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A Novel Entry to Spirofurooxindoles Involving Tandem Dearomatization of Furan Ring and Intramolecular Friedel–Crafts Reaction

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Abstract: A copper sulfate pentahydrate-catalyzed intramolecular Friedel–Crafts reaction using an oxocarbenium species derived from a furan ring as the alkylating agent was developed for the first time. By using this protocol, spirofurooxindoles **9** with multi-reactive sites were synthesized simply and concisely. In addition, selective hydrogenation of the *endo*-cyclic double bond and full hydrogenation of the *endo* and *exo*-cyclic double bonds of spirofurooxindoles **9** provided spirofurooxindoles **11** and **12**, respectively.

Keywords: dearomatization; Friedel–Crafts reaction; selective hydrogenation; spirofurooxindoles

The heterocyclic spirooxindoles **1** with diverse B rings, of synthetic or natural origin, have attracted much attention due to their significant biological activities.[1] For example, spiro[pyrrolidine-3,3′-oxindoles] have recently been found to be a novel inhibitor of the MDM2-p53 interaction.[2] Gelsedine-type indole alkaloids showed strong cytotoxic effects against the A431 human epidermoid carcinoma cell line.[3] Spiro[isoxazolidine-3,3′-oxindoles] were demonstrated to have significant cytostatic activity on the human breast cancer cell line, MCF-7.[4] Spiro[furo-2,3′-oxindoles] inhibited the growth of lung adenocarcinoma (A549) cells and hepatocellular carcinoma (HepG2) cells.[5] Presently, the development of efficient methods for the synthesis of novel heterocyclic spiro-oxindoles and investigation of their bioactivities are of great significance in organic and medicinal chemistry.

To date, most of the documented methods for the synthesis of heterocyclic spiro-oxindoles start with substituted indoles (**2a**) or isatins (**2b**) containing ring A, followed by the construction of the spiro-carbon and formation of ring B (Pathway a, Figure 1).[6,7] However, sometimes these methods suffer from inherent drawbacks such as functional group compatibility, harsh reaction conditions, multiple-step manipulation, and poor availability of the starting material to diversify the molecular structure. It is highly desirable to develop simple and complementary methods for the construction of the spiro-carbon of **1** and formation of ring A from readily available B-ring-containing amides **3** (Pathway b).[8]

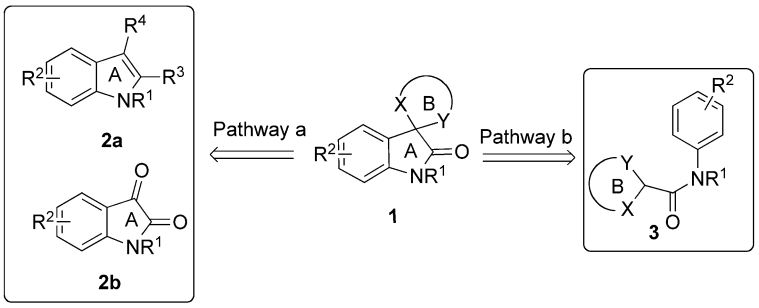

Figure 1. Construction of the spiro-carbon of **1**.

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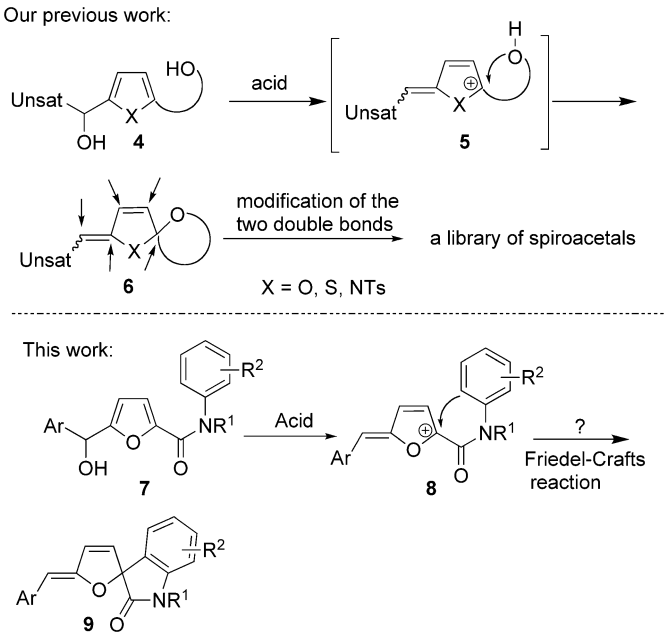
In our continuous efforts to search for bioactive spiro compounds, we have recently developed a general and concise method for the construction of a library of spiroacetals (Scheme 1).[9,10] The synthetic strategy involves: (i) the dearomatization of the five-membered aromtic ring of **4**, which generates a carbocation **5** when exposed to suitable acids; (ii) trapping of **5** with an intramolecular hydroxy group as a nucleophile to form spiroacetals; and (iii) further modification of multiple reaction sites of **6** for diversity-oriented synthesis (DOS). We envisaged that the diversification of the nucleophiles to trap carbocation **5** could produce a series of useful spiro-compounds with structural novelty.

