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Facile Synthesis of Spiro-substituted Cyclopropanes Through Reaction of Electron-Deficient Olefins and 1,3-Indandione

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ABSTRACT

An efficient and facile approach for the synthesis of spiro-substituted cyclopropane derivatives has been described. The reaction of 1,3-indandione with arylidenemalononitrile in the presence of molecular iodine and dimethylaminopyridine occurred to give cyclopropanes in moderate to excellent yields. The structures of the products were characterized by NMR and X-ray diffraction analysis. A possible mechanism of this reaction process is proposed.

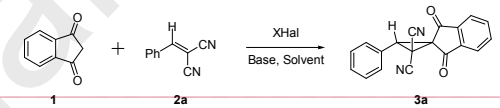
Recently, there has been an increasing use of the cyclopropyl ring in both organic synthesis and medicinal chemistry.[1] Due to the strain associated with the cyclopropane systems, they can be employed as building blocks for construction of more complex compounds that exhibit biological and pharmaceutical activities.[2]

Among the synthetic methods of cyclopropanation reported, the Simmons-Smith-type reaction has attracted much attention.[3] Metal-catalyzed cyclopropanation of alkenes with diazo compounds is also widely used.[4] The cyclopropanation reaction involving ylides and electron-deficient olefins, Michael-initiated ring closure (MIRC) has been reported.[5] However, these reported procedures often required severe reaction conditions or transition metal catalysts, an operationally simple, mild and competent strategy using less toxic reagents is still rare and highly desirable.[6]

As part of our continued efforts to develop stereoselective cyclopropanation with olefins,[7] we report here a new approach for synthesis of spiro-substituted cyclopropane derivatives from 1,3-indandione and the electron-deficient alkenes in the presence of molecular iodine.

The experiment began with the reaction of 1,3-indandione, phenylidenemalononitrile, Et_3N and molecular iodine in DCM at room temperature. After simple workup, the main product was isolated in a low yield. Further analysis of the NMR spectra revealed that the structure of this new compound was a spiro-substituted cyclopropane derivative **3a**. Encouraged by the result, we further optimized the reaction conditions. The results are listed in Table **1**. Of all solvents screened, CH_3CN was found to be the best in terms of the reaction time and the yield. Other halogen sources such as Br_2, NBS were also screened, the results indicated that the reaction using Br_2 appeared to proceed more rapidly than the reaction using molecular iodine. However, all of them gave the final product in low yields (Table 1, entries 6 - 7). Furthermore, the screening for a suitable base was performed in CH_3CN at room temperature. It was found that DMAP was the best base for this reaction (Table 1, entry 9). With 1.2 equiv of molecular iodine and 3 equiv of DMAP, phenylidenemalononitrile was able to react with 1.05 equiv of 1,3-indandione at 40 °C to afford product **3a** in good yield (Table 1, entry 10).

Table 1. Optimization of reaction conditions for cyclopropanation with 1,3-indandione and phenylidenemalononitrile [a]



1 2a 3a

XHal = I_2, Br_2, NBS

Entry	Base	Solv.	XHal	Temp.(°C)	Time (h)	Yield (%)
1	Et_3N	DCM	I_2	rt	6	34
2	Et_3N	CH_3CN	I_2	rt	6	47
3	Et_3N	EtOH	I_2	rt	6	24
4	Et_3N	benzene	I_2	rt	6	11
5	Et_3N	THF	I_2	rt	6	40
6	Et_3N	CH_3CN	NBS	rt	6	27
7	Et_3N	CH_3CN	Br_2	rt	0.5	8
8	C_5H_5N	CH_3CN	I_2	rt	6	31
9	DMAP	CH_3CN	I_2	rt	6	67
10	DMAP	CH_3CN	I_2	40	4	69

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An efficient approach of facile synthesis of spiro-substituted cyclopropane derivatives has been described. Promoted by molecular iodine, 1,3-indandione **1** reacted smoothly with the electron-deficient alkenes **2** to give cyclopropanes **3** in good to excellent yields.

