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FULL PAPER

An Efficient Synthesis of Spiropyrroloquinolines by Domino Reaction of α-Dicarbonyl Compounds and Anilinosuccinimides

Man Xiao[a], Qiu Sun[a], Jing Sun[a], and Chao-Guo Yan[a]*

Abstract: Under the catalysis of Brønsted acid, the domino annulation reaction of different α-dicarbonyl compounds with anilinosuccinimides under microwave irradiation afforded functionalized spiropyrroloquinolines involving the activation of *ortho*-H in different aniline derivatives.

Introduction

Recently, the development of spiro compounds has emerged as a field of strong attention owing to their attractive conformational features, potential medicinal applications, catalysis, and optical materials.[1] Spirooxindolines which comprise many natural products, pharmaceuticals and biologically active molecules[2], containing biological activities, which include cholinesterase inhibition,[3] anticancer,[4] antibacterial,[5] and anti-inflammatory activities.[5] Among them, some alkaloids like horsifiline, alstonisine,[6] and spirotryprostatins **A** and **B**, isolated from the fermentation broth of Aspergillus fumigatus, were found to completely inhibit the G2/M progression of cellular division in mammalian tsFT210 cells (Figure 1).[7]

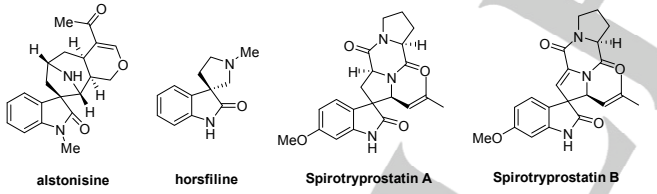

Figure. 1 Examples of natural products and synthetic therapeutic agents containing spiroxindole core

On the other hand, 1,4-dihydropyridines are of particular interest, owing to their biological and pharmacological actions. First of all, they represent one of the most important groups of calcium-channel modulating agents and they are used in the treatment of cardiovascular diseases.[8] In addition, it is also the common core structure of various biologically active compounds having selective adenosine-A3 receptor antagonism, along with radioprotective activity, anticonvulsant activity, sirtuin activation, and inhibition.[9,10] Because of the intense utility of these two cores, several groups have paid their full attention on the development of the synthetic methodology for the synthesis of spiro[dihydropyridineoxindoles].[11,12] In recent years, domino or tandem processes have become an efficient method for the synthesis of various spirooxindoles due to its simple process, easy operation, efficiency and high atomic economy.[13] The cascade reaction of isatins with *β*-enaminones is one of convenient way for synthesis of these useful spiro[dihydropyridineoxindoles]. However, we found very few examples on the synthesis of this spiro core involving the activation of *ortho*-H in different aniline derivatives.[14,15,16] To synthesis this useful products efficiently and under green chemical conditions, with our continuous effort, we have successfully synthesized spiro[dihydropyridineoxindole] derivatives using substituted anilinosuccinimides with various α-dicarbonyl compounds by domino reaction where the *ortho*-attack of the aniline system occurs to form the spiro center under microwave irradiation.

Results and Discussion

Initially, we set the reaction of 4-methoxy-anilinosuccinimide (**1a**) and 1-benzyl-5-chloro-indoline-2,3-dione (**2a**) as the model reaction for optimizing reaction conditions. Various solvents, the ratio of solvent, temperature and reaction time were examined (Table 1). In the first attempt, 1,4-Dioxane and Ac_2O was used for this reaction under microwave irradiation at 120 °C, the reaction scarcely proceeded to give desired product **3a** (Table 1, entry 1). To our pleased, when Ac_2O was changed to AcOH, spiropyrroloquinolines **3a** was isolated in 62% yield, which is different from the [3+2] type cyclization frequently reported (entry 2), eventually, the structural of single crystal **3a** was unequivocally determined by X-ray diffraction (Figure 1). Encouraged by this result, other reaction conditions were detailly optimized. Experiments were carried out in different acidic sysytem solvents of *p*-TsOH/Diox, AcOH/Tol, AcOH/CAN and AcOH/EtOH, which were found to be inefficient for this transformation (entries 3-6). Raise the temperature to 150 °C, desired product **3a** could been isolated in 86% yield (entry 7). Prolonging reaction time to 30 minutes led to the same yield (entry 8). Meanwhile, different ratio of co-solvents resulted in lower yield of 43% and 28% (entries 9-10). The reaction cannot proceed in a single solvent of 1,4-Dioxane or AcOH (entries 11-12), and also cannot proceed without microwave irradiation (entry 13). On the basis of these results, we found

