

## FULL PAPER

# A Convenient 1,3-Dipolar Cycloaddition Reaction for the Synthesis of Spirooxindoles and Some Other Spirocompounds Containing the 1,3,4-Oxadiazole Moiety

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A series of spiro[indoline-3,2'-[1,3,4]oxadiazol]-2-ones were prepared from the reaction of isatin derivatives and hydrazoneyl chlorides through the 1,3-dipolar cycloaddition reaction. This method has some important aspects, such as mild reaction condition, easy purification, and high yield of products. Also, the synthesis of spiro[acenaphthylene-1,2'-[1,3,4]oxadiazol]-2-one and spiro[[1,3,4]oxadiazole-2,9'-phenanthren]-10'-one were studied under the same condition. The structures were confirmed spectroscopically (IR,  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR, and EI-MS) and by elemental analyses. A plausible mechanism for this reaction is proposed.

**Keywords:** Isatin, Hydrazoneyl chloride, Nitrile imine, Spirooxindole, 1,3,4-Oxadiazole, 1,3-Dipolar cycloaddition reaction.

## Introduction

The spirooxindole framework has been found as a core structure of many pharmacological agents and natural alkaloids such, as welwitindolinone A [1], coerule-scine [2], and (+)-elacomine [3] (Fig. 1).

The biological activity of spirooxindole derivatives is fully established ranging from antimicrobial [4], antibacterial [5], antifungal [6], antitumor [7], antitubercular [8], and antimalarial [9] to antioxidant activities [10]. Similar to spirooxindoles, heterocycles containing a 1,3,4-oxadiazole moiety have considerable synthetic interest due to significant biological activities, such as antibacterial [11], antifungal [12], anti-inflammatory [13], anticancer [14], and anticonvulsant [15]. Also oxadiazoles are employed as fluorescent whiteners and act as muscle relaxants [16].

The 1,3-dipolar cycloaddition reactions has been studied extensively to construct important heterocyclic

compounds through a relatively simple procedure [17] [18]. Among the 1,3-dipoles, nitrile imines are widely used in 1,3-dipolar cycloaddition reaction [19][20]. One of the convenient methods for the synthesis of nitrile imines involves dehydrohalogenation of hydrazoneyl chloride in the presence of a base [21] (Fig. 2).

Cycloaddition of nitrile imine to C=O groups represents an efficient method for the construction of the oxadiazole structure [22].

Although various procedures are found in the literature for the synthesis of spirooxindole scaffolds [23][24], methods for the synthesis of molecules having both the spirooxindole and oxadiazole moieties are still limited. *Bouhfid et al.* [25] have reported a two-component reaction of allylisatin and hydrazoneyl bromide for the synthesis of the mentioned compounds with moderate yield after extended reaction time.

The most common approaches to the synthesis of spirooxindole containing 1,3,4-oxadiazole derivatives are the reaction of isatins with carbohydrazone [26] or cyanoacetic acid hydrazone [27] by a multistep procedure. These methods are associated with several disadvantages, such as extended reaction time, moderate yield of products, high temperature, and harsh reaction conditions.

In continuation of our efforts for the synthesis of spirooxindole scaffolds [28][29], we describe in this paper a simple procedure for the construction of spiro[indoline-3,2'-[1,3,4]oxadiazol]-2-one derivatives **3** via 1,3-dipolar cycloaddition reaction of isatins **1** and hydrazoneyl chlorides **2** in the presence of  $\text{Et}_3\text{N}$  in EtOH at room temperature (Scheme 1).

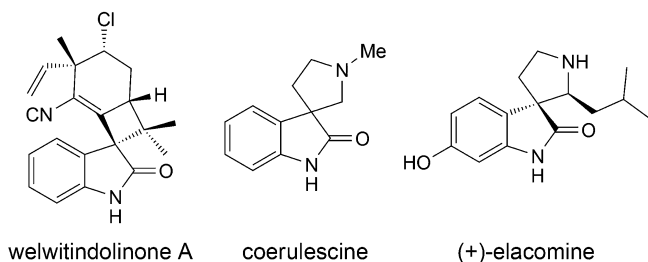


Fig. 1. Selected examples of natural products with spiro-fused oxindoles motif.

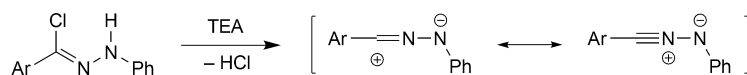
