatic yield loss. The comparison of efficiency of catalyst on repeated use is reported in Fig. **4**.

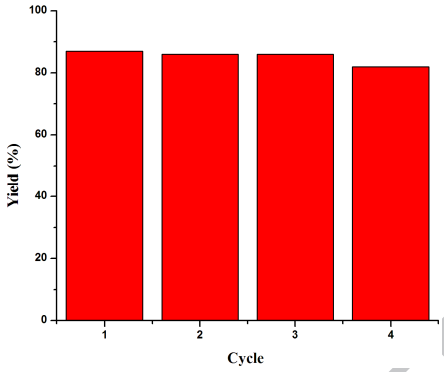


Fig. 4 Reusability of CuO nanoparticles

Conclusion

In conclusion, we have developed a simple and efficient protocol for the synthesis of xanthene substituted 1,2,3-triazoles through 1,3-dipolar cycloaddition of aromatic azides with acetylenic xanthenes using Copper oxide nanoparticles as an efficient and recyclable catalyst. The above protocol has been performed efficiently to provide the desired products in good yields. Simple operation, short reaction times, easy separation and inexpensive and recyclable catalyst are the salient features of this method. The photo-physical studies of the synthesized compounds are under the progress in our group.

Acknowledgements

Authors are thankful to the administration, VIT University, Vellore, India for providing facilities to carry research work and also thankful to SIF-Chemistry, VIT University for providing NMR and XRD facilities. Authors are thankful to Nano Facilities, IIT Madras for providing TEM facility. Author P. Iniyavan is thankful to the VIT University for providing Research Associateship.

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36. General procedure for the synthesis of xanthenes (5, 6 and 7).

A mixture of hydroxy benzaldehydes (1 mmol) and 5,5-Dimethylcylcohexane-1,3-dione (2 mmol) was refluxed in ethanol with BF_3:OEt_2 as catalyst for 3-4 hrs. After the completion of the reaction (monitored by TLC), the resulting precipitate was filtered, washed with water and a small amount of ice cold ethanol. The crude product was recrystallized from absolute ethanol and it was found to be pure and no further purification was necessary.

37. General procedure for the synthesis of alkyne substituted xanthenes (10-13)

To a solution of 1 equiv. of xanthenes **5**, **6** and **7** in 5 ml of dry DMF, 2 equiv. of powdered K_2CO_3 was added, stirred well for 30 min at room temperature. To that, propargyl bromide (1.2 equiv) dissolved in minimum amount of DMF was added drop wise and the reaction mixture was stirred at room temperature for 2 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into a beaker containing ice cold water and stirred well. The precipitate was collected and dried. No chromatographic separation required.

38. General synthetic procedure for the aromatic azides (14-20)

The aniline substrate (10 mmol) was dissolved in hydrochloric acid (37% w/w, 15 ml) in a round-bottom flask and cooled to 0° C in an ice bath. The sodium nitrite (12 mmol) solution was added drop wise into the aniline/acid solution and stirred for 10 min. NaN_3 (12 mmol) was then added in portions and stirred for 1 h, while the reaction mixture was allowed to warm to room temperature. Finally, the solution was extracted with dichloromethane and the organic layers were combined and washed with H_2O and saturated brine sequentially before being dried over Na_2SO_4. Solvent removal under reduced pressure afforded azidobenzene derivatives.

39. General synthetic procedure for the xanthene substituted triazole derivatives (21-46)

azides (1.2 mmol), acetylenic xanthenes (1 mmol) and sodium ascorbate (20 mol%) were added over 10 mol % of the CuO nanoparticles suspension in TBA-H_2O solvent mixture and it was kept for stirring at room temperature. After completion of the reaction as indicated by thin-layer chromatography (TLC), the reaction mixture was centrifuged to separate the catalyst. The filtrate was quenched with water and the product was extracted with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrate under reduced pressure, and then the residue was purified by column chromatography on silica gel (hexane/ ethyl acetate, 70/30) to afford the pure products.

40. 3,3,6,6-tetramethyl-9-(4-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**21**): white solid; mp. 190-192 ^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98, 1.09 (s, 12H, CH_3), 2.21 (m, 4H, CH_2), 2.45 (s, 4H, CH_2), 4.70 (s, 1H, CH), 5.22 (s, 2H, CH_2), 6.88 (d, J = 7.6 Hz, 2H, ArH), 7.23 (d, *J* = 8.4 Hz, 2H, ArH), 7.46 (t, *J* = 7.6 Hz, 1H, ArH), 7.54 (t, J = 7.6 Hz, 2H, ArH), 7.73 (d, J = 7.6 Hz, 2H, ArH), 8.01 (s, 1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 27.38, 29.25, 31.01, 32.22, 40.87, 50.78, 62.03, 76.73, 77.05, 77.25, 77.36, 114.38, 115.72, 120.67, 120.94, 128.90, 129.50, 129.78, 136.97, 137.33, 145.34, 156.64, 162.20, 196.57. DEPT-135 (100 MHz, $CDCl_3$): δ 27.39 (CH_3, C-11, 11'), 29.27 (CH_3, C-11, 11'), 31.01 (CH, C-3), 40.88 (CH_2, C-7, 7'), 50.79 (CH_2, C-8, 8'), 62.06 (CH_2, C-16), 114.37 (CH, C-15, 15'), 120.68 (CH, C-20, 20'), 128.87 (CH, C-18), 129.50 (CH, C-21, 21'), 129.77 (CH, C-13, 13') ppm; ESI-MS (*m/z*): calcd 523.6 Found: 524.3 (M+1). Anal. calcd. for $C_{32}H_{33}N_3O_4$ C, 73.40; H, 6.35; N, 8.02. Found C, 72.10; H, 6.42; N, 7.89.

Graphical Abstract

CuO Nanoparticles: Synthesis and application as an efficient Reusable Catalyst for the preparation of xanthene substituted 1,2,3-triazoles via click chemistry

P. Iniyavan, G.L. Balaji, S. Sarveswari, V. Vijayakumar*

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