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Rapid and Efficient Ultrasound-Assisted Method for the Combinatorial Synthesis of Spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] Derivatives

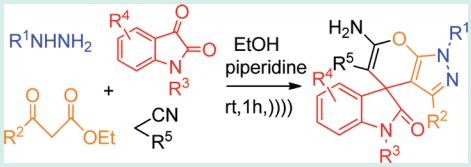
Yi Zou,[†,‡] Yu Hu,[†] Hai Liu,[†] and Daqing Shi*[,†]

[†]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P.R. China

[‡]School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, P.R. China

Supporting Information

ABSTRACT: An efficient one-pot synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives by four-component reaction of hydrazine, *β*-keto ester, isatin, and malononitrile or ethyl cyanoacetate catalyzed by piperidine under ultrasound irradiation is described. This synthesis was confirmed to follow the group-assistant-purification chemistry (GAP) chemistry process, which can avoid traditional chromatography and recrystallization purifications.



KEYWORDS: *combinatorial synthesis, ultrasound irradiation, multicomponent reaction, heterocycle, spiroindoline*

INTRODUCTION

Use of ultrasound as a means of accelerating reactions has long been known in both industry and academia. Nevertheless, the "green" value of the nonhazardous acoustic radiation has been recognized by synthetic and environmental chemists only recently.[1] The role of sonochemistry in the creation of "benign-by-design" synthetic methods is clear from the definition: low level of waste, inherently safe, material- and energy-saving, with an optimized use of nonrenewable resources, and a preferential exploitation of renewable ones. The application of ultrasound in organic synthesis has been increasing because of its advantages such as shorter reaction times, milder reaction condition, and higher yields in comparison with the classical methods.[2] The chemical and physical effects of ultrasound arise from the cavitational collapse which produces extreme conditions locally and thus induce the formation of chemical species not easily attained under conventional conditions.[3]

Traditional structure−activity relationship evaluations in medicinal chemistry typically involve the preparation of an advanced intermediate that can be analogued readily to introduce the molecular diversity necessary to prepare a collection, or library, of structurally related compounds. One strategy that potentially meets the goals of total synthesis and library production is multicomponent reactions (MCRs) chemistry, in which three or more starting materials are brought together in a highly convergent approach to rapidly build up molecular structure and complexity.[4] According to this method, the products are formed in one-pot and the diversity can be achieved simply by varying the reacting components.

The indole nucleus is a well-known heterocyclic component in a variety of natural products and medicinal agents.[5] Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.[6] Furthermore, it has been reported that C-3 spiroindoline derivatives highly enhance biological activity.[7] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[8] As a consequence, a number of methods have been reported for the preparation of spirooxindole-fused heterocycles.[9]

Dihydropyrano[2,3-*c*]pyrazoles play an essential role in biologically active compounds and therefore represent an interesting template for medicinal chemistry. They have been widely used as medicinal intermediates because of their useful biological and pharmacological properties. Many of those compounds are known as antimicrobial,[10] and anti-inflammatory.[11] Furthermore, dihydropyrano[2,3-*c*]pyrazoles showed molluscicidal activity[12,13] and were identified as a screening hit for Chk1 kinase inhibitor.[14] Recently, Shestopalov et al. reported the synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]-pyrazol]-2-ones via one-pot, two-step reaction of isatin, hydrazine, malononitrile, and *β*-keto ester catalyzed by Et_3N.[15]

As a consequence of our interest in ultrasonic-assisted organic synthesis (UAOS)[16] and our continued work on the synthesis of indole derivatives[17] guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably, we investigated the sonocatalytic synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*] pyrazole] derivatives in the presence of piperidine at room temperature.

RESULTS AND DISCUSSION

Initial studies were carried out by reaction of hydrazine **1**{*1*}, ethyl acetoacetate **2**{*1*}, isatin **3**{*1*}, and malononitrile **4**{*1*} under various reaction conditions (Scheme 1).

