

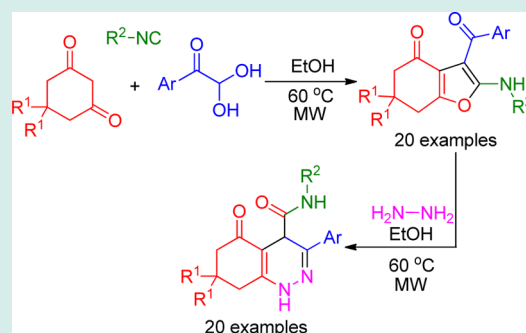
Efficient Domino Strategy for the Synthesis of Polyfunctionalized Benzofuran-4(5*H*)-ones and Cinnoline-4-carboxamides

Guan-Hua Ma, Xing-Jun Tu, Yi Ning, Bo Jiang,\* and Shu-Jiang Tu\*

School of Chemistry and Chemical Engineering, and Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou, 221116, Jiangsu, P. R. China

## Supporting Information

**ABSTRACT:** An efficient, three-component strategy for the improved synthesis of multifunctionalized 6,7-dihydrobenzofuran-4(5*H*)-ones under microwave irradiation in ethyl alcohol within short periods has been established. The synthesized benzofuran-4(5*H*)-ones have been readily converted into polyfunctionalized cinnoline-4-carboxamides by treating with hydrazine hydrate in the same solvent through a regioselective ring-opening of the furan. Tedious workup procedures can be avoided because of the direct precipitation of products from the reaction solution by water addition, thus rendering the two-steps process ecofriendly.



**KEYWORDS:** domino reaction, benzofuran-4(5*H*)-ones, cinnoline-4-carboxamides, microwave irradiation, isocyanides

## INTRODUCTION

The structural range and biological importance of functional cinnolines and their derivatives have made them striking targets in research over many years.<sup>1</sup> A variety of synthetic cinnoline derivatives have shown a wide range of biological activities including antibacterial, antitumor, anti-inflammatory, antifungal, anticancer, and phosphodiesterase inhibitors in the pharmaceutical industry.<sup>2</sup> Cinnolines were also widely used as agrochemicals and pharmaceuticals,<sup>3</sup> including as microbicides, pollen suppressants, fungicides and herbicides.<sup>4</sup> In addition, some of these compounds show interesting physical characteristics, such as electrochemical, luminescent, and nonlinear optical properties.<sup>5</sup> Therefore, the synthesis of functional cinnolines occupied a key place in the area of synthetic organic chemistry because of their important chemical and physical properties. Many methodologies for synthesizing these compounds have been developed,<sup>6</sup> most of them involved arenediazonium salts,<sup>7</sup> arylhydrazones,<sup>8</sup> arylhydrazines,<sup>9</sup> and nitriles,<sup>10</sup> as well as aryl phenylallylidene hydrazones as the starting materials.<sup>11</sup> However, these synthetic procedures suffered from limitations involving poor yields, multiple steps, or metal catalysts. These undesirable conditions encouraged us to develop a new methodology for their syntheses.

Domino reactions for total synthesis of natural products or natural-like structures have become a challenging topic in modern organic chemistry.<sup>12</sup> These reactions have attracted special attention because of their simplicity, efficiency, selectivity, convergence, and atom-economy.<sup>13</sup> They have been powerful tools for the synthesis of numerous complex molecules. Therefore, the development of a selective domino strategy for the efficient synthesis of cinnoline derivatives is highly desired. Recently, we have accomplished various domino

reactions leading to useful functionalized heterocycles of chemical and pharmaceutical interest.<sup>14</sup> In a continuation of our efforts, herein, we would like to report a new and efficient domino strategy for rapid, regioselective synthesis of highly functionalized cinnoline derivatives. The reaction can be conducted by using readily available and inexpensive substrates, such as cyclic-1,3-diones (Figure 1), isocyanides (Figure 2), and

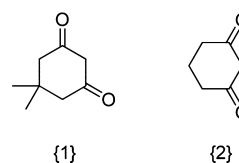


Figure 1. Diversity of cyclic-1,3-diones 1.

arylglyoxals (Figure 3) under microwave irradiation for short short periods, providing a series of benzofuran-4(5*H*)-ones with good to excellent yields. The resulting benzofuran-4(5*H*)-ones have been readily converted into cinnoline derivatives by treating with hydrazine hydrate (80% in aqueous solution)

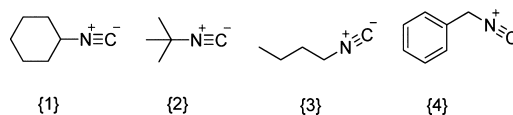


Figure 2. Diversity of isocyanides 2.