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† Footnotes relating to the title and/or authors should appear here.
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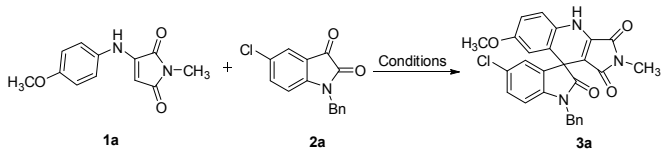
that the optimized reaction conditions for the domino reaction was in the co-solvents of Diox/AcOH with the ratio of 1:1 under microwave irradiation for approximately 20 minutes at 150 °C.

Table 1. Reaction Optimization for the Synthesis of **3a**[a]



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

Entry	Acid/Solvent	Ratio[b]	T (°C)	t (min)	Yield (%)[c]
1	Ac_2O/Diox	1:1	120	20	Trace
2	AcOH/Diox	1:1	120	20	62
3	*p*-TsOH/Diox	1:1	120	20	Trace
4	AcOH/Tol	1:1	120	20	Trace
5	AcOH/CAN	1:1	120	20	Trace
6	AcOH/EtOH	1:1	120	20	Trace
7	AcOH/Diox	1:1	150	20	86
8	AcOH/Diox	1:1	150	30	86
9	AcOH/Diox	2:1	150	20	43
10	AcOH/Diox	1:2	150	20	28
11	Diox	-	150	20	trace
12	AcOH	-	150	20	trace
13[d]	AcOH/Diox	1:1	150	20	trace

[a]Reaction conditions: **1a** anilinosuccinimide (0.5 mmol), **2a** 1-benzylindoline-2,3-dione (0.5 mmol), solvent (2 mL) under microwave irradiation. [b]The ratio of the amount of solvent and acid; [c]Isolated yield. [d]Without microwave irradiation.

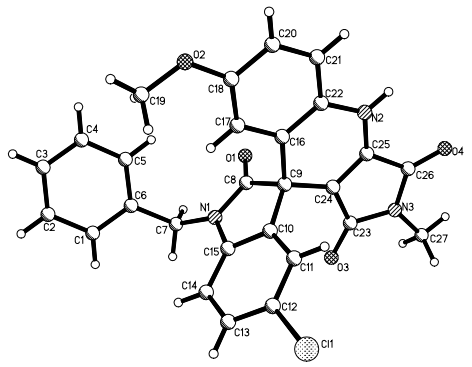
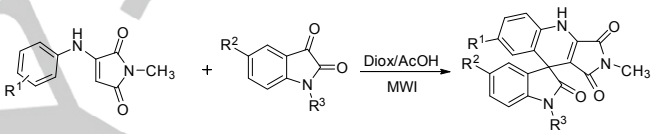