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The cyclopropyl moiety plays an important role in many synthetic and naturally occurring compounds for their intrinsic utility of key intermediates for further transformations

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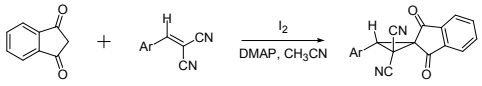
11	DMAP	CH_3CN	I_2	60	2	54
12	DMAP	THF	I_2	rt	6	52
13	DMAP	THF	I_2	40	4	57
14	K_2CO_3	CH_3CN	I_2	rt	4	59
15	Na_2CO_3	CH_3CN	I_2	rt	6	16
16	$NaHCO_3$	CH_3CN	I_2	rt	6	trace

[a] The reaction was carried out with 1,3-indandione (1.05 equiv), phenylidenemalononitrile (1.0 equiv), and base (3.0 equiv).

Under the optimized conditions, the scope and limitation of the current cyclopropanation were investigated by employing various arylidene derivatives as substrates. In all cases, the spiro-substituted cyclopropane **3** was obtained as the sole product. The structures of compounds (**3a-3o**) were characterized by ^1H NMR, ^{13}C NMR and X-ray diffraction analysis (Fig. 1).[8] As exhibited in Table **2**, both electron-donating and electron-withdrawing substituents on the benzene ring were well tolerated and all gave the desired products in good yields (Table 2, entries 2 - 14). For example, cyclopropanation product with 94% yield was obtained for para-substituted **3c** (entry 3). Surprisingly, the result showed that increasing the electron density of the arylidene derivatives was unfavorable to the reactivity of the reaction. When an electron-donating group was introduced into the benzene ring of phenylidenemalononitrile, the reaction rate became slow (Table 2, entries 9 - 13). 3-Pyridinyl group also afforded corresponding cyclopropane in moderate yield (Table 2, entry 15). Moreover, it should be mentioned that aliphatic aldehydes afforded corresponding cyclopropanes mainly in low yields at the present reaction conditions.

Table 2. Synthesis of spiro-substituted cyclopropanes from 1,3-indandione and arylidenemalononitrile [a]



1 2a - 2o 3a - 3o

Ar = Ph; 4-FC_6H_4; 4-ClC_6H_4; 4-BrC_6H_4; 4-$NO_2C_6H_4$; 3-ClC_6H_4; 3-$NO_2C_6H_4$; 3,4-$Cl_2C_6H_3$; 4-$OCH_3C_6H_4$; 4-$CH_3C_6H_4$; 3,4-$(CH_3O)_2C_6H_3$; 3,4-$(CH_3)_2C_6H_3$; 3,4-$OCH_2OC_6H_3$; 2-ClC_6H_4; 3-pyridinyl.

Entry	Product	Ar	Time (h)	Yield (%)[b]
1	**3a**	Ph	4	69
2	**3b**	4-FC_6H_4	2	91
3	**3c**	4-ClC_6H_4	2	94
4	**3d**	4-BrC_6H_4	2	93
5	**3e**	4-$NO_2C_6H_4$	2	87
6	**3f**	3-ClC_6H_4	2	93
7	**3g**	3-$NO_2C_6H_4$	2	89
8	**3h**	3,4-$Cl_2C_6H_3$	2	94
9	**3i**	4-$OCH_3C_6H_4$	6	59
10	**3j**	4-$CH_3C_6H_4$	6	71
11	**3k**	3,4-$(OCH_3)_2C_6H_3$	6	57
12	**3l**	3,4-$(CH_3)_2C_6H_3$	6	62
13	**3m**	3,4-$OCH_2OC_6H_3$	6	69
14	**3n**	2-ClC_6H_4	4	67
15	**3o**	3-pyridinyl	2	45

[a] The reaction was carried out with 1,3-indandione (1.05 equiv), arylidenemalononitrile (1.0 equiv), iodine (1.2 equiv) and DMAP (3 equiv) at 40 °C.

[b] Yield of isolated product.

