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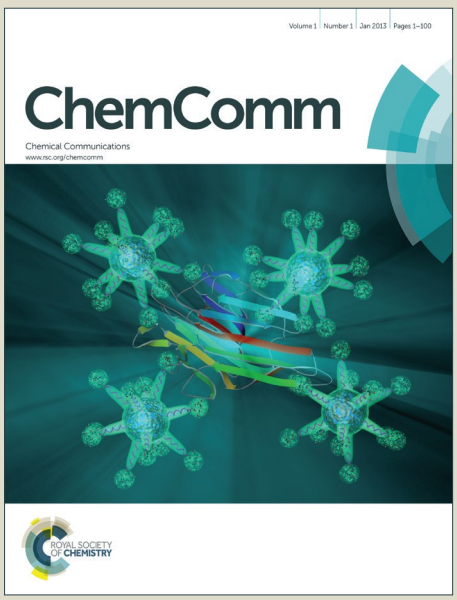

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Copper(I)-Y Zeolite Catalyzed N-Sulfonlyketenimine Mediated Annulation of Hydroxynaphthoquinones: Syntheses of Naphtho[2,1-*b*]furan-2,5-diones and Benzo[*de*]chromene-2,6-diones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x
www.rsc.org/

Devenderan Ramanathan,[a] Kayambu Namitharan,[a] Kasi Pitchumani*[a,b]

An efficient one pot synthesis for the construction of novel naphtho[2,1-*b*]furan-2,5-diones and benzo[*de*]chromene-2,6-diones is reported using copper(I)-Y zeolite catalyzed reaction of *N*-sulfonylketenimine with 2-hydroxy-1,4-naphthoquinone and 5-hydroxy-1,4-naphthoquinone followed by the elimination of *p*-toluenesulfonamide. The intermediate *N*-sulfonylketenimine, generated by (3+2) cycloaddition/ ring-opening reaction/ retro-Wolff rearrangement, cascade, annulation promotes the reaction involving the inter- and intramolecular nucleophilic addition/dehydration followed by hydrolysis and elimination of *p*-toluenesulfonamide to afford the target products in good yield.

Many drug molecules, which are small organic compounds with molecular mass less than 1000,[1] are difficult to synthesize in large quantities because of the complex multi-step syntheses that have dampened interest in developing them.[2] Consequently newer strategies with reduced numbers of steps and atom economy are in demand and catalysed cascade reactions which employ a single catalyst capable of promoting the various individual steps and strategies that utilize metal and metal-free routes in novel cascade reactions are immensely desirable.[3,4] Due to their unique redox properties, naphthoquinones are considered as privileged molecular scaffolds in medicinal chemistry and have attracted attention in recent years. They serve as vital links in the electron transport chains in the metabolic pathways and participate in multiple biological oxidative processes. Quinones are both oxidants and electrophiles, and the relative contributions of these properties to both their toxic and therapeutic activities is influenced by their chemical structure, and the substituent effects in the quinone nucleus (Fig. 1).[5] The 1,2- and 1,4-naphthoquinones fused with furan or pyran rings possess broad biological activities. For example, naphtho[1,2-b]furan-4,5-dione (NFD) exhibits potent cytotoxicity against human cancer cell lines (KB, HeLa, HepG2 cell lines) and inhibits the metastasis in various tumors, including breast carcinoma and lung adenocarcinoma. NFDs display anticancer, antifungal activities, and have therapeutic potential in breast cancer treatment.[6]

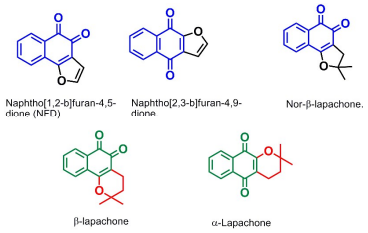


Fig 1. Biologically important naphthofurandiones (NFD) and benzochromenediones.