Figure. 1 Molecular structure of compound **3a**

With the optimized reaction conditions (Table 1, entry 7) in hand, we examined the substrate scope. The results are summarized in Table 2. Derivatives of anilinosuccinimide bearing different electron-donating substituents at ortho-, meta-, or para-positions reacted smoothly with various indoline-2,3-diones under established conditions, and afforded the expected spiropyrroloquinolines **3b–3q** in moderate to good yields of 65–85% (Table 2, entries 1-15). The substituent on the other position seems to influence the results, due to the steric effect, reactions of *o*-methyl-anilinosuccinimide gave **3c** in only 65% yield (entry 2). However, anilinosuccinimide bearing electron-withdrawing substituents, showed poor activity even after prolonged reaction time of 1 h (entries 17-18). Apparently, the reaction is currently limited to electron-rich anilinosuccinimide. On the other hand, both electron-rich (entries 3, 9, 11, and 15) and electron-deficient (entries 1-2, 4-8, 10, 12, 14-15) indoline-2,3-dione led to the desired spiropyrroloquinolines in more than 65% yields. The substituents on N atom also does not seem to influence the results (entries 1-15). The structures of the compounds **3a-3o** were fully characterized by IR, HRMS, ^{1}H and ^{13}C NMR spectroscopy. The single-crystal structures of the spiro compounds **3e**, **3g** and **3o** (Figure S1-S3) were successfully determined by X-ray diffraction.

Table 2. Substrate scope **3b-r**[a]



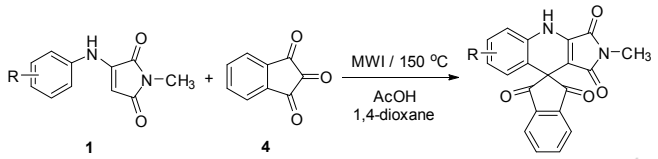
1 **2** **3b-r**

Entry	Compd	R^1	R^2	R^3	Yield (%)[b]
1	**3b**	H	Cl	Bn	78
2	**3c**	*o*-CH_3	F	Bn	65
3	**3d**	*m*-CH_3	CH_3	C_4H_9	76
4	**3e**	*m*-CH_3	Cl	Bn	78
5	**3f**	*p*-CH_3	Cl	H	80
6	**3g**	*p*-CH_3	Cl	Bn	82
7	**3h**	*p*-CH_3	F	Bn	85
8	**3i**	*p*-CH_3	Cl	C_4H_9	82
9	**3j**	*m*-OCH_3	CH_3	C_4H_9	77
10	**3k**	*m*-OCH_3	Cl	C_4H_9	75
11	**3l**	*p*-OCH_3	CH_3	H	76
12	**3m**	*p*-OCH_3	Cl	H	72
13	**3n**	*p*-OCH_3	H	Bn	78
14	**3o**	*p*-OCH_3	F	Bn	86
15	**3p**	*p*-$C(CH_3)_3$	CH_3	C_4H_9	82
16[c]	**3q**	*p*-F	CH_3	Bn	Trace
17[c]	**3r**	*p*-Br	CH_3	Bn	Trace

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), solvent (2 mL, V(Diox/AcOH) = 1:1) under microwave irradiation at 150 °C , 20 mins; [b]Isolated yield; [c]1h reaction time.

For developing the scope of this reaction, other α-dicarbonyl compounds were also used in the reaction. As to ninhydrin, the results were summarized in Table 3. For anilinosuccinimide bearing a single electron-donating group, the expected spiro compounds were obtained in yields of 68−87% (Table 3, entries 2-7). The reaction showed its limit with the bulkier *o*-methyl-anilinosuccinimide, which resulted in the corresponding spiro compounds (**5b**) in 65% yield. It is worth mentioning that anilinosuccinimide bearing electron-withdrawing group at the meta or para position resulted in the spiro products in 70-76% yields. However, these results could not be observed in other α-dicarbonyl compounds. The structures of the compounds **5a**-**5k** were fully characterized by IR, HRMS, ^{1}H and ^{13}C NMR spectroscopy. The single-crystal structures of the two spiro compounds **5b** (Figure. 3) and **5c** (Figure. S4) were successfully determined by X-ray diffraction.

