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Communication

A recyclable metal-organic framework MOF-199 catalyst in coupling and cyclization of β-bromo-α,β-unsaturated carboxylic acids with terminal alkynes leading to alkylidenefuranones

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ABSTRACT

β-Bromo-α,β-unsaturated carboxylic acids react with terminal alkynes in DMF in the presence of a catalytic amount of metal-organic framework MOF-199 along with a base under microwave irradiation to afford the corresponding alkylidenefuranones in good yields. The catalytic system could be easily recovered and reused 5 times without any loss of catalytic activity.

1. Introduction

It is known that many furanone-containing compounds exhibit a wide spectrum of biological activities such as antibacterial, cytotoxic, antimicrobial, antibiotic, and antitumor [1]. Thus, many furanone-containing compounds have been synthesized and tested for biological activity [1]. In connection with this report, during the course of our continuing studies directed towards transition metal-catalyzed cyclization reactions of β-bromo-α,β-unsaturated aldehydes and their derivatives, we have identified several new methods for the synthesis of carbo- and heterocyclic compounds [2]. β-bromo-α,β-unsaturated aldehydes and their derivatives are readily prepared from α-methylene group-containing ketones by bromination under Vilsmeier-Haack conditions [3], and the products can serve as valuable building blocks for the construction of various cyclic compounds [4]. Among such cyclization reactions, we have shown that β-bromo-α,β-unsaturated carboxylic acids are coupled and cyclized with terminal alkynes in the presence of Pd on C/PPh_3 or CuI/amino acid to give alkylidenefuranones [5]. However, these protocols have some drawbacks requiring an expensive consumable transition metal catalyst or an additional ligand. The present work was disclosed during the discovery of a reusable catalyst alternative for such coupling and cyclization. Metal-organic frameworks (MOFs) have been widely used as materials in numerous fields [6]. Besides such exploitations, quite recently, it is also known that MOFs are used as a catalyst or catalyst support for versatile organic and organometallic reactions [7]. Under these circumstances, this report describes a recyclable MOF-199-catalyzed coupling and cyclization of β-bromo-α,β-unsaturated carboxylic acids with terminal alkynes leading to alkylidenefuranones under microwave irradiation [8].

2. Results and discussion

First we optimized the conditions for the coupling and cyclization of 2-bromocyclohex-1-enecarboxylic acid (**1a**) with phenylacetylene (**2a**) (Table 1). Treatment of acid **1a** with 1.5 equivalent of **2a** in DMF at 100 °C for 15 min in the presence of a catalytic amount of MOF-199 and K_2CO_3 under microwave irradiation (100 W initial power) gave (3*Z*)-3-benzylidene-4,5,6,7-tetrahydroisobenzofuran-1(3*H*)-one (**3a**) in 69% isolated yield with incomplete conversion of **1a** (entry 1). Increasing the initial microwave power to 200 W gave no significant change in **3a** yield (entry 2). The yield of **3a** increases on prolonging the reaction time to 30 min with complete conversion of **1a**, which was monitored until **1a** had disappeared on thin-

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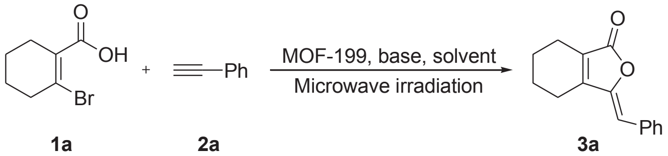
Table 1
Optimization of conditions for the reaction of **1a** with **2a**.[a]



Entry	Bases	Solvents	Temp (°C)	Time (min)	Yield (%)
1	K_2CO_3	DMF	100	15	69
2[b]	K_2CO_3	DMF	100	15	71
3	K_2CO_3	DMF	100	30	81
4	K_2CO_3	DMF	30	30	0
5	K_2CO_3	DMF	50	30	22
6	Na_2CO_3	DMF	100	30	68
7	K_3PO_4	DMF	100	30	63
8	NaO^{t}Bu	DMF	100	30	60
9	Cs_2CO_3	DMF	100	30	68
10	NaOAc	DMF	100	30	60
11	Bu_3N	DMF	100	30	0
12	–	DMF	100	30	0
13	K_2CO_3	Toluene	100	30	69
14	K_2CO_3	1,4-Dioxane	100	30	65

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), MOF-199 (0.03 mmol), base (0.6 mmol), solvent (3 mL), 100 °C, under microwave irradiation (100 W initial power).

[b] 200 W initial power.

layer chromatography (entry 3). The reaction did not proceed at all at 30 °C and lowering the reaction temperature to 50 °C resulted in lower yield of **3a** (entries 4 and 5). The reaction also proceeded in the presence of other inorganic bases such as Na_2CO_3, K_3PO_4, NaO^{t}Bu, Cs_2CO_3, and NaOAc, but the yields of **3a** were generally lower than that obtained in the presence of K_2CO_3 (entries 6–10). However, the reaction did not proceed at all in the presence of organic base or in the absence of base (entries 11 and 12). Among the solvents examined, DMF was found to be that of choice (entries 13 and 14). The best results in terms of the yield of product **3a** and complete conversion of **1a** were achieved by the using the set of reaction conditions shown in entry 3 of Table 1.

Having optimized the reaction conditions, β-bromo-α,β-unsaturated carboxylic acids **1** were subjected to reaction with terminal alkynes **2** to investigate the scope of the reaction and several representative results are summarized in Table 2. 2-Bromocyclohex-1-enecarboxylic acid (**1a**) reacted with aryl alkynes (**2b** and **2c**) having electron-donating and –withdrawing group substituents on aromatic ring and the corresponding benzylidenefuranones (**3b** and **3c**) were produced invariably irrespective of the electronic nature of such substituents. The acid **1a** also coupled and cyclized with terminal alkynes (**2e** and **2f**) having straight and branched alkyl chains to give the corresponding alkylidenefuranones (**3d** and **3e**) in good yields. These results clearly indicate that the present catalytic system exhibit higher catalytic activity compared with Pd on C/CuI/PPh_3 and CuI/L-proline [5]. The yields under both catalytic systems are shown in parentheses of Table 2. The coupling and cyclization of six-membered β-bromo-α,β-unsaturated carboxylic acids **1b** and **1c** reacted with terminal alkynes to give the corresponding furanones in similar yields, irrespective of the presence of the methyl and phenyl substituents on **1b** and **1c**. With cyclic β-bromo-α,β-unsaturated carboxylic acids (**1d-g**) having various ring sizes, the corresponding coupled and cyclized benylidenefuranones **3h-k** were also formed in 72–84% yields, and the product yield was not significantly affected by the ring size. To test for the effect of the position of bromide and carboxy group on β-bromo-α,β-unsaturated carboxylic acids **1h** and **1i** were employed. Even though the coupling and cyclization took place irrespective of the position, higher product yield was observed with **1h**. As is case for the reaction of **1h** with **2a** under CuI/L-proline system, the product **3l** was obtained as stereoisomeric mixture [5b]. Here again (*Z*)-isomer was formed in preference to (*E*)-isomer. In the reaction with **1i**, (*Z*)-3-benzylidenenaphtho[2,1-*c*]furan-1(3*H*)-one (**3m**) was produced by dehydrogenation of (*Z*)-3-benzylidene-4,5-dihydronaphtho[2,1-*c*]furan-1(3*H*)-one initially formed by intrinsic coupling and cyclization between **1i** and **2a** under the employed conditions. The high resolution mass spectrum of **3m** shows peak at $m/z = 272.0835$ (M+, 100% intensity). Similar dehydrogenation was observed by our recent report on the coupling and cyclization of β-bromo-α,β-unsaturated amides with formamide [9].

The configuration of stereoisomeric product **3m** was clarified by quantum chemical calculations compared with observed NMR chemical shifts. On two possible (*E*)- and (*Z*)-stereoisomers the energy-minimized geometry, energy and chemical shift calculations were performed based on density functional theory (DFT) with B3LYP functional as implemented in the Spartan program [10]. The energetics and chemical shifts of each geometry were calculated using high level 6-311G* basis set.

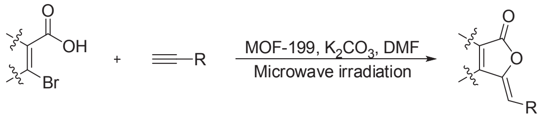
Shown in Fig. 1 are electrostatic potential maps on ball-and-spoke of each isomer. It is easily recognized that (*Z*)-stereoisomer is more stable than (*E*)-isomer destabilized due to steric hindrance caused between phenyl and naphtofuranone moieties. These two aromatic planes are planar for (*Z*)-isomer, but almost orthogonal for (*E*)-isomer, resulting in destabilization due to the π-electron deconjugation of (*E*)-isomer which is 6.05 kcal/mol more unstable by DFT calculation. Also the chemical shift of the proton H8 of naphthofuranone moiety is noticeably indicative to clarify whether the obtained product is (*Z*)- or (*E*)-isomer, because the proton of (*E*)-isomer is located just above phenyl ring due to steric hindrance, which will be highly shielded by the magnetic anisotropic effect. The DFT/6-311G* calculation predicted it resonancing at 6.65 ppm instead of 7.80 ppm in the (*Z*)-isomer. The corresponding chemical shift is observed at 7.78 ppm in $CDCl_3$. This sharp doublet ($J = 8.4$ Hz) of the proton is easily assignable from the other five protons on the naphtofuranone moiety which are all doublets of doublet with long-range coupling. The chemical shift of the vinylic proton is further indicative, which is observed at 6.53 ppm. The DFT/6-311G* calculation resulted in 6.46 ppm for (*Z*)-isomer and 7.24 ppm for (*E*)-isomer. All calculations and observed chemical shifts support that the isolated product has (*Z*)-configuration.

The initial model reaction between the acid **1a** and alkyne **2a** was chosen to test recyclability of MOF-199 (recyclability test was performed on 5 times larger scale). The recycling potential of the catalytic system could be reused five times without any loss of catalytic activity, the yield of **3a** remained nearly constant from 1st (81%), 2nd (81%), 3rd (80%), 4th (80%) to 5th (79%). XRD of the fresh and reused (after fifth run) MOF-199 demonstrated that the crystallinity of the catalyst was kept unchanged during the course of the reaction (Fig. 2). The FT-IR spectra of the fresh and reused (after fifth run) MOF-199 also exhibited nearly same absorption bands (Fig. 3). Cu_2 dimeric units in MOF-199 are coordinated by four carboxylate ions as paddle-wheel and two water molecules in axial positions [11]. The axial water molecules can be dissociated in DMF, in which the axial sites show catalytic activities for the present reaction.

3. Conclusion

In summary, it has been shown that β-bromo-α,β-unsaturated carboxylic acids are coupled and cyclized with terminal alkynes in the presence of a catalytic amount of MOF-199 along with a base to

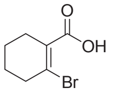
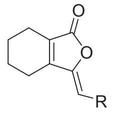
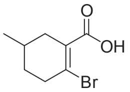
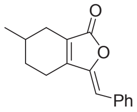
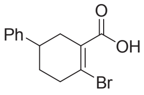
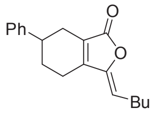
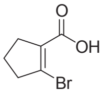
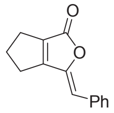
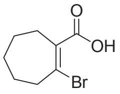
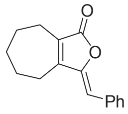
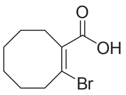
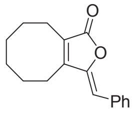
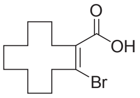
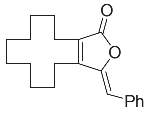
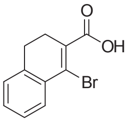
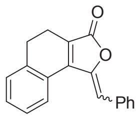
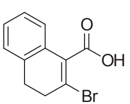
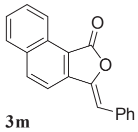
Table 2
MOF-199-catalyzed synthesis of furanones **3** from **1** and **2**.[a]



1

2a R = Ph
2b R = 4-MeC$_6$H$_4$
2c R = 4-FC$_6$H$_4$
2d R = butyl
2e R = hexyl
2f R = isobutyl

3

Carboxylic acids **1**	Alkynes **2**	Furanones **3**	Yield[b] (%)
 **1a**	**2a**	 **3a**	81 (60)
	2b	**3b**	71 (51)
	2c	**3c**	74 (55)
	2e	**3d**	72 (51)[c]
	2f	**3e**	54
 **1b**	**2a**	 **3f**	81 (65)
 **1c**	**2d**	 **3g**	59 (51)[c]
 **1d**	**2a**	 **3h**	72 (50)
 **1e**	**2a**	 **3i**	84 (70)
 **1f**	**2a**	 **3j**	75 (42)
 **1g**	**2a**	 **3k**	73 (56)
 **1h**	**2a**	 **3l**	71[d] (0)
 **1i**	**2a**	 **3m**	21

[a] Reaction condition: **1** (0.3 mmol), **2** (0.45 mmol), MOF-199 (0.03 mmol), K_2CO_3 (0.6 mmol), DMF (3 mL), 100 °C, 30 min, under microwave irradiation (100 W initial power).
[b] Yields under CuI/amino acids are shown in parentheses unless otherwise stated [5b].
[c] Under Pd on C/CuI/PPh$_3$ catalytic system [5a].
[d] (*E*)- and (*Z*)-isomers were isolated in 25% and 46% yields, respectively.

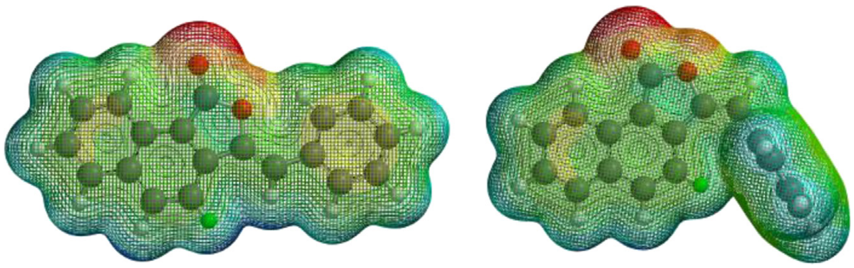


Fig. 1. Electrostatic potential maps on ball-and-spoke model of (*Z*)- and (*E*)-isomer of **3m** as obtained with DFT/6-311G* calculation. The proton H8 of naphtofuranone moiety is shown in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

give alkylidenefuranones in good yields. The MOF-199 catalyst could be easily recovered by simple filtration and solvent washing and reused 5 times without any loss of catalytic activity. Further study of catalytic applications of the present recyclable MOF-199 system to organic reactions is currently under investigation.

4. Experimental

^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Standford Research Inc. MPA100 automated melting point apparatus. X-ray diffraction experiments (XRD) were performed in a Bragg-Brentam $\theta/2\theta$ Rigaku D/Max-2500 diffractrometer using a Cu source working at 40 kV and 200 mA over the range of 5-90° (2θ). FT-IR spectra (ATR) were recorded on Shimadzu IR Prestige-21 spectrophotometer. High-resolution mass spectrometry (HRMS) was performed with a Jeol JMS-700 spectrometer at the Korea Basic Science Center, Daegu Korea. The isolation of pure products was carried out via thin layer (silica gel 60 GF$_{254}$, Merck) chromatography. The starting β-bromo-α,β-unsaturated carboxylic acids were prepared via two steps from the corresponding ketones according to literature procedures [3,12]. Commercially available organic and inorganic compounds were used without further purification.

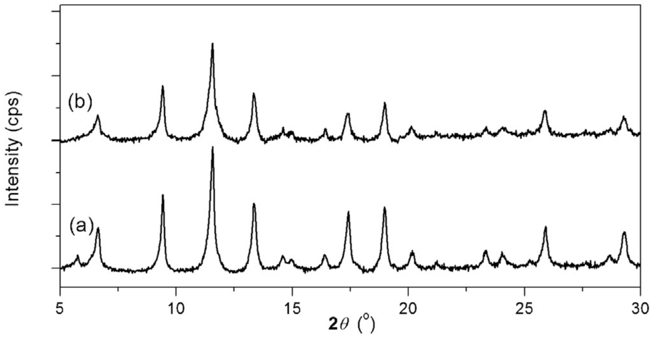


Fig. 2. X-ray powder diffraction pattern of MOF-199: (a) fresh; (b) reused.

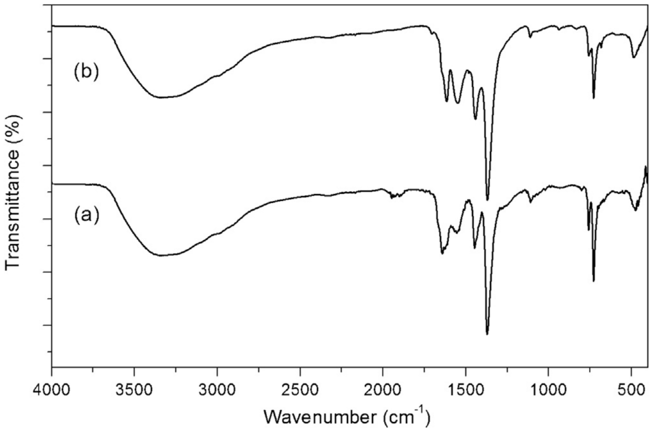


Fig. 3. FT-IR spectra of MOF-199: (a) fresh; (b) reused.

4.1. *General procedure for MOF-199-catalyzed coupling and cyclization of β-bromo-α,β-unsaturated carboxylic acids with terminal alkynes under microwave irradiation*

A 10 mL microwave reaction tube was charged with β-bromo-α,β-unsaturated carboxylic acid **1** (0.3 mmol) and terminal alkyne **2** (0.45 mmol), together with MOF-199 (0.018 g, 0.03 mmol), K_2CO_3 (0.083 g, 0.6 mmol), and DMF (3 mL). The mixture was heated to 100 °C for 30 min by microwave irradiation (CEM Discover Microwave System) at 100 W initial power. After cooling to room temperature, the solid was filtered out, washed with water and MeOH, and dried under vacuum. The recovered MOF-199 was subjected to a second run by charging with **1**, **2**, K_2CO_3, and DMF (recyclability test was performed on 5 times larger scale). Removal of the solvent from the filtrate left an oil, which was purified by thin layer chromatography (silica gel, ethyl acetate/hexane) to give desired products **3**. Except for **3m**, all products were characterized by spectroscopic comparison with authentic samples synthesized by our recent reports [5].

4.1.1. *(Z)-3-Benzylidenenaphtho[2,1-c]furan-1(3H)-one (**3m**)*

Solid, m.p. 133–134 °C (from CH_2Cl_2-hexane); ^{1}H NMR ($CDCl_3$): δ 6.53 (s, 1H), 7.35 (tt, *J* = 7.2, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.4, 7.2 Hz, 2H), 7.64 (dd, *J* = 8.1, 7.7, 1.2 Hz, 1H), 7.75 (dd, *J* = 8.0, 7.7, 1.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.92 (td, *J* = 7.4, 1.4 Hz, 2H), 7.97 (td, *J* = 8.1 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.92 (dd, *J* = 8.0, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 108.51, 116.68, 117.96, 124.17, 127.86, 128.83, 128.87, 129.06, 129.19, 129.68, 130.61, 133.42, 133.97, 135.92, 141.56, 145.08, 167.50; HRMS (EI) Anal. Calc. for $C_{19}H_{12}O_2$ (M^+): 272.0837. Found: 272.0835.

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[10] Low energy conformations of both (E)- and (Z)-stereoisomers were searched by molecular mechanics using MMFF force fields with Monte Carlo minimization procedures, and their equilibrium geometries in methylene chloride were obtained using 6-31G* basis set. And the energetics and chemical shifts of each geometry were calculated using high level DFT/B3LYP/6-311G* basis set. The complete proton chemical shifts of (E)- and (Z)-stereoisomers were summarized along with the observed chemical shifts of product 3m; δ observed proton chemical shift (assignment, calculated chemical shift of (Z)-isomers; (E)-isomers): δ 7.78 (H8, 7.80; 6.65), δ 8.15 (H7, 8.11; 7.72), δ 7.97 (H6, 7.98; 7.86), δ 7.64 (H5, 7.76; 7.74), δ 7.75 (H4, 7.92; 7.89), δ 8.92 (H3, 9.24; 9.29), δ 6.53 (H14, 6.46; 7.24), δ 7.92 (H17 and H21, 8.15; 7.52), δ 7.45 (H18 and H20, 7.55; 7.65), δ 7.35 (H19, 7.42; 7.62)

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