In recent years, ketenimine based cascade reactions have gained wider interest in organic synthesis, in view of their high efficiency, diverse reactivity, bond forming ability and selectivity for the construction of complex organic compounds in a cascade manner.[7] Commonly, they involve nucleophilic and radical additions to the central electrophilic carbon atom and also pericyclic reactions such as cycloaddition, sigmatropic rearrangements and 6π-electrocyclic ring closure, leading to synthesis of different ring sizes with good atom economy and milder reaction conditions.[8] However, in ketenimine-based chemistry, compared to nitrogen analogues, reports on synthesis of oxygen-containing heterocyclic compounds are rare and, to the best of our knowledge, only few examples such as synthesis of coumarin and iminocoumarin derivatives from inter- and intramolecular nucleophilic addition of 2-hydroxyacetophenone,[8k,9a-e] oxazepan-7-one from intramolecular ring closure followed by hydrolysis of 1-aryl-2-(aryl(prop-2-ynyl)amino)ethanol,[9f] dihydrofuran from inter- and intramolecular ring closure reactions of active methylenes,[9g] benzoxazolines from [2+2] cycloaddition reaction of phenolic Schiff's base followed by intramolecular nucleophilic addition of phenoxide ion.[9h] Inspired by these features we have focused our attention on the synthesis of novel and unique naphtho[2,1-*b*]furan-2,5-diones and benzo[*de*]chromene-2,6-diones and the observed results are given below.

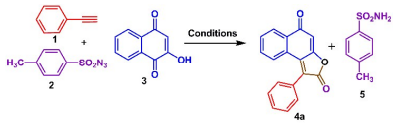
Initial studies and optimization of reaction conditions are given in Table 1. Phenylacetylene **1a** and tosyl azide **2a** were chosen as model substrates. Upon addition of one equiv. of

[a] *School of Chemistry, Madurai Kamaraj University, Madurai – 625 021, India.*
[b] *Centre for Green Chemistry Processes, School of Chemistry, Madurai Kamaraj University, Madurai – 625 021, India*

† Electronic Supplementary Information (ESI) available: Experimental procedures, supplementary data and the ^{1}H-, ^{13}C-NMR spectra. See DOI: 10.1039/x0xx00000x

2-hydroxy-1, 4-napthoquinone **3** and two equiv. of Et_3N with 10 mol% of CuI in CH_2Cl_2 at room temperature under nitrogen atmosphere, **3** was consumed completely and the corresponding product **4a** was observed in 45% yield within 30 min. (Table 1, entry 1). The structure of **4a** was established unambiguously by its single crystal (Fig. 2), NMR and HRMS-ESI analyses. To improve the yield, a commercially available 4 Å molecular sieve was added as a drying agent. Use of other copper sources afforded lower yields compared to CuI (Table 1, entries 2-4). Thus it is evident that the nature of the catalyst played a prominent role in the above reaction.

Table 1. Optimization of reaction conditions in syntheses of naphtho[2,1-b]furan-2,5-diones.[a]



Entry	Catalyst	Base	Solvent	Yield (%)[b] 4a
1[c]	CuI	Et_3N	CH_2Cl_2	45
2	CuI	Et_3N	CH_2Cl_2	49
3	CuCl	Et_3N	CH_2Cl_2	35
4	CuBr	Et_3N	CH_2Cl_2	39
5	Cu^IY	Et_3N	CH_2Cl_2	58
6	Cu-HT	Et_3N	CH_2Cl_2	NR
7	Cu^IY	Et_3N	$CHCl_3$	54
8	Cu^IY	Et_3N	THF	60
9	Cu^IY	Et_3N	toluene	46
10	Cu^IY	Et_3N	1,4-dioxane	63
11	Cu^IY	Et_3N	DMSO	48
12	Cu^IY	Et_3N	DMF	55
13	Cu^IY	K_2CO_3	1,4-dioxane	41
14	Cu^IY	DIPEA	1,4-dioxane	53
15	Cu^IY	Pyridine	1,4-dioxane	28
16[d]	Cu^IY	Et_3N	1,4-dioxane	53
17[e]	-	Et_3N	CH_2Cl_2	NR
18[f]	CuI	Et_3N	CH_2Cl_2	NR

[a]Reaction conditions: p-Toluenesulfonyl azide (1.0 mmol), phenylacetylene (1.0 mmol), 2-hydroxy-1,4-napthoquinone(1.0 mmol), base (2.0 mmol), catalyst (10 mol%), 4Å molecular sieves (100 mg), solvent (3.0 mL), rt, N_2, 30 minutes. [b] Isolated yield. [c] Without 4Å molecular sieves. [d] Reaction at 70 °C. [e] Absence of Cu source. [f] Absence of sulfonyl azide. NR = No reaction.