Table 3 Substrate scope **5a**-**k**[a]



1 4 **5a**-**k**

Entry	Compd	R	Yield (%)[b]
1	**5a**	H	82
2	**5b**	*o*-CH_3	68
3	**5c**	*m*-CH_3	77
4	**5d**	*p*-CH_3	84
5	**5e**	*m*-OCH_3	78
6	**5f**	*p*-OCH_3	87
7	**5g**	*p*-$C(CH_3)_3$	82
8	**5h**	*m*-Cl	73
9	**5i**	*p*-Cl	76
10	**5j**	*m*-Br	70
11	**5k**	*p*-Br	72

[a]Reaction conditions: **1** (0.5 mmol), **4** (0.5 mmol), solvent (2 mL, V(Diox/AcOH) = 1:1) under microwave irradiation at 150 °C , 20 mins; [b]Isolated yield.

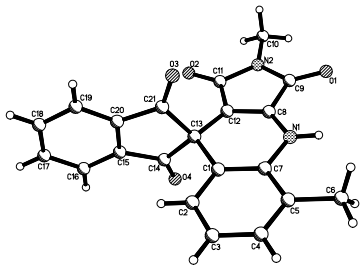
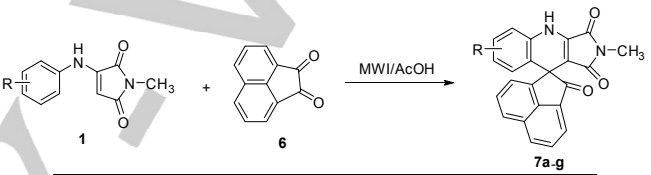


Figure. 3 Molecular structure of compound **5b**

When acenaphthequinone was employed in the reaction, we found that the reaction proceeded sluggishly in the above mentioned system of AcOH/Diox. When acetic acid was used both as acid catalyst and solvent, the expected spiro compounds were prepared in satisfactory yields. The results are summaried in Table 4. For anilinosuccinimide bearing a single electron-donating group at the meta or para position, good yields of 74−82% were obtained (Table 4, entries 2-6). Only trace yield was obtained for the bulkier substrate with substituent at the *ortho* position and anilinosuccinimide bearing with electron-withdrawing groups. Meanwhile, the structures of the compounds **7a**-**7f** were also fully characterized by IR, HRMS, ^{1}H and ^{13}C NMR spectroscopy. The single-crystal structures of the spiro compound **7d** (Figure S5) was successfully determined by X-ray diffraction.

Table 4 Substrate scope **7a**-**f**[a]



1 6 **7a**-**g**

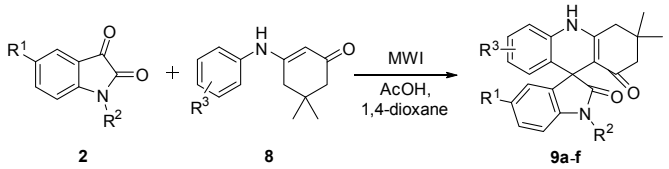
Entry	Compd	R	Yield (%)[b]
1	**7a**	H	68
2	**7b**	*m*-CH_3	74
3	**7c**	*p*-CH_3	80
4	**7d**	*m*-OCH_3	76
5	**7e**	*p*-OCH_3	82
6	**7f**	*p*-$C(CH_3)_3$	78
7[c]	**7g**	*p*-F	trace
8[c]	**7h**	*p*-Cl	trace

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), AcOH as solvent (2 mL) under microwave irradiation at 150 °C, 20 mins; [b]Isolated yield; [c]1h reaction time.

To demonstrate the utility of the reactions, we also carried out the reaction of indoline-2,3-diones (**2**) with 5,5-dimethyl-3-(phenylamino)cyclohex-2-en-1-one (**8**) with different substituents under microwave irradiation. The results are listed in Table 5. The reaction proceeded smoothly for both electron-rich (Table 5, entry 5) and electron-deficient (entries 1-4) indoline-2,3-diones in more than 67% yields. Similarly, the reaction also limited to electron-rich 5,5-dimethyl-3-(phenylamino)cyclohex-2-en-1-one. The indoline-2,3-dione without substituent at N atom shows lower reactivity than those substituted isatins at N atom (entry 6). This finding is totally different from those of reactions reported by Shi et al., in which only pyrrolo[2,3,4-kl]acridin-1-one derivatives products were formed in refluxing condition catalyzed by L-proline.[12b] The single crystal structure of the compound **9a** (Figure 4) and **9c** (Figure S6) were also determined by X-ray

diffraction method. These results reveal that the reaction have a wide variety of substrates.

