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CuO/CNTs-catalyzed heterogeneous process: a convenient strategy to prepare furan derivatives from electron-deficient alkynes and α-hydroxy ketones[†]

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As heterogeneous catalysts and nanoparticle support materials, CNTs have attracted great interest in organic chemistry. This paper reports facile CuO/CNTs-catalyzed cyclization to form furan derivatives from electron-deficient alkynes and α -hydroxy ketones. It represents a facile synthetic route, and the eco-friendly catalyst can be easily separated by filtration and reused.

Transition-metal-catalyzed reactions^{1–8} are versatile tools for the straightforward and facile construction of new carbon–carbon bonds from readily accessible starting materials in a single operation under mild conditions. Many significant reactions in this area have been achieved with a variety of homogeneous metal catalysts.^{9–16} However, homogeneous catalysis, in general, suffers from the deficits in recovery of homogeneous catalysts, the separation of products, the use of expensive ligands, such as phosphanes or carbenes, and additives^{17–21} that are difficult to prepare and handle. These problems are of particular environmental and economic concern in large-scale syntheses. The heterogenization of homogeneous catalysts can facilitate their use for practical processes to avoid these problems.^{22,23} There has been considerable interest in the development of heterogeneous catalytic systems that can be efficiently re-used whilst keeping the inherent activity of the catalytic center.^{24–31}

Carbon nanotubes (CNTs) have recently emerged as promising supports for immobilization due to their high surface area, excellent electrical conductivity and unique structure, and also supported catalysts can be easily separated from the reaction medium.^{32–38} Copper(II) was one of the most powerful and extensively used catalyst for synthesis of bio-active molecules, such as drugs and agrochemicals.^{39–41} In this context, the development of a promising copper/CNTs heterogeneous catalyst

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opens new possibilities for the achievement of desirable catalytic activity and effective separability.

Furan derivatives are one of the most important heterocyclic compounds⁴² and are worth our attention, for functionalized furans exhibit a wide range of biological activities,^{43–48} and many naturally occurring compounds containing furan skeletons as a key structural unit.^{49,50} Recently, our group have reported facile one-pot nano-Cu₂O-catalyzed⁵¹ and other homogeneous catalyzed^{52–57} domino reactions to synthesize highly functionalized polysubstituted furan derivatives. These advantages encouraged us to develop the heterogeneous catalytic systems and design a new method to prepare furan molecules.^{58–67} Herein, we anticipated to report an environmentally friendly CuO/CNTs-catalyzed cyclization process to synthesize furan derivatives from electron-deficient alkynes and α -hydroxy ketones.

Initially, substrates 1a and 2a were used as the starting materials. The intermediate product diethyl 2-(2-oxopropoxy)maleate 3a was easily prepared through nucleophilic addition of diethyl but-2-ynedioate 1a with 3-hydroxybutan-2-one 2a in the presence of DABCO in CH₂Cl₂ at room temperature for ten minutes. Then the CH₂Cl₂ was evaporated to dryness under reduced pressure and a pure sample of 3a was obtained by column chromatography. Subsequently, our study focused on cyclization of **3a** by testing various copper catalysts, substrates, additives, solvents, and reaction times, respectively (the results are outlined in Table 1). Several 5 mol% copper(II) and copper(I) salts, such as CuCl₂, CuBr₂, Cu(OAc)₂, CuO, CuI, CuBr, and CuCl (Table 1, entries 1-7), were screened in the initial experiments at 60 °C. Most gave yields of less than 10%. Only Cu(OAc)₂ and CuO could gave 24% and 25% yields respectively. It was indicated that Cu(OAc)₂ and CuO could catalyze this transformation. Stimulated by these results, we attempted to prepare CuO/CNTs to improve the yields during the reaction. According to previous reports,⁶⁵ CuO/CNTs were synthesized by a simple hydrothermal method. The formation of the CuO/CNTs was confirmed by TEM (Fig. 1a), XRD (Fig. 2) and XPS analysis (Fig. SI-1a, ESI[†]).

To our delight, the reaction yield of **4aa** was dramatically increased to 58% (Table 1, entry 8), when CuO/CNTs was examined in DMF at 60 °C. We were pleased to find that the reaction time has decreased from 20 h to 6 h. This indicated that the excellent electrical conductivity of CNTs could promote the cyclization reaction. Some additives, such as CH_3CO_2H ,

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CO ₂ E1	HO 2a	$\frac{BCO}{I_2 Cl_2, rt} EtO_2$	$\frac{1}{100}$ $\frac{1}$	EtO C EtO ₂ C	2 ^C 4aa
Entry	Catalyst	Additive	Solvent	<i>t</i> (h)	$\mathrm{Yield}^{b}(\%)$
$ \begin{array}{c} 1\\ 2\\ 3\\ 4\\ 5\\ 6\\ 7\\ 8\\ 9\\ 10\\ 11\\ 12\\ 13\\ 14\\ 15\\ 16\\ 17\\ 18\\ 19\\ 20\\ 21\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22\\ 22$	CuCl ₂ CuBr ₂ Cu(OAc) ₂ CuU CuI CuBr CuCl CuO/CNTs CuO/CNTS		DMF DMF DMF DMF DMF DMF DMF DMF DMF DMF	$\begin{array}{c} 20\\ 20\\ 20\\ 20\\ 20\\ 20\\ 20\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\ 6\\$	$ \begin{array}{c} 10\\ 8\\ 24\\ 25\\\\\\ 58\\ 89\\ Trace\\ 78\\ Trace\\ Trace\\ 70\\\\ 87\\ 86\\ 50\\ 43\\ 71\\ 78\\ 63 (82)^c \end{array} $

 Table 1
 Screen of reaction conditions^a

^{*a*} Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), catalyst (5% mol) (entries 1–7); 6% mol (entries 8–20), additive (10% mol), solvent (3.0 mL), at 60 °C for 6–20 h. ^{*b*} GC-yield. ^{*c*} The yield obtained after reaction for 12 h.