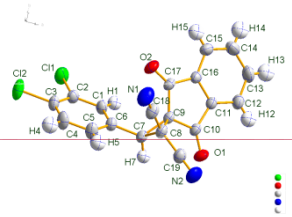
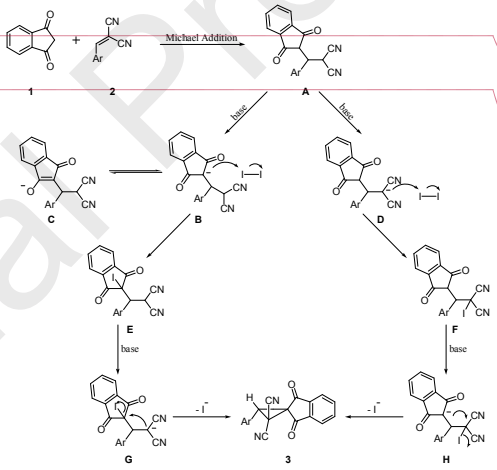


Figure 1. X-ray crystal structure of **3h.**

On the basis of experimental observation and the literature,[9] a possible reaction mechanism is proposed (Scheme 1). Michael addition of 1,3-indandione to arylidenemalononitrile led to intermediate **A** and followed by the generation of **B** or **D** respectively in the presence of DMAP. Then, the reaction of **B** or **D** with iodine provided iodide **E** or **F** as the key intermediate. Finally, the nucleophilic C-attack via **G** or **H** gave cyclopropanes **3**.



Scheme 1. Proposed mechanism of the formation of **3**.

In summary, we have presented a novel reaction of 1,3-indandione with arylidene derivatives to selectively afford spiro cyclopropanes in moderate to excellent yields under mild conditions. This iodine-mediated oxidative cycloaddition provides a unique and facile protocol for the preparation of cyclopropane derivatives.

Acknowledgments

The author thanks the National Natural Science Foundation of China (Nos. 21662019 and 21864015) for financial support.

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Commented [l10]: Original text: **3a-n**

Commented [l11]: Original text: (Table 2, entries 2 - 14)

Commented [l12]: Original text: (entry 9-13)

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On the basis of experimental observation and the literature,[9] a possible reaction mechanism is proposed (Scheme 1). Addition of the anion of 1,3-indandione to arylidenemalononitrile leads to anion **A**, which exist in the equilibrium with the anion **B**. The reaction of anion B with iodine gave iodide **C** as the key intermediate, and then an intramolecular nucleophilic *C*-attack with an elimination of iodide ion gave product **3**.

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Moreover, it should be mentioned that aliphatic aldehydes and heteroaromatic aldehydes afforded corresponding cyclopropanes mainly in low yields at the present reaction conditions.

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Arsine involved cyclopropanation with methyl bromoacetate and olefins[a]

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8. CCDC-1935006 contains the crystallographic data for compound **3h**. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.; or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk. Unit cell parameters (**3h**): *a*: 16.9346(11) Å; b: 8.4312(6) Å; c: 13.6305(11) Å; α: 90; β: 111.043(9); γ: 90; space group: P21/c.
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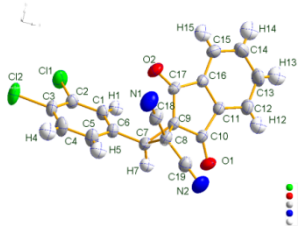
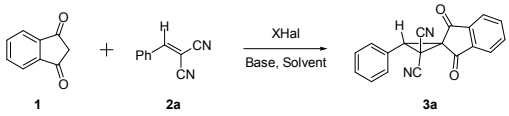


Figure 1. X-ray crystal structure of **3h.**

Table 1. Optimization of reaction conditions for cyclopropanation with 1,3-indandione and phenylidenemalononitrile [a]



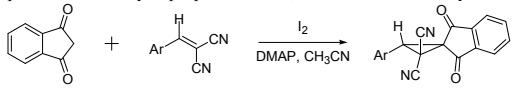
1 **2a** **3a**

XHal = I_2, Br_2, NBS

Entry	Base	Solv.	XHal	Temp.(°C)	Time (h)	Yield (%)
1	Et_3N	DCM	I_2	rt	6	34
2	Et_3N	CH_3CN	I_2	rt	6	47
3	Et_3N	EtOH	I_2	rt	6	24
4	Et_3N	benzene	I_2	rt	6	11
5	Et_3N	THF	I_2	rt	6	40
6	Et_3N	CH_3CN	NBS	rt	6	27
7	Et_3N	CH_3CN	Br_2	rt	0.5	8
8	C_5H_5N	CH_3CN	I_2	rt	6	31
9	DMAP	CH_3CN	I_2	rt	6	67
10	DMAP	CH_3CN	I_2	40	4	69
11	DMAP	CH_3CN	I_2	60	2	54
12	DMAP	THF	I_2	rt	6	52
13	DMAP	THF	I_2	40	4	57
14	K_2CO_3	CH_3CN	I_2	rt	4	59
15	Na_2CO_3	CH_3CN	I_2	rt	6	16
16	$NaHCO_3$	CH_3CN	I_2	rt	6	trace