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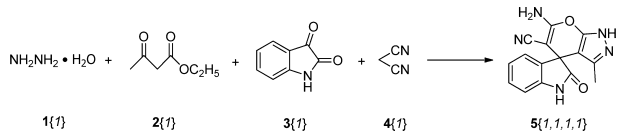
Scheme 1. Model Reaction



The ultrasonic-assisted reaction to obtain **5**{*1,1,1,1*} was examined using a variety of solvents (Table 1). Although the reaction was successful both with and without ultrasound in all solvents tested, the use of ultrasound afforded higher yielding product quicker in every solvent. Ethanol proved to be the solvent of choice and was adopted for all future studies.

Table 1. Solvent Optimization for the Synthesis of 5{*1,1,1,1*}[a]

			yield[b] (%)	
entry	solvent	time (h)	without US[c]	with US[d]
1	acetonitrile	1	12	34
2	ethanol	1	56	92
3	methanol	1	48	88
4	THF	1	15	37
5	chloroform	1	9	27
6	1,4-dioxane	1	11	33
7	water	1	20	25

[a]Reaction conditions: hydrazine (1.5 mmol), ethyl acetoacetate (1 mmol), isatin (1 mmol), malononitrile (1 mmol), solvent (15 mL), and piperidine (20 mol %). [b]Yields of isolated products. [c]Reaction under thermal condition. [d]Reaction under ultrasonic waves at room temperature and the ultrasonic power 250 W, irradiation frequency 40 kHz.

Liquids irradiated with ultrasound can produce tiny bubbles that can undergo a violent collapse known as cavitation, which generates localized microscopic "hot spots" with transient high temperatures and pressures to induce favorable conditions for reactions.[18] In some cases sonication can also provide more efficient stirring of the reaction.[19]

Next, the effects of catalysts were evaluated for this model reaction, and the results are summarized in Table 2. It was found that when the reaction was carried out without any catalysts no product was detected (Table 2, entry 1). Common bases, such as C_2H_5ONa, NaOH, Na_2CO_3, and KOH, can catalyze this reaction with low yields (Table 2, entries 2−5). However, piperidine was identified as the optimal catalyst with **5**{*1,1,1,1*} being isolated in 80% yield (Table 2, entry 6). Subsequently, we further turned to testing the effect of catalyst loading. Ten mol %, 20 mol %, 30 mol % of piperidine were tested respectively. The results are summarized in Table 2 showing that 20 mol % loading of piperidine was optimal. Higher amounts of piperidine did not lead to significant change in the reaction yields (Table 2, entry 8).

Table 2. Effect of Catalyst on Model Reaction under Ultrasound Irradiation[a]

entry	catalyst (mol %)	temperature (°C)[c]	time (h)	yield[b] (%)
1	no cat. (-)	r.t.	1	0
2	C_2H_5ONa (10)	r.t.	1	57
3	NaOH (10)	r.t.	1	45
4	Na_2CO_3 (10)	r.t.	1	67
5	KOH (10)	r.t.	1	72
6	piperidine (10)	r.t.	1	80
7	piperidine (20)	r.t.	1	92
8	piperidine (30)	r.t.	1	90

[a]Reaction conditions: hydrazine (1.5 mmol), ethyl acetoacetate (1 mmol), isatin (1 mmol), malononitrile (1 mmol), and ethanol (15 mL), under ultrasonic waves at room temperature and the ultrasonic power 250 W, irradiation frequency 40 kHz . [b]Yields of isolated products. [c]r.t. = room temperature.

To further improve the yield and decrease the reaction time, we tried to increase the reaction temperature under ultrasound irradiation. The results are summarized in Table 3. It can been seen from the Table 3 that there was no remarkable temperature effect on this reaction.