Table 5 Substrate scope **9a-f**[a]



Entry	Compd	R^1	R^2	R^3	Yield (%)[b]
1	**9a**	Cl	Bn	*p*-OCH_3	76
2	**9b**	F	Bn	*p*-OCH_3	78
3	**9c**	Cl	C_4H_9	*p*-OCH_3	71
4	**9d**	Cl	Bn	*p*-CH_3	74
5	**9e**	CH_3	C_4H_9	*p*-CH_3	67
6	**9f**	CH_3	H	*p*-OCH_3	51

[a]Reaction conditions: **2** (0.5 mmol), **8** (0.5 mmol), solvent (2 mL, V(Diox/AcOH) = 1:1) under microwave irradiation at 150 °C , 20 mins; [b]Isolated yield.

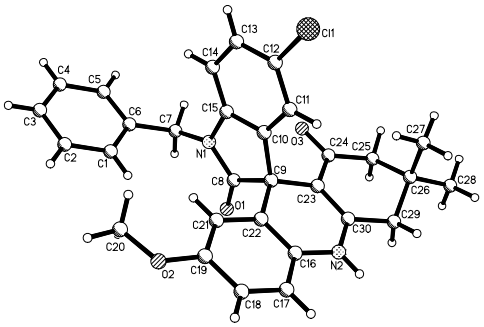
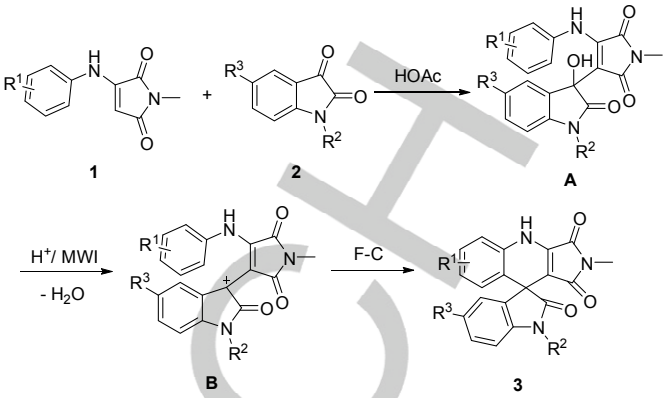


Figure. 4 Molecular structure of compound **9a**

The mechanism hypothesis for these reactions was proposed and shown in Scheme 1. Firstly, the nucleophilic addition of anilinosuccinimide to the carbonyl group of isatin afforded the intermediate **A.** In the presence of acetic acid and microwave irradiation, a carbocation **B** was generated in the system. Then, the further intramolecular Friedel–Crafts alkylation gave the final spiro compound. Apparently, the reaction could not compatible with the electron-withdrawing groups on the β-enaminone and no spiro compound was obtained. This finding is totally different from that of reaction between β-enaminone with dicarbonyl compounds under other conditions.



Scheme 1 Plausible reaction mechanism for domino reaction

Conclusions

In summary, we have successfully established a facile and green domino annulation reaction for the synthesis of functionalized spiro[dihydropyridine-oxindoles]. The synthesized spiro system here involves the activation of ortho-H atom of various aniline derivatives. All different α-dicarbonyl compounds studied with good chemoselectivity under microwave irradiation. This domino reaction established a very practical application for the domino C–C coupling reaction in organic synthesis. Further studies on domino coupling reactions for the synthesis of spiro[dihydropyridine-oxindoles] and the effective of biological activity about these useful products are in progress in future studies.