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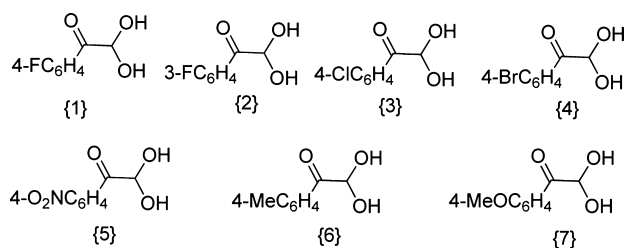


Figure 3. Diversity of arylglyoxals 3.

under microwave irradiation through a regioselective ring-opening of the furan (Scheme 1). A tedious workup procedure is avoided because of the direct precipitation of products from the reaction solution.

It is well-known that the benzofuran subunit plays a prominent role in organic and medicinal chemistry, and they exist in a wide variety of naturally occurring compounds and rationally designed pharmaceutical agents.<sup>15</sup> Benzofurans are integral to a large number of drug substances with activities including anticoagulant, insecticide, anthelmintic, hypnotic, antifungal, and HIV protease inhibition properties.<sup>16</sup> Some benzofurans serve as versatile synthetic intermediates that can synthesize various useful compounds.<sup>17</sup> Therefore, their syntheses have been attractive considerable attention. Recently, Anary-Abbasinejad and co-workers reported the synthesis of benzofuran-4(*SH*)-ones via a three-component reaction of 5,5-dimethyl-1,3-cyclohexandione with arylglyoxals and alkyl isocyanides.<sup>18</sup> However, this method suffered from long reaction times (5 h), and the preparation of products only reserved in milligram level. These facts limited the application of benzofuran-4(*SH*)-ones. Since benzofuran-4(*SH*)-ones can serve as an important intermediate to prepare cinnoline derivatives, we attempted to improve the synthesis of benzofuran-4(*SH*)-ones.

## RESULTS AND DISCUSSION

The similar three-component reaction was performed in EtOH under microwave heating for 25 min. Good yields (71%–92%) of benzofuran-4(*SH*)-ones were obtained on a multigram scale. Various isocyanides 2 and arylglyoxals 3 were explored to establish the applicability of this protocol. The results are listed in Table 1. A variety of arylglyoxal monohydrates 3 bearing either electron-withdrawing or electron-donating groups can react with above cyclic-1,3-diones 1 and isocyanides 2 to give corresponding benzofuran-4(*SH*)-one products 4{1,1,1}–4{2,4,7}. Cyclohexyl-, *t*-butyl-, *n*-butyl-, and benzyl-substituted isocyanides all worked efficiently in this reaction.

After we accomplished the above three-component reaction, we then subjected the resulting benzofuran-4(*SH*)-ones 4 to the reaction with hydrazine hydrate 5 (80% in aqueous solution) under similar conditions. The expected hexahydrocinnoline-4-carboxamides 6 were regioselectively afforded in

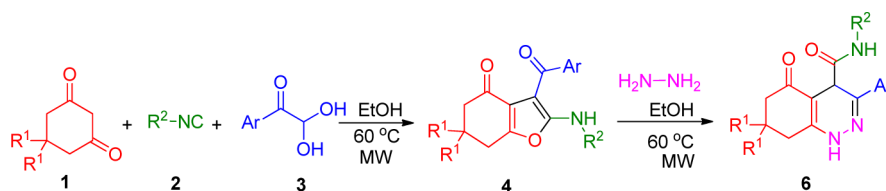
Table 1. Three-Component Domino Synthesis of Compounds 4