Table 3. Effect of Temperature on Model Reaction under Ultrasound Irradiation[a]

entry	catalyst (mol %)	temperature (°C)[c]	time (h)	yield[b] (%)
1	piperidine (20)	r.t.	1	92
2	piperidine (20)	40	1	90
3	piperidine (20)	50	1	88
4	piperidine (20)	60	1	88
5	piperidine (20)	70	1	90
6	piperidine (20)	reflux	1	89

[a]Reaction conditions: hydrazine (1.5 mmol), ethyl acetoacetate (1 mmol), isatin (1 mmol), malononitrile (1 mmol), and ethanol (15 mL), under ultrasonic waves at room temperature and the ultrasonic power 250 W, irradiation frequency 40 kHz. [b]Yields of isolated products. [c]r.t. = room temperature.

The optimized reaction conditions were then tested for library construction with four hydrazines **1**{*1−4*}, three *β*-keto esters **2**{*1−3*}, nine isatins **3**{*1−9*}, and two acetonitrile derivatives **4**{*1−2*} (Figure 1 and Scheme 2). The corresponding spiro-[indoline-3,4′-pyrano [2,3-*c*]pyrazole] derivatives **5** were obtained in good yields at room temperature in ethanol under ultrasonic irradiation. The results are summarized in Table 4. The protocol was effective with isatins having either electron-withdrawing (halides) or electron-donating groups (alkyl).

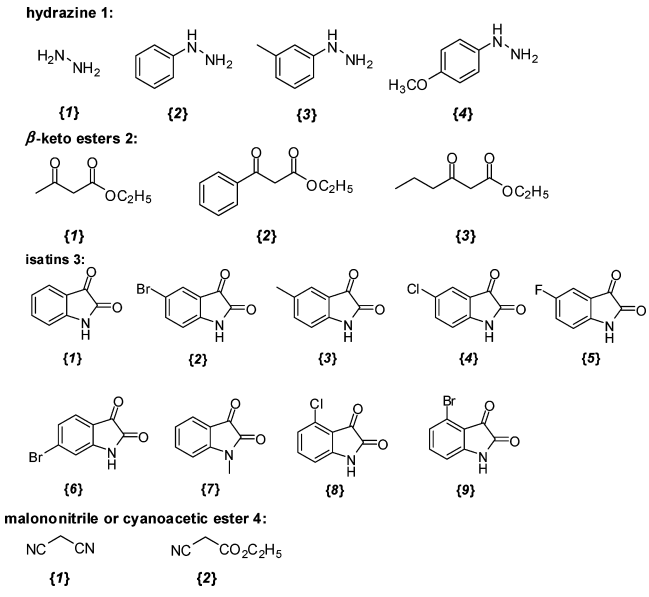


Figure 1. Diversity of Reagents.

The yield of compound **5**{*1,1,1,1*} (92%) prepared by our method was higher than in a previously reported protocol

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Scheme 2. Synthesis of Spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] Derivatives 5

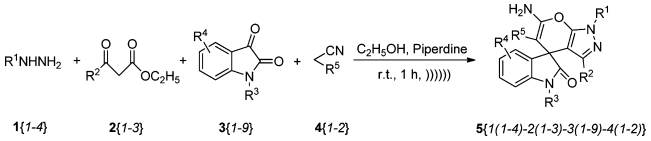


Table 4. Synthesis of Spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] Derivatives 5[a]