Experimental Section

1. General procedure for the synthesis of 3: 1-methyl-3-(phenylamino)-1H-pyrrole-2,5-dione (1 mmol), indoline-2,3-dione or 1H-indene-1,2,3-trione (1 mmol), acetic anhydride (1 mL) and dioxane (1 mL) were introduced in a 10 mL initiator reaction vial. Subsequently, the reaction vial was capped and then pre-stirring for 20 second. The mixture was irradiated (Time: 20 min, Temperature: 150 °C; Absorption Level: High; Fixed Hold Time) until TLC (petroleum ether: ethyl acetate 4:1) revealed that conversion of the starting material **1**was completed. The reaction mixture was then cooled to room temperature and then diluted with cold water (25 mL). The solid product was collected by Büchner filtration and was washed with 95% EtOH to give almost pure **3** and **5**. The solid was further purified by flash column chromatography (silica gel, mixtures of ethyl acetate / n-hexane, 4:1, v/v) for its NMR and HRMS analysis.

1-benzyl-5-chloro-7'-methoxy-2'-methylspiro[indoline-3,9'-pyrrolo[3,4-*b*]quinoline]-1',2,3'(2'H,4'H)-trione (3a). Yellow solid, 82%, m.p. >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.97 (s, 1H, NH), 7.44 (d, *J* = 7.6 Hz, 2H, ArH), 7.36 (t, *J* = 7.2 Hz, 2H, ArH), 7.30 (t, *J* = 7.6 Hz, 2H, ArH), 7.27-7.22 (m, 2H, ArH), 6.94-6.92 (m, 1H, ArH), 6.70 (d, *J* = 8.2 Hz, 1H, ArH), 5.92 (s, 1H, ArH), 5.07-4.96 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3), 2.83 (s, 3H, CH_3); ^{13}C NMR(100 MHz, DMSO-d_6) δ:177.4, 169.1, 165.3, 156.6, 142.5, 140.7, 138.4, 136.3, 130.0, 129.0, 127.9, 127.7, 127.6, 125.3,

123.7, 120.2, 115.2, 112.7, 111.3, 96.3, 55.6, 50.3, 43.6, 23.4; IR (KBr) *υ*: 3204, 2962, 1766, 1699, 1609, 1542, 1438, 1328, 1317,1229, 1174, 1083, 1036, 995, 877, 748, 701 cm^{-1}; MS (m/z): HRMS (ESI) Calcd For $C_{27}H_{20}ClN_3O_4$ ($[M+Na]^+$): 508.1040. Found: 508.1026.

General procedure for the synthesis of 7: 1-methyl-3-(phenylamino)-1*H*-pyrrole-2,5-dione (1 mmol), acenaphthequinone (1 mmol) and acetic acid (2 mL) were introduced in a 10 mL initiator reaction vial. Subsequently, the reaction vial was capped and then pre-stirring for 20 second. The mixture was irradiated (Time: 20 min, Temperature: 150 °C; Absorption Level: High; Fixed Hold Time) until TLC (petroleum ether: ethyl acetate 4:1) revealed that conversion of the starting material **1** was completed. The reaction mixture was then cooled to room temperature and then diluted with cold water (25 mL). The solid product was collected by Büchner filtration and was washed with 95% EtOH to give almost pure **7**. The solid was further purified by flash column chromatography (silica gel, mixtures of ethyl acetate / n-hexane, 4:1, v/v) for its NMR and HRMS analysis.