entry	product 4 <sup>a</sup>	yield (%) <sup>b</sup>
1	4{1,1,1}	72
2	4{1,1,3}	89
3	4{2,1,4}	71
4	4{2,1,5}	72
5	4{1,2,3}	89
6	4{1,2,4}	73
7	4{1,2,7}	77
8	4{2,2,3}	73
9	4{2,2,4}	82
10	4{2,2,6}	77
11	4{1,3,3}	80
12	4{1,3,4}	75
13	4{1,3,6}	72
14	4{2,3,3}	77
15	4{2,3,7}	80
16	4{1,4,1}	85
17	4{1,4,2}	92
18	4{1,4,5}	90
19	4{2,4,3}	71
20	4{2,4,7}	78

<sup>a</sup>Reactions were performed on a 10-mmol scale, and 1, 2, and 3 was in 1:1:1 ratio. <sup>b</sup>Isolated yields.

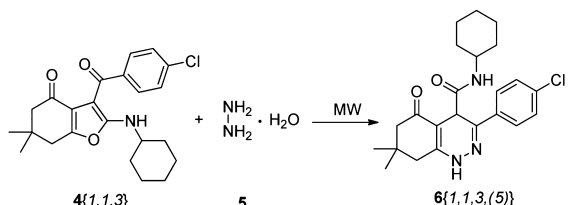
good yields. In the initial experiment, the reaction between benzofuranes 4{1,1,3} and hydrazine hydrate 5 was run with a 1:1 mol ratio at 60 °C under microwave heating using EtOH as a solvent. The expected hexahydrocinnoline-4-carboxamides 6{1,1,3,(5)} was isolated in 46% yield. The yield of product 6{1,1,3,(5)} was increased from 46 to 83% as the mol ratio of 4 and 5 varied from 1:1 to 1:3. Further increase of mol ratio failed to improve the yield of product 6{1,1,3,(5)}. The solvent effect was then investigated. The reaction scarcely proceeded in toluene or DCM even at an enhanced temperature of boiling point under MW irradiation (entries 5–6). The polar solvent, DMF, resulted in low yield of product 6{1,1,3,(5)} (entry 7). Other two polar solvents, acetonitrile and methanol gave slightly lower yields than that in EtOH. A lower yield of product was obtained when the reaction was performed in EtOH at lower (40 °C) or higher (80 °C) reaction temperature (entries 10–11). Next, the three-component reaction of 1{1} with 2{1} and 3{3} was carried out for 25 min under microwave heating. Without isolation, hydrazine hydrate 5 was then added into this mixture system. The two-step, one-pot reaction led to much lower chemical yield of 6{1,1,3,(5)}

Scheme 1. Two-Step Domino Synthesis of Cinnoline Derivatives



(entry 12). Four-component one-pot reaction of 1{1}, 2{1}, 3{3}, and 5 did not give the expected product 6{1,1,3,(5)} under similar conditions (entry 13).

Table 2. Optimization for the Synthesis of 6{1,1,3,(5)}



entry	solvent	temp (°C)	mol ratio <sup>a</sup>	time (min)	yield (%) <sup>b</sup>
1	EtOH	60	1:1	30	46
2	EtOH	60	1:2	30	69
3	EtOH	60	1:3	30	83
4	EtOH	60	1:4	30	72
5	toluene	60	1:3	50	trace
6	CH <sub>2</sub> Cl <sub>2</sub>	60	1:3	50	trace
7	DMF	60	1:3	50	21
8	MeOH	60	1:3	30	65
9	CH <sub>3</sub> CN	60	1:3	30	67
10	EtOH	40	1:3	30	55
11	EtOH	80	1:3	30	81
12	EtOH	60	1:3	30	28 <sup>c</sup>
13	EtOH	60	1:3	30	ND <sup>d</sup>

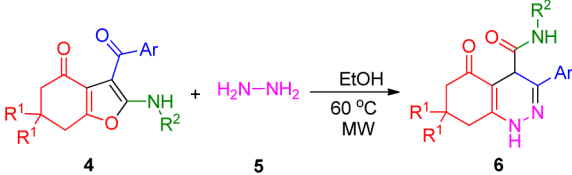
<sup>a</sup>Reactions were performed on a 1.0-mmol scale. <sup>b</sup>Isolated yields.