entry	product	yield[b] (%)	mp (°C)	m.p.[c] (°C)
1	5{*1,1,1,1*}	92	285−286	275
2	5{*1,1,2,1*}	93	282−283	>300
3	5{*1,1,3,1*}	90	279−281	269−271
4	5{*1,1,4,1*}	89	297−298	306−307
5	5{*1,1,5,1*}	86	274−275	
6	5{*1,1,6,1*}	80	>300	
7	5{*1,1,7,1*}	81	270−272	260
8	5{*2,1,1,1*}	86	227−229	220
9	5{*2,1,3,1*}	76	222−224	230−232
10	5{*2,1,8,1*}	69	>300	
11	5{*2,1,9,1*}	72	288−290	
12	5{*1,2,1,1*}	87	280−281	279−280
13	5{*1,2,2,1*}	80	256−257	258−259
14	5{*1,2,5,1*}	87	255−257	
15	5{*1,2,7,1*}	79	284−286	
16	5{*1,2,3,1*}	78	247−249	
17	5{*1,2,8,1*}	70	>300	
18	5{*1,2,9,1*}	68	>300	
19	5{*1,2,1,2*}	79	242−243	
20	5{*1,2,2,2*}	81	257−259	
21	5{*1,2,5,2*}	73	258−260	
22	5{*1,2,3,2*}	76	260−263	
23	5{*1,2,7,2*}	73	224−226	
24	5{*1,2,4,2*}	75	265−267	
25	5{*3,1,1,1*}	83	198−200	
26	5{*3,1,2,1*}	85	221−222	
27	5{*3,1,3,1*}	89	220−221	
28	5{*1,3,1,1*}	80	268−270	
29	5{*4,1,1,1*}	87	270−272	

[a]Reaction of hydrazine, *β*-keto esters, isatins, and malononitrile or ethyl cyanoacetate at room temperature in ethanol in the presences of piperdine (20 mol %), and the ultrasonic power 250 W, irradiation frequency 40 kHz. [b]Yields of isolated products. [c]Already reported in literature[20].

(85%).[15] Moreover, this synthesis was confirmed to follow the GAP chemistry (group-assistant-purification chemistry)[21] process, which can avoid traditional chromatography and recrystallization purifications, that is, all the pure products can be simply obtained by washing the solid crude products with ethanol.

The structures of all products **5** were characterized by IR, ^{1}H NMR, and HRMS analysis. Some new compounds were also established by ^{13}C NMR spectroscopy. The structures of 5{*1,1,6,1*} and 5{*3,1,1,1*} were further confirmed by X-ray diffraction analysis. The molecular structures of 5{*1,1,6,1*} and 5{*3,1,1,1*} are shown in Figure 2 and Figure 3, respectively.

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compounds **5** could be explained by the reaction sequence in Scheme 3. First, a condensation of hydrazine **1** with *β*-keto esters **2** is proposed to give the intermediate **6**. A Knoevenagel condensation of isatin **3**

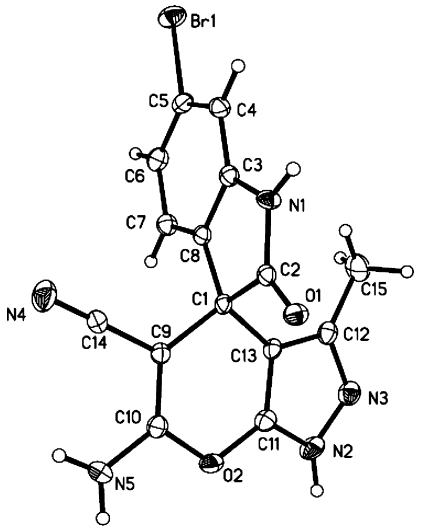


Figure 2. Crystal structure of compound 5{*1,1,6,1*}.