[a] The reaction was carried out with 1,3-indandione (1.05 equiv), phenylidenemalononitrile (1.0 equiv), and base (3.0 equiv).

Table 2. Synthesis of spiro-substituted cyclopropanes from 1,3-indandione and arylidenemalononitrile [a]



1 **2a - 2o** **3a - 3o**

Ar = Ph; 4-FC_6H_4; 4-ClC_6H_4; 4-BrC_6H_4; 4-$NO_2C_6H_4$; 3-ClC_6H_4; 3-$NO_2C_6H_4$; 3,4-$Cl_2C_6H_3$; 4-$OCH_3C_6H_4$; 4-$CH_3C_6H_4$; 3,4-$(CH_3O)_2C_6H_3$; 3,4-$(CH_3)_2C_6H_3$; 3,4-$OCH_2OC_6H_3$; 2-ClC_6H_4; 3-pyridinyl.

Entry	Product	Ar	Time (h)	Yield (%)[b]
1	**3a**	Ph	4	69
2	**3b**	4-FC_6H_4	2	91
3	**3c**	4-ClC_6H_4	2	94
4	**3d**	4-BrC_6H_4	2	93
5	**3e**	4-$NO_2C_6H_4$	2	87
6	**3f**	3-ClC_6H_4	2	93
7	**3g**	3-$NO_2C_6H_4$	2	89
8	**3h**	3,4-$Cl_2C_6H_3$	2	94
9	**3i**	4-$OCH_3C_6H_4$	6	59
10	**3j**	4-$CH_3C_6H_4$	6	71
11	**3k**	3,4-$(OCH_3)_2C_6H_3$	6	57
12	**3l**	3,4-$(CH_3)_2C_6H_3$	6	62
13	**3m**	3,4-$OCH_2OC_6H_3$	6	69
14	**3n**	2-ClC_6H_4	4	67
15	**3o**	3-pyridinyl	2	45

[a] The reaction was carried out with 1,3-indandione (1.05 equiv), arylidenemalononitrile (1.0 equiv), iodine (1.2 equiv) and DMAP (3 equiv) at 40 °C.

[b] Yield of isolated product.

Facile synthesis of spirocyclopropanes by 1,3-indandione and arylidenemalononitrile
The reaction occurred in the presence of molecular iodine and dimethylaminopyridine
Various substituents on the benzene ring were well tolerated and gave good yields

The structures of products were confirmed by NMR and X-ray diffraction analysis
A possible mechanism of this reaction process is proposed

Declaration of interests

√ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical Abstract

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Facile Synthesis of Spiro-substituted cyclopropanes Through Reaction of Electron-Deficient Olefins and 1,3-Indandione

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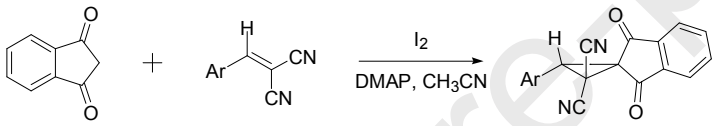

1 **2a - 2o** **3a - 3o**

Ar = Ph; 4-FC_6H_4; 4-ClC_6H_4; 4-BrC_6H_4; 4-$NO_2C_6H_4$; 3-ClC_6H_4; 3-$NO_2C_6H_4$; 3,4-$Cl_2C_6H_3$; 4-$OCH_3C_6H_4$; 4-$CH_3C_6H_4$; 3,4-$(CH_3O)_2C_6H_3$; 3,4-$(CH_3)_2C_6H_3$; 3,4-$OCH_2OC_6H_3$; 2-ClC_6H_4; 3-pyridinyl.