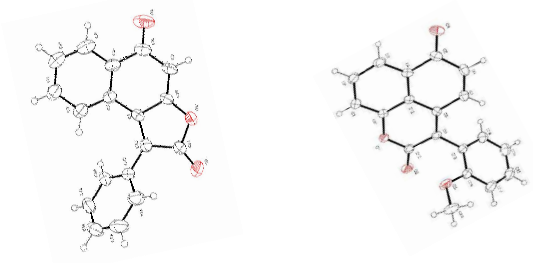
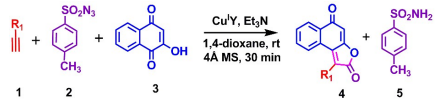


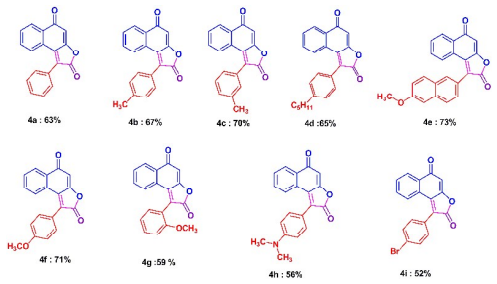
Fig 2. ORTEP diagrams of compounds 4a and 7d.

Our ongoing efforts,[10] to explore the scope of Cu^I-exchanged zeolite as catalysts for organic syntheses, prompted us to probe the utility of Cu^I–Y zeolite[11] as catalyst for this cascade reaction. CuI-exchanged Y-zeolite was prepared by following the literature procedure[12] and characterized by powder X-ray diffraction (PXRD), Energy-dispersive X-ray (EDX) spectroscopy and UV-Diffuse Reflectance Spectroscopy (UV-DRS) (Fig.S1-S3, ESI). In presence of Cu^I-Y zeolite, the reaction proceeded readily and afforded 58% yield of 4a (Table 1, entry 5). The reaction however failed, when other heterogeneous copper catalysts like Cu-HT were employed (Table 1, entry 6). Further screening with various solvents (Table 1, entries 7-12) revealed that 1,4-dioxane was the best solvent of choice, affording the corresponding product 4a in 63% yield. Among the different bases, TEA (triethylamine) gave better yield than other bases like K_2CO_3 (potassium carbonate), DIPEA (N, N-diisopropylethylamine) and pyridine (Table 1, entries 12-15). When the reaction temperature was increased to 70 °C, no improvement in yield was observed (Table 1, entry 16). In control experiments, formation of 4a was not observed in the absence of copper source and tosyl azide (Table 1, entries 17, 18). Thus, the optimized reaction conditions are Cu^I-Y zeolite as catalyst, 1,4-dioxane as solvent, triethylamine (TEA) as base, under nitrogen atmosphere at room temperature for 30 minutes.

The effect of sulfonyl azide in the reaction was also studied and the results are summarized in (Table 1, ESI). Various electron-donating, withdrawing, halogens substituted and fused ring sulfonyl azides were used. The results showed that electron-rich azide (Table 1, ESI, entry 1) gave better yields than electron-deficient (Table 1, ESI, entries 3 and 4), fused and halogen substituted sulfonyl azides (Table 1, ESI, entries 5 and 6).

Table 2. Substrate scope of naphtho[2,1-b]furan-2,5-diones[a,b]





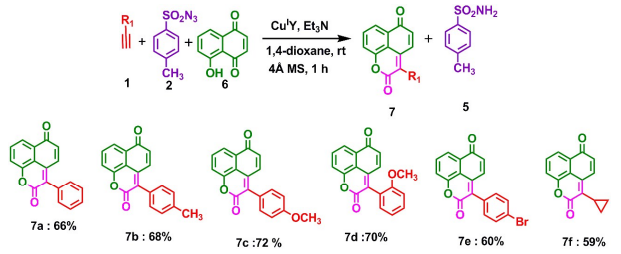
[a]**Reaction conditions:** p-Toluenesulfonyl azide (1.0 mmol), alkyne (1.0 mmol), 2-hydroxy-1,4-naphthoquinone (1.0 mmol), Et_3N (2.0 mmol) and Cu^IY (10 mol %), molecular sieves (100mg), 1,4-dioxane (3.0 mL), rt, N_2, 30 min. [b] Isolated yield.