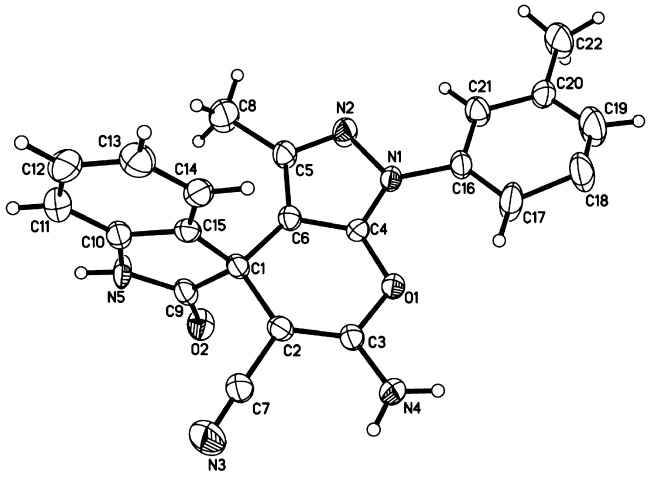
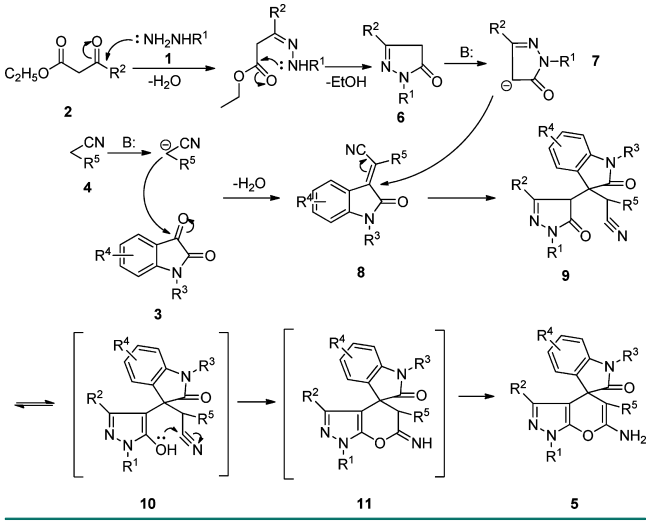


Figure 3. Crystal structure of compound 5{*3,1,1,1*}.

Scheme 3. Proposed Mechanism for the Synthesis of 5



with malononitrile or ethyl cyanoacetate **4** is also proposed to give the intermediate **8**. Michael addition of intermediate **6** to **8** catalyzed by base should then occur to provide intermediate **9**, which undergoes intramolecular cyclization to give intermediate

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11. In the last step, the intermediate **11** is tautomerized to product **5**.

CONCLUSION

The new GAP synthesis of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives has been achieved by four-component reaction of hydrazine, *β*-keto esters, isatin, and malononitrile or ethyl cyanoacetate at room temperature under ultrasound irradiation. Excellent chemical yields have been achieved without the use of the traditional purifications, chromatography and recrystallization.

EXPERIMENTAL PROCEDURES

General Information. Commercial solvents and reagents were used as received. Melting points are uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr with absorptions in wavenumbers (cm^{-1}). ^1H NMR and ^{13}C NMR were determined on Varian Inova-300 MHz or Inova-400 MHz spectrometer in DMSO-d_6 solution. *J* values are in hertz (Hz). Chemical shifts are expressed in parts per million downfield from internal standard TMS. High-resolution mass spectra (HRMS) were obtained using Bruker microTOF-Q instrument. X-ray diffractions were recorded on a Rigaku Mercury CCD/AFC diffractometer.

Ultrasonication was performed in a KQ-250E medical ultrasound cleaner with a frequency of 40 kHz and an output power of 250 W (Built-in heating, 30−110 °C thermostatically adjustable). The reaction flask was located at the maximum energy area in the cleaner, and the surface of the reactants was placed slightly lower than the level of the water. Observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General Procedure for the Synthesis of 5{*1,1,1,1*} (Without US). A 100 mL flask was charged with hydrazine **1**{*1*} (1 mmol), ethyl acetoacetate **2**{*1*} (1 mmol), isatin **3**{*1*} (1 mmol), malononitrile **4**{*1*} (1 mmol), and piperdine (20 mol %, 0.2 mmol) in ethanol (15 mL). The mixture was stirred at room temperature. After the completion of the reaction (monitored by TLC), the resulting precipitate was filtered and washed with ethanol to afford the pure product as solid in good to excellent yields.