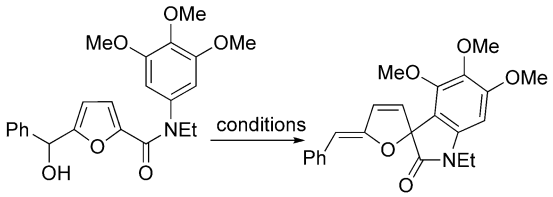
In this paper we wish to report a reaction in which the carbocation **8**, derived from 2-furancarboxamide **7**, is trapped by an intramolecular electron-rich phenyl ring (Friedel–Crafts reaction). This protocol would allow easy access to spirofurooxindoles **9**. To the best of our knowledge, such type of Friedel–Crafts reaction using oxocarbenium adjacent to an electron-withdrawing carbonyl group as an alkylation agent has never been reported.



Scheme 1. Intramolecular trapping of the carbocation derived from a five-membered aromatic ring.

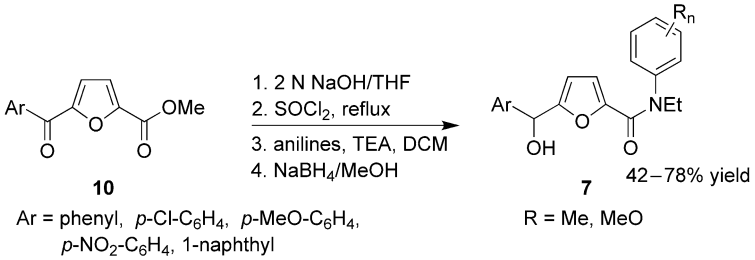
With the above-mentioned strategy in mind, we set out to synthesize precursor **7**. As shown in Scheme 2, **7** was prepared from a keto ester **10**[11] in middle to good overall yields over 4 steps including hydrolysis, acetyl chlorination, amidation and reduction. To optimize the reaction conditions for the cyclization of **7** into **8**, **7aa** was used as the substrate under the influence of various acids and the results were summarized in Table 1. Possibly due to the polymerization of the furan ring, strong Lewis acids such as $TiCl_4$, $SnCl_4$ and

Table 1. Optimization of the reaction conditions for cyclization.[a]



Entry	Acid	Solvent	Temp. [°C]	Time [h]	Yield [%][b]
1	$TiCl_4$[c]	DCM	−78	1	ND
2	$SnCl_4$[c]	DCM	−78	1	ND
3	$BF_3{\cdot}Et_2O$[c]	THF	−78	1	ND
4	CSA[c]	DCM	r.t.	72	25
5	PTSA[c]	toluene	r.t.	6	25
6	$Yb(OTf)_3$[c]	toluene	60	2	ND[e]
7	$CuSO_4$[d]	toluene	110	12	NR[f]
8	$CuSO_4{\cdot}5H_2O$[d]	toluene	100	18	62
9	$CuSO_4{\cdot}5H_2O$[d] and AcOH[c]	toluene	100	5	85
10	$CuSO_4{\cdot}5H_2O$[d] and AcOH[c]	toluene	110	1.5	78

[a] All reactions were carried out on a 0.3 mmol scale.
[b] Isolated yield.
[c] 0.1 equiv. was used.
[d] 1.5 equiv. were used.
[e] ND: not detected.
[f] NR: no reaction.



Scheme 2. Synthesis of precursors **7** for cyclization.