<sup>c</sup>Two-step one-pot reaction of 1{1}, 2{1}, 3{3}, and hydrazine hydrate. <sup>d</sup>Four-component one-pot reaction of 1{1}, 2{1}, 3{3}, and hydrazine hydrate.

With the optimal conditions in hand, we next examined the reaction scope by using benzofuran-4(*SH*)-ones **4** generated from above three-component transformation. A range of hydrocinnoline derivatives were prepared from 6,7-dihydrobenzofuran-4(*SH*)-one **4** and hydrazine hydrate **5**. As shown in Table 3, the substituents on 6,7-dihydrobenzofuran-4(*SH*)-one ring did not hamper the domino reaction process. Reactions of dihydrobenzofurans **4**, derived from dimedone or cyclohexane-1,3-dione, with **5** all worked well in this transformation to afford the desired products in moderate to good yields. The substituent variation at dihydrobenzofuran C2 position, including cyclohexylamino, *t*-butylamino, *n*-butylamino, and benzylamino groups, were smoothly transformed into corresponding cinnoline-4-carboxamides **6**{1,1,1,(5)}–**6**{2,4,7,(5)} within 30 min (Table 3, entries 1–20), which provides a valuable asset for further catalytic functionalization chemistry. It was also found that phenyl groups bearing either electron-withdrawing or electron-donating groups on the benzofuran ring were tolerated under the reaction conditions, leading to the desired cinnoline derivatives in satisfactory yields (up to 83%). It is worth mentioning that it affords a new example for a heterocyclization involving ring-opening of furan ring in an economical and atom-efficient fashion, providing a unique pathway to discover new bioactive compounds.

Similar to our previous domino processes, the present new reactions showed the following attractive characteristics: the reaction occurred rapidly in all cases allowing energy and manpower to be saved in potential industrial production. In most cases, the products precipitated from the reaction mixture when poured into cold water. The structures of products **4** and **6** were characterized using their IR, <sup>1</sup>HNMR, <sup>13</sup>CNMR, and

Table 3. Domino Synthesis of Cinnoline-4-carboxamides **6**



entry	product	yield (%) <sup>a</sup>
1	6{1,1,1,(5)}	75
2	6{1,1,3,(5)}	83
3	6{2,1,4,(5)}	73
4	6{2,1,5,(5)}	80
5	6{1,2,3,(5)}	81
6	6{1,2,4,(5)}	79
7	6{1,2,7,(5)}	73
8	6{2,2,3,(5)}	82
9	6{2,2,4,(5)}	70
10	6{2,2,6,(5)}	74
11	6{1,3,3,(5)}	72
12	6{1,3,4,(5)}	79
13	6{1,3,6,(5)}	74
14	6{2,3,3,(5)}	81
15	6{2,3,7,(5)}	73
16	6{1,4,1,(5)}	80
17	6{1,4,2,(5)}	71
18	6{1,4,5,(5)}	73
19	6{2,4,3,(5)}	78
20	6{2,4,7,(5)}	83

<sup>a</sup>Isolated yields.

HRMS spectra. Furthermore, the structure of compound **6**{1,2,7,(5)} was unequivocally confirmed by X-ray analysis (Figure 4).