2'-methyl-2*H*-spiro[acenaphthylene-1,9'-pyrrolo[3,4-*b*]quinoline]-1',2,3'(2'H,4'H)-trione(**7a**). Yellow solid, 68%, m.p. >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.91 (s, 1H, NH), 8.36 (d, *J* = 8.0 Hz, 1H, ArH), 8.07 (d, *J* = 7.2 Hz, 1H, ArH), 7.99 (d, *J* = 8.0 Hz, 1H, ArH), 7.91 (t, *J* = 8.0 Hz, 1H, ArH), 7.65 (t, *J* = 7.6 Hz, 1H, ArH), 7.36 (d, *J* = 6.8 Hz, 1H, ArH), 7.16 (t, *J* = 7.6 Hz, 1H, ArH), 6.74 (t, *J* = 7.6 Hz, 1H, ArH), 6.09 (d, *J* = 7.6 Hz, 1H, ArH), 2.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 203.7, 165.4, 145.0, 142.3, 141.6, 136.5, 132.7, 132.5, 131.6, 130.2, 129.9, 129.4, 129.0, 128.9, 128.8, 128.4, 125.2, 124.8, 124.4, 123.7, 122.1, 121.6, 118.7, 100.6, 54.9, 23.3; IR(KBr) *υ*: 3248, 2917, 1764, 1707, 1663, 1527, 1468, 1359, 1207, 1032, 969, 804, 758 cm^{-1}; MS (m/z): HRMS (ESI) Calcd For $C_{23}H_{14}N_2O_3$ ($[M+H]^+$): 367.1083. Found: 367.1098.

2. General procedure for the synthesis of 9: 5,5-dimethyl-3-(phenylamino)cyclohex-2-en-1-one (1 mmol), indoline-2,3-dione (1 mmol) acetic anhydride (1 mL) and dioxane (1 mL) were introduced in a 10 mL initiator reaction vial. Subsequently, the reaction vial was capped and then pre-stirring for 20 second. The mixture was irradiated (Time: 20 min, Temperature: 150 °C; Absorption Level: High; Fixed Hold Time) until TLC (petroleum ether: ethyl acetate 4:1) revealed that conversion of the starting material **2** was completed. The reaction mixture was then cooled to room temperature and then diluted with cold water (25 mL). The solid product was collected by Büchner filtration and was washed with 95% EtOH to give almost pure **9**. The solid was further purified by flash column chromatography (silica gel, mixtures of ethyl acetate / n-hexane, 4:1, v/v) for its NMR and HRMS analysis.

1'-benzyl-5'-chloro-7-methoxy-3,3-dimethyl-3,4-dihydro-2*H*-spiro[acridine-9,3'-indoline]-1,2'(10*H*)-dione(**9a**)**.** White solid, 76%, m.p. >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.76 (s, 1H, NH), 7.54 (d, *J* = 7.2 Hz, 2H, ArH), 7.35 (t, *J* = 7.6 Hz, 2H, ArH), 7.28 (t, *J* = 7.2 Hz, 1H, ArH), 7.17-7.14 (m, 1H, ArH), 6.98-6.96 (m, 1H, ArH), 6.85 (d, *J* = 7.2 Hz, 1H, ArH), 6.83-6.82 (m, 1H, ArH), 6.81-6.79 (m, 1H, ArH), 5.92-5.91 (m, 1H, ArH), 5.01-4.91 (m, 2H, CH_2), 3.43 (s, 3H, OCH_3), 2.52-2.51 (m, 2H, 2CH), 2.14-2.00 (m, 2H, 2CH), 1.06 (s, 3H, CH_3), 1.03 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 192.3, 179.2, 153.4, 141.4, 141.1, 137.1, 133.1, 132.7, 129.3, 128.9, 128.1, 127.8, 127.4, 126.7, 126.5, 123.0, 122.9, 116.6, 110.4, 103.8, 51.1, 50.4, 43.6, 41.0, 32.6, 28.6, 27.6, 20.7; IR(KBr)*υ*: 3066, 3111, 1695, 1595, 1496, 1345, 1169, 1032, 948, 881, 746 cm^{-1}; MS (m/z): HRMS (ESI) Calcd For $C_{30}H_{27}ClN_2O_3$ ($[M+H]^+$): 498.1788. Found: 498.1801.

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Keywords: domino annulation reaction• spiro[dihydropyridine-oxindoles]• cyclization• microwave irradiation• chemoselectivity

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