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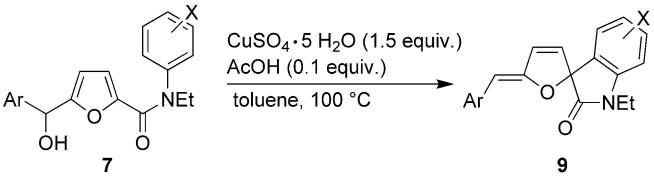
$BF_3{\cdot}Et_2O$ led to very complicated reaction systems (entries 1–3), although they have been frequently used as catalysts for Friedel–Crafts reactions utilizing acetals as alkylating agents. Weaker protonic or Lewis acids such as CSA, PTSA, $Yb(OTf)_3$, and $CuSO_4$ were also screened (entries 4–7). To our delight, the desired product **9aa** was obtained in 62% yield when $CuSO_4{\cdot}5H_2O$ (or $CuSO_4$ with a small amount of H_2O) as a catalyst (entry 8). The structure of **9aa** was confirmed by single-crystal X-ray data analysis (Figure 2). Interestingly, under the same reaction conditions as in entry 8, addition of a catalytic amount of AcOH improved the yield remarkably to 85% (entry 9). Further increases of the reaction temperature to 110 °C resulted in a lower yield (entry 10). Under the catalysis of $CuSO_4{\cdot}5H_2O$, AcOH might react with the hydroxy group of **7**, forming the corresponding acetate. The acetoxy group is a good leaving group which helps to form carbocation **8**.

To understand the generality of this reaction, we subjected various 2-furylcarbinol amides **7** to provide the spirofurooxindoles (**9aa**–**9ed**) under the same reaction conditions as entry 9 in Table 1. The results are summarized in Table 2. As expected, the electron density of the phenyl ring of the anilines influenced the yields remarkably. Higher electron density generally led to higher yields (**9aa** > **9ab** > **9ac** > **9ad**). The failure with **9af** might result from the low electron density of its phenyl ring (entry 6). In entries 13–16 where the Ar group is 1-naphthyl, compounds **9ea**–**9ed** were obtained as a mixture of two isomers with a ratio about 5:1. Products **9ea**–**9ed** may be viewed as *trans*-1,2-diarylethylenes where rotational isomerism seems to exist.[12] Therefore, the isomers are probably the rotamers about the naphthyl-CH= linkage. On the basis of the ORTEP diagram of the major isomer of **9ed**,[15] the structures of the two isomers are proposed in Figure 3. It is worth noting that when the X group was 3,4-dimethoxy, the cyclization occurred exclusively at the 6-position of the phenyl ring (entries 3, 15). In contrast, when the X group was 3-methoxy, the cyclization occurred predominately at the 6-position, leading to two regioisomers, (entries 5 and 10).

To diversify the spirofurooxindoles scaffold, we modified the *endo* and *exo*-cyclic double bonds of **9** (Scheme 3, Table 3). Selective hydrogenation of the *endo*-cyclic double bond was achieved by reduction of **9** with $NaBH_4$ (10 equiv.) in the presence of $NiCl_2$ (1.5 equiv.) in DME-MeOH, yielding **11** with moderate to good yields (60–75%). The substituted 2-methylenetetrahydrofuran ring of **11** is likely to adopt two different conformations (the bent and twisted forms) which may have a high barrier to pseudorotation.[13]

Table 2. Synthesis of spirofurooxindoles.[a]



Entry	Ar	X	Time [h]	9[b]	Yield[c] [%]
1	Ph	3,4,5-tri-MeO	5	**9aa**	85
2	Ph	3,5-di-MeO	0.5	**9ab**	83
3	Ph	3,4-di-MeO	1.5	**9ac**	66
4	Ph	3,5-di-Me	6	**9ad**	46
5	Ph	3-MeO	1	**9ae**	57 (3/1)[d]
6	Ph	H	16	**9af**	0
7	*p*-Cl-C_6H_4	3,4,5-tri-MeO	1	**9ba**	92
8	*p*-Cl-C_6H_4	3,5-di-MeO	1	**9bb**	89
9	*p*-Cl-C_6H_4	3,5-di-Me	5	**9bd**	60
10	*p*-Cl-C_6H_4	3-MeO	5	**9be**	64 (4/1)[d]
11	*p*-NO_2-C_6H_4	3,4,5-tri-MeO	3	**9ca**	85
12	*p*-MeO-C_6H_4	3,4,5-tri-MeO	7	**9da**	33
13	1-naphthyl	3,4,5-tri-MeO	2	**9ea**	87(5/1)[d]
14	1-naphthyl	3,5-di-MeO	1.5	**9eb**	80 (4.8/1)
15	1-naphthyl	3,4-di-MeO	1.5	**9ec**	91 (3.7/1)
16	1-naphthyl	3,5-di-Me	5	**9ed**	71 (3/1)[d]