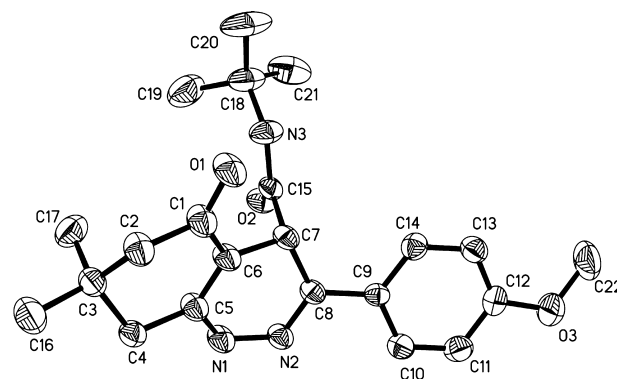
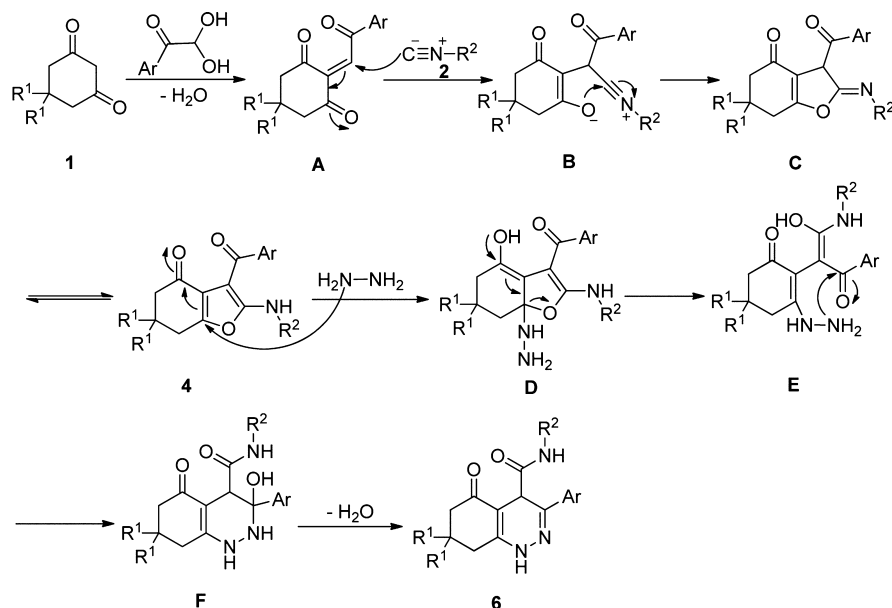


Figure 4. X-ray structure of 6{1,2,7,(5)}.

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of products **6** could be explained by the reaction sequence in Scheme 2. First, the Knoevenagel condensation between cyclic-1,3-diones **1** and arylglyoxals **3** occurs, leading to intermediate **A**, which undergoes a Michael addition and intramolecular cyclization with isocyanides **2** to afford an imine intermediate **C**. Intermediate **C** undergoes a [1,3]-H shift to yield benzofuran-4(*SH*)-ones **4**, which is attacked by hydrazine hydrate **5** through intermolecular Michael addition to give intermediate **D**. The final products **6** are obtained through a ring-opening of

Scheme 2. Proposed Mechanisms for Forming Compounds 4 and 6



furan (D to E), intramolecular addition (E to F), and dehydration (F to 6) sequence.

In conclusion, a convenient, rapid three-component reaction of cyclic-1,3-diones, isocyanides, and arylglyoxals has been improved for efficient synthesis of polysubstituted benzofuran-4(5*H*)-ones, which was trapped by hydrazine hydrate to regioselectively form cinnoline-4-carboxamides through domino ring-opening of furan process. Undoubtedly, this domino strategy provides a straightforward and facile pathway to construct the target molecules in an atom-economic fashion, avoiding the use of strong acid or base and transition metal catalysts. Other features of this tactic include convenient operation, short reaction times, high bond-forming efficiency, and excellent regioselectivity.

## EXPERIMENTAL PROCEDURES

**General Procedure for the Synthesis of Compounds 4 and 6.** Typically, 5,5-dimethylcyclohexane-1,3-dione (10 mmol) was introduced in a 25-mL initiator reaction vial, isocyanocyclohexane (10 mmol), and 4-fluorophenylglyoxal monohydrate (10 mmol), as well as ethanol (6 mL), were then successively added. Subsequently, the reaction vial was closed and then prestirred 10 s. The mixture was irradiated (time = 25 min, temperature = 60 °C; absorption level: high; fixed hold time) until TLC (petroleum ether (60–90 °C)/ethyl acetate 3:1) revealed that the conversion of the starting material 4-fluorophenylglyoxal monohydrate was complete. The reaction mixture was then cooled to room temperature and diluted with cold water (150 mL). The solid product was collected by Büchner filtration and was purified by recrystallization from 95% EtOH to afford the desired pure 4{1,1,1}.