Fig. 1 TEM images of catalyst: (a) before reaction; (b) after reaction.

 F_3CCO_2H , $PhCO_2H$, H_2SO_4 , HCl and L-proline (Table 1, entries 9–14), were added to the system, but most of them provided much worse results. When F_3CO_2H , H_2SO_4 or HCl were used, the yield of **4aa** decreased sharply and only trace amounts of the product were found by TLC. Interestingly, when CH_3CO_2H was added, the yield of **4aa** was increased to 89%. Solvent effects were also investigated. Reactions in a polar solvent, such as CH_3CN , DMF and DMSO, afforded good results, while non-polar solvents, such as toluene or $ClCH_2CH_2Cl$, deteriorated the yields.

With the establishment of a viable reaction system, we set out to explore the scope of this sequential process (the results were indicated in Scheme 1). In order to explore the scope of the cyclization reaction, a variety of electron-deficient alkynes and



Fig. 2 XRD pattern of CuO/CNTs (# represents carbon nanotubes).

 α -hydroxy ketones were examined in the presence of CuO/CNTs to form the corresponding furan derivatives.

By using **1a** as a fixed substrate, we first carried out the reactions with various types of α -hydroxy ketones. From Scheme 1, we found that the reaction conditions have proven to be useful for α -hydroxy ketones **2a–2h**. It was obvious that the reaction between diethyl but-2-ynedioate (**1a**) and different α -hydroxy ketones **2a–2h** had a beneficial effect on the reaction products, and in most cases the corresponding products **4aa–4ah** were obtained in moderate to good yields. It was also shown that no matter whether R³ and R⁴ were aromatic or aliphatic substituted groups, the cyclization had no effect on this transformation.

To further expand the scope of this transformation, other electron-deficient alkynes, such as dimethyl but-2-ynedioate (1b), ethyl but-2-ynoate (1c), ethyl propiolate (1d), ethyl 3-phenylpropiolate (1e), 1,3-diphenylprop-2-yn-1-one (1f) and methyl oct-2-ynoate (1g) were employed. The results showed that electron-deficient alkynes 1b–1g were also well tolerated under the optimum conditions and afforded the corresponding products in good yields. These results indicated that the electron-deficient alkynes with different substitute groups could react smoothly, and the corresponding products were obtained in good yields. Finally, all those cases showed that the reaction conditions were useful for a range of electron-deficient alkynes 1b–1g and substituted α -hydroxy ketones.

Subsequently, we turned our attention to catalyst recycling and reuse. After completion of the reaction, within 40–50 s, the reaction mixture turned clear and the catalysts were deposited on the button (Fig. 3), which was recovered by filtration, and then reused in the next reaction. The results are shown in Table 2, and indicate that the catalytic activity was maintained even when the catalyst was reused for 5 times (Fig. 1b and Fig. SI-2b†).

To gain further insight into the mechanism of this transformation, we envisioned the possibility of trapping the intermediates of the reaction. Firstly, intermediate A has been isolated successfully, then the control experiments were carried out and are shown in Scheme 2. Finally, the results indicate that the CuO/ CNTs and H^+ is essential for these reactions, however, intermediate B and C had hardly been detected.

Based on the control experiments, a possible mechanism is depicted in Scheme 3. Firstly, DABCO-promoted nucleoaddition of 2a to 1b formed intermediate A which is activated by CuO/



Scheme 1 CuO/CNTs-catalyzed synthesis of furans.



Fig. 3 Photographs showing the separation of catalyst.

Table 2The catalyst reuse^a

CO ₂ Et	01)DABCO,	CH ₂ Cl ₂ , rt EtO ₂ C		
+ CO₂Et ⁺ 1a	10 2)CuO/CN ⁻ CH ₃ CO ₂ H, 2a	rs, DMF, 60 ⁰ C EtO₂0	e o o o o o o o o o o o o o o o o o o o	
Entry	Catalyst	Run	$\mathrm{Yield}^{b}\left(\%\right)$	
1	CuO/CNTs	1	89	
2	CuO/CNTs (reuse)	2	89	
3	CuO/CNTs (reuse)	3	89	
4	CuO/CNTs (reuse)	4	88	
5	CuO/CNTs (reuse)	5	87	
6	CuO/CNTs (reuse)	6	85	

^{*a*} Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), 10% mol AcOH, DMF 3.0 mL, at 60 °C for 6 h. ^{*b*} GC-yield.



Scheme 2 Control experiment.

CNTs and H⁺ to give adduct **B**. The coordination of H⁺ to the carbonyl group lowers the electron density of the carbon–oxygen double bond, which makes the nucleophilic attack of the α -carbon toward the carbonyl carbon generate intermediate **C**. Finally, the desired product was obtained by hydration of intermediate **C**.

In conclusion, we have synthesized carbon nanotube supported CuO and developed a highly active, easily recoverable, and practical heterogeneous catalyst for cyclization reactions, which provides efficient access to the construction of highly substituted furans from electron-deficient alkynes and α -hydroxy ketones. In particular, the performance of the catalyst fully promoted the transformation and shortened reaction times due to the excellent electrical conductivity of the carbon nanotubes. In addition, further studies will focus on utilizing this



Scheme 3 Possible mechanism.

heterogeneous catalytic system in organic synthesis and applications of these methodologies are underway and will be reported in future publications.

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