[a] All reactions were carried out on a 0.3 mmol scale.
[b] All compounds were fully characterized (see Supporting Information).
[c] Isolated yield.
[d] Based on ^1H NMR.

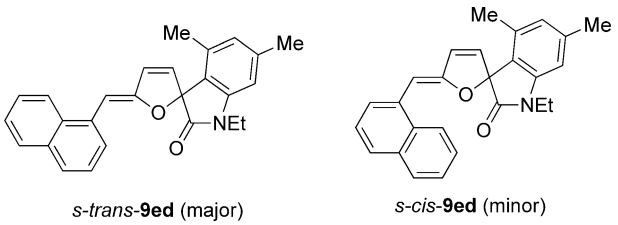


Figure 3. The structures of *s-trans*-**9ed** and *s-cis*-**9ed**.

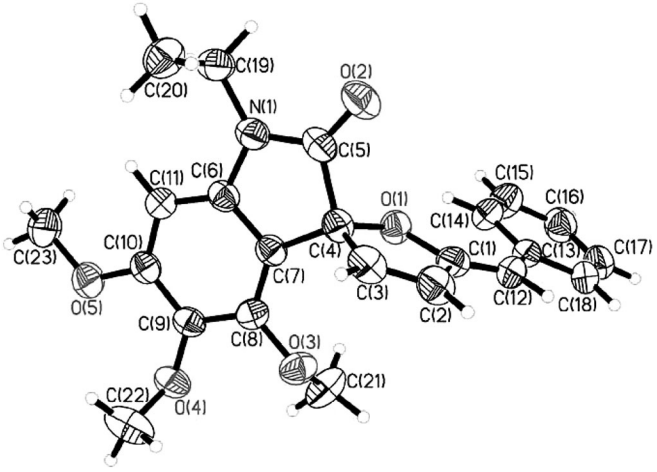


Figure 2. ORTEP diagram of **9aa**.[15]

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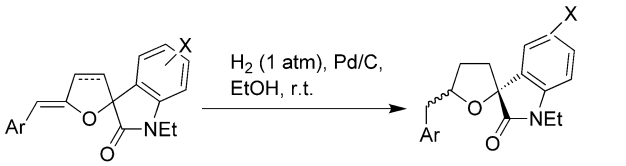
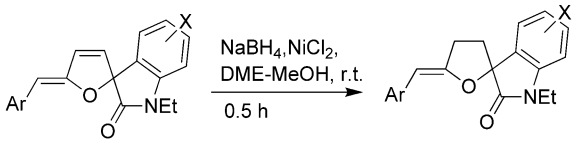


9aa **12aa** 93%, *cis/trans* = 1.9/1
9ab **12ab** 91%, *cis/trans* = 2.1/1
11ad **12ad** 92%, *cis/trans* = 1.3/1
9ed **12ed** 91%, *cis/trans* = 2.2/1

Scheme 3. Synthesis of spirofurooxindoles **12**.

Table 3. Synthesis of spirofurooxindoles **11**.[a]



9 **11**

Entry	**9**	Major product	Ratio[b]	Yield[c] [%]
1	**9aa**	**11aa**	1/0.35	70
2	**9ab**	**11ab**	1/0.37	60
3	**9ad**	**11ad**	1/0.43	65
4	**9ba**	**11ba**	1/0.31	71
5	**9bb**	**11bb**	1/0.71	63
6	**9bd**	**11bd**	1/0.85	75
7	**9ea**	**11ea**	1/0.35	70
8	***Z*-9eb**	**11eb**	1/0.41	68

[a] All reactions were carried out on a 0.3 mmol scale.
[b] The ratio of two conformational isomers is based on ^{1}H NMR.
[c] Isolated yield.

In the ^{1}H NMR spectrum of **11**, some proton signals, such as the enol ether proton, are divided into two parts. This is consistent with the existence of two conformations. The X-ray crystal structure of **11ea** indicates the non-coplanarity of the its naphthyl ring with the enol ether (Figure 4).[14] A mixture of fully reduced products **12** was obtained upon palladium-catalyzed hydrogenation, in favor of the *cis* isomer (benzyl *cis* to carbonyl). The realative configuration of **12aa** was verified by NOESY experiments and single-crystal X-ray data analysis (see Supporting Information).[15]

In summary, three kinds of novel spirofurooxindoles (**9, 11, 12**) with structural diversity were prepared using readily available furan derivatives as starting material in a concise and effective way. The key step involves an intramolecular Friedel–Crafts reaction of the tethered electron-rich anilide with the oxocarbenium derived from the furan ring. This protocol represents a potential and novel strategy for the synthesis of new heterocyclic spirooxindoles. Further studies on the trapping of **5**, derived from the dearomatization of the corresponding thiophene and pyrrole rings, to achieve molecular diversity of spirooxindoles and investigation of their bioactivities are under way, and the results will be disclosed in due course.

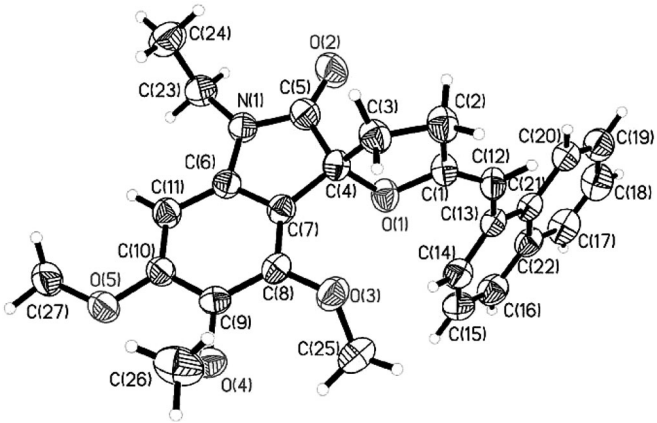


Figure 4. ORTEP diagram of **11ea**.[15]

Experimental Section

General Procedure for the Synthesis of Spirooxindole 9 from 7

The mixture of **7** (0.3 mmol), $CuSO_4 \cdot 5H_2O$ (112.5 mg, 0.45 mmol), acetic acid (1.7 μL) and toluene (5 mL) was stirred at 100 °C until the disappearance of **7** according to the TLC. The mixture then was cooled to room temperature and the solid was filtered off. The removal of the organic solvent provided the crude product which was purified by flash chromatography to give **9**.

General Procedure for the Synthesis of Spirooxindole 11 from 9

To a solution of **9** (0.2 mmol) in DME (2 mL) and anhydrous methanol (2 mL) was added $NaBH_4$ (76.0 mg, 2 mmol), $NiCl_2$ (38.1 mg, 0.3 mmol) in portions. The mixture was stirred for 20 min until the starting material had disappeared according to the TLC. The organic solvents were removed under reduced pressure, and then water (20 mL) was added. The resulting mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with saturated brine (20 mL), dried over sodium sulfate, and concentrated under reduced pressure to provide the crude product. The crude mixture was purified using silica gel flash chromatography to give the product **11**.

General Procedure for the Synthesis of Spirooxindole 12 from Spirooxindole 9 or 11

To a round-bottom flask (50 mL) was added spirooxindole **9** or **11** (0.2 mmol), ethanol (15 mL) and Pd/C (10%, 42.6 mg). Then the flask was purged with hydrogen (1 atm). The resulting solution was stirred vigorously at room temperature for 2 h. The reaction mixture was filtered through a short silica gel column. The organic solvent was removed under

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reduced pressure providing the crude product which was purified by flash chromatography to give the product **12**.

Acknowledgements

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[14] We also checked the ^{1}H NMR spectrum of the crystal in $CDCl_3$, which was exactly the same as that before crystallization.

[15] Crystallographic data for the structures of **9aa**, *s-trans*-**9ed**, **11ea** and **12ea** have been deposited with the Cambridge Crystallographic Data Center as supplementary publications number CCDC 822029, CCDC 822031, CCDC 822030, and CCDC 822032, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc. cam.ac.uk.

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