Ultrasound-Promoted Synthesis of 5 (With US). Another 100 mL flask was charged with hydrazine **1**{*1*} (1 mmol), ethyl acetoacetate **2**{*1*} (1 mmol), isatin **3**{*1*} (1 mmol), malononitrile **4**{*1*} or ethyl cyanoacetate **4**{*2*} (1 mmol) and piperdine (20 mol %, 0.2 mmol) in ethanol (15 mL). The mixture was sonicated in the water bath of an ultrasonic cleaner at 25−30 °C. After the completion of the reaction (monitored by TLC), the resulting precipitate was filtered and washed with ethanol to afford the pure product as solid in good to excellent yields.

*6′-Amino-3′-methyl-2-oxo-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5**{1,1,1,1}).* mp: 285−286 °C. IR (KBr) *ν*: 3420, 3389, 3337, 3134, 2182, 1710, 1642, 1583, 1517, 1409, 1320, 1207, 1155, 1054, 931, 696 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) *δ*: 1.54 (s, 3H, CH_3), 6.91 (s, 1H, ArH), 7.02 (s, 2H, ArH), 7.17 (s, 2H, NH_2), 7.23 (s, 1H, ArH), 10.55 (s, 1H, NH), 12.25 (s, 1H, NH). HRMS calculated for $C_{15}H_{11}N_5O_2Na$ $[M+Na]^+$: 316.0805, found: 316.0805.

*Ethyl 6′-Amino-5-bromo-2-oxo-3′-phenyl-1′H-spiro-[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5**{1,2,2,2}).* mp: 257−259 °C. IR (KBr) *ν*: 3421, 3260, 1718, 1677, 1618, 1543, 1491, 1475, 1380, 960 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) *δ*: 0.70 (t, *J* = 6.0 Hz, 3H, CH_3), 3.70 (q, *J* = 6.8 Hz, 2H, CH_2O), 6.42 (d, *J* = 8.0 Hz, 1H, ArH), 6.67 (d, *J* = 6.4 Hz, 2H, ArH), 7.11 (s, 1H, ArH), 7.21 (d, *J* = 7.2 Hz, 3H, ArH), 7.32 (s, 1H, ArH), 8.12 (s, 2H, NH_2), 10.11 (s, 1H, NH), 12.68 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 13.25, 58.93, 74.27, 97.51, 110.94, 112.92, 125.66, 127.98, 128.63, 128.96, 130.15, 139.35, 140.52, 141.99, 154.54, 162.78, 165.94, 168.04, 179.46. HRMS calculated for $C_{22}H_{17}{}^{79}BrN_4O_4$ $[M]^+$: 480.0433, found: 480.0455.

*6′-Amino-5-bromo-3′-methyl-2-oxo-1′-(m-tolyl)-1′H-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5**{3,1,2,1}).* mp: 221−222 °C. IR (KBr) *ν*: 3368, 3315, 3186, 3041, 2206, 1703, 1650, 1611, 1517, 1476, 1398, 1283, 1135, 1038, 808, 773 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) *δ*: 1.58 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 6.90 (s, 1H, ArH), 7.16 (s, 1H, ArH), 7.39−7.66 (m, 7H, ArH and NH_2), 10.90 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) *δ*: 11.79, 21.06, 48.03, 55.53, 95.64, 111.86, 114.43, 117.43, 118.03, 120.90, 127.30, 127.90, 129.24, 132.11, 134.75, 137.21, 139.11, 140.86, 143.66, 145.05, 161.13, 177.21. HRMS calculated for $C_{22}H_{16}{}^{79}BrN_5O_2Na$ $[M+Na]^+$: 484.0380, found: 484.0392.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, IR, ^1H NMR, ^{13}C NMR, and HRMS spectra for compounds **5**, and the X-ray crystallographic information for compound **5**{*1,1,6,1*} and **5**{*3,1,1,1*}. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: dqshi@suda.edu.cn.

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