The studies were extended further to the synthesis of various substituted naphtho[2,1-b]furan-2,5-diones from the corresponding alkynes, 2-hydroxy-1,4-naphthoquinone and tosyl azide. An evaluation of the results showed that the reaction was tolerated among the various substitutions on the terminal alkyne (Table 2). Electron-rich and fused ring substituted alkynes (Table 2, 4a-4f) gave better yields than halogen substituted alkynes (Table 2, 4i). 2-Methoxy and 4-N,N-dimethylphenyl substituted alkynes (Table 2, 4g and 4h) gave moderate yields.

The observed encouraging results with 2-hydroxy-1,4-naphthoquinone prompted us to extend the scope of the reaction to 5-hydroxy-1,4-naphthoquinone (6). Under similar reaction conditions, the same type of inter and intramolecular nucleophilic addition product namely, benzo[de]chromene-2,6-dione (7) was obtained readily. The effect of substituents was also tested with various alkynes such as electron-rich,

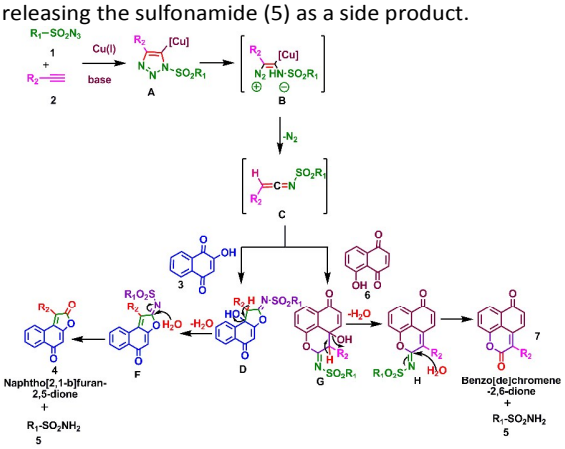
electron-deficient, halogen substituted and nonaromatic alkynes. Electron-rich (table 3, 7a-7d) and halogen substituted alkynes (table 3, 7e) gave good yields compared to nonaromatic alkynes (table 3, 7f). An electron-deficient alkyne namely 4-nitrophenylacetylene was unreactive giving only trace amounts of products.

Table 3. Substrate scope in benzo[*de*]chromene-2,6-diones[a,b]



[a]**Reaction conditions:** *p*-Toluenesulfonyl azide (1.0 mmol), alkyne (1.0 mmol), 5-hydroxy-1,4-naphthoquinone (1.0 mmol), Et_3N (2.0 mmol) and $Cu^{I}Y$ (10 mol%), molecular sieves (100 mg), 1,4-dioxane (3.0 mL), rt, N_2, 1 h. [b] Isolated yield.

Based on the observed experimental results, a plausible mechanistic pathway for the three component cascade reaction is proposed (Scheme 1). In presence of triethylamine and Cu(I)-Y zeolite, phenylacetylene and sulfonyl azide form a copper-triazolyl intermediate (A).[13] This is followed by a ring opening reaction to give (B)[14] which undergoes rearrangement and extrusion of nitrogen to give N-sulfonylketenimine (C), simultaneously regenerating the copper catalyst. The N-sulfonylketenimine (C), as an energetic dipolar intermediate, reacts simultaneously as an electrophile as well as nucleophile, (involving nucleophilic addition of -hydroxyl group of 2- and 5-hydroxy-1,4-naphthoquinones) to give the intramolecular nucleophilic addition product D/G followed by dehydration to give F/H. Due to instability of N-sulfonylimine group, the hydrolysis proceeds readily to give stable five- and six-membered lactones, namely naphtho[2,1-b]furan-2,5-dione(4) and benzo[de]chromene-2,6-dione (7) simultaneously releasing the sulfonamide (5) as a side product.



Scheme 1. Proposed mechanism for the formation of naphtho[2,1-b]furan-2,5-dione and benzo[de]chromene-2,6-dione.

The catalyst is found to be reusable. The catalyst was found to be very efficient for at least four runs. A slight decrease in yield was observed after the three first runs, but the yields from recovered catalyst after isolation were still high after the fourth reuse (53%) (Table 2, ESI).

The presence of an π-extended naphthoquinone skeleton (bis-enone chromophore), prompted us to study the absorption and emission spectra of naphtho[2,1-b]furan-2,5-dione and benzo[de]chromene-2,6-dione derivatives (Figure 2) in acetonitrile solution (1 $X10^{-5}$ M). Naphtho[2,1-b]furan-2,5-dione derivatives exhibited absorbance maximum in the region of 370 to 550 nm and emission at 453 to 611 nm (Fig. 2). All the molecules, except 4e and 4h show dual emission. While the weaker shorter wavelength emission band is due to the localized emission, the longer more intense and broad wavelength emission peak is attributed to the twisted intramolecular charge transfer (TICT). In 4e, both the bands merge and in 4h, due to the presence of dimethylamino and carbonyl groups, ground state intramolecular charge transfer may have occurred, which consequently suppress the emission. Benzo[de]chromene-2,6-dione derivatives also showed absorbance in the region of 387 to 410 nm and emission at 543 to 546 nm (Fig. 2). Here also the emission bands are very broad. However the shift in λ emission is less pronounced than the naphtho[2,1-b]furan-2,5-dione (Table 3, ESI).

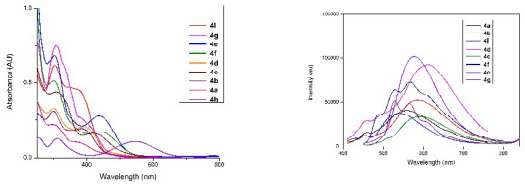


Figure 2. UV-Vis.absorbance and emission spectra of naphtho[2,1-b]furan-2,5-dione derivatives in CH_3CN at $1x10^{-5}$ M.

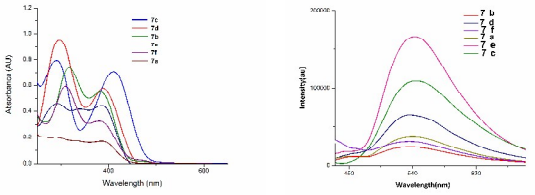


Figure 3. UV-Vis.absorbance and emission spectra of benzo[*de*]chromene-2,6-dione derivatives in CH_3CN at $1x10^{-5}$ M.

The potential redox properties of the extended naphthoquinone moiety (bis-enone chromophore) prompted us to study the biological applications of naphtho[2,1-b]furan-2,5-dione 4a (R_1= -C_6H_5), 4f (R_1= *p*-OCH_3-C_6H_4), 4i (R_1= *p*-Br-C_6H_4) and benzo[de]chromene-2,6-dione 7a (R_1= -C_6H_5), 7c (R_1= *p*-OCH_3-C_6H_4) and 7e (R_1= *p*-Br-C_6H_4) against Liver cancer cell line Hep3B, breast cancer cell line MB231 and gastric cell line AGS. The percentage cell viability was determined using the MTT assay.[15] The results indicate that, compared to AGS and MB231 cell lines, Hep3B cell line showed good biological activity. The cell viability results of compounds 4a, 4f, 4i, 7a, 7c and 7e against the Hep3B cell line at 10 μM are 94%, 41%, 66%, 59%, 52%, 26% respectively (Table 4, ESI), indicating that excepting 4a, all other compounds exhibit good biological activity. The results also show that benzo[de]chromene-2,6-dione (7) and their derivatives (7a, 7c and 7e) exhibit good biological activity compared to naphtho[2,1-b]furan-2,5-dione (4) and their derivatives (4a, 4f and 4i) (Fig. S4, ESI). These results thus highlight the potential biological activity of these molecules towards various therapeutic applications.

Conclusions

In summary, we have demonstrated a novel and facile copper(I)-Y zeolite catalyzed synthesis of biologically important five- and six- membered lactones namely naphtho[2,1-b]furan-2,5-dione, benzo[de]chromene-2,6-dione through *in situ* generated N-sulfonylketenimines and 2- and 5-hydroxy-1,4-naphthoquinones. The methodology of this study is simple, cost-effective and environmentally friendly. The milder reaction conditions enable the utilization of a wide range of substrates that deliver products in high yield and excellent purity. This reaction utilizes inexpensive copper(I)-Y zeolite giving improved yield compared to its homogeneous equivalents and the catalyst can be reused at least four times without any marked change in the overall yield. The presence of an π-extended bis-enone chromophore in naphtho[2,1-b]furan-2,5-dione, benzo[de]chromene-2,6-dione derivatives is evidenced from good absorption and emission spectra in acetonitrile solution and these compounds show good biological activity against human hepatocellular carcinoma cell Hep3B.

Acknowledgements

We thank CSIR, New Delhi, India for financial support and Dr. G. Kumaresan, Department of Genetics, School of Biological Sciences, Madurai Kamaraj University, for biological studies.

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