**2-(Cyclohexylamino)-3-(4-fluorobenzoyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5*H*)-one 4{1,1,1}:** Yellow solid (mp 129 °C); IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ) 2940, 2856, 1643, 1602, 1541, 1468, 1222, 1151, 1068, 770;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.43 (d,  $J$  = 8.0 Hz, 1H, NH), 7.62–7.44 (m, 2H, ArH), 7.09–6.96 (m, 2H, ArH), 3.79–3.67 (m, 1H, CH), 2.71 (s, 2H,  $\text{CH}_2$ ), 2.30 (s, 2H,  $\text{CH}_2$ ), 2.09–1.98 (m, 2H,  $\text{CH}_2$ ), 1.80–1.78 (m, 2H,  $\text{CH}_2$ ), 1.65–1.62 (m, 1H,  $\text{CH}_2$ ), 1.46–1.35 (m, 4H,

$\text{CH}_2$ ), 1.29–1.31 (m, 1H,  $\text{CH}_2$ ), 1.14 (s, 6H,  $\text{CH}_3$ ). HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{26}\text{FNNaO}_3$  406.1794 [ $\text{M} + \text{Na}$ ] $^+$ ; found 406.1777.

Typically, 2-(cyclohexylamino)-3-(4-fluorobenzoyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5*H*)-one (1 mmol) was introduced in a 10-mL initiator reaction vial, hydrazine hydrate (80% in aqueous solution, 3.75 mmol), as well as ethanol (1.5 mL), were then successively added. Subsequently, the reaction vial was closed and then prestirred for 10 s. The mixture was irradiated (time = 30 min, temperature = 60 °C; absorption level = high; fixed hold time) until TLC (petroleum ether (60–90 °C)/ethyl acetate 1:1) revealed that the conversion of the starting material 4-fluorophenylglyoxal monohydrate was complete. The reaction mixture was then cooled to room temperature and diluted with cold water (20 mL). The solid product was collected by Büchner filtration and was purified by recrystallization from petroleum ether (60–90 °C)/diethyl ether 4:1 to afford the desired pure 6{1,1,1(5)}.

***N*-Cyclohexyl-3-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydrocinnoline-4-carboxamide 6{1,1,1(5)}:** White solid, mp (291–293 °C); IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ) 3258, 3199, 3076, 2927, 1656, 1596, 1498, 1393, 1333, 1250, 1153, 838, 566;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.57 (s, 1H, NH), 7.76–7.73 (m, 2H, ArH), 7.13 (d,  $J$  = 8.4 Hz, 1H, NH), 7.06 (t,  $J$  = 8.6 Hz, 2H, ArH), 4.91 (s, 1H, CH), 3.78–3.67 (m, 1H, CH), 2.35–2.13 (m, 4H,  $\text{CH}_2$ ), 1.91 (d,  $J$  = 10.0 Hz, 1H), 1.84–1.56 (m, 4H,  $\text{CH}_2$ ), 1.41–1.33 (m, 3H,  $\text{CH}_2$ ), 1.11–1.16 (m, 2H,  $\text{CH}_2$ ), 1.00 (s, 3H,  $\text{CH}_3$ ), 0.96 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ) ( $\delta$ , ppm) 195.9, 170.8, 163.6 ( $^1J_{\text{CF}}$  = 248.5), 149.8, 143.4, 132.3 ( $^4J_{\text{CF}}$  = 3.1), 128.1 ( $^3J_{\text{CF}}$  = 8.3), 115.4 ( $^2J_{\text{CF}}$  = 21.6), 98.3, 50.6, 48.2, 38.3, 37.3, 32.5, 29.8, 26.2, 25.5; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{27}\text{FN}_3\text{O}_2$  396.2088 [ $\text{M} - \text{H}$ ] $^-$ ; found 396.2077.

## ASSOCIATED CONTENT

### Supporting Information

$^1\text{H}$  NMR spectra of all pure products. This material is available free of charge via the Internet at <http://pubs.acs.org>.



## AUTHOR INFORMATION

### Corresponding Authors

\*Fax: 86-516-83500065. E-mail: jiangchem@jnsu.edu.cn.

\*E-mail: laotu@jnsu.edu.cn.

### Notes

The authors declare no competing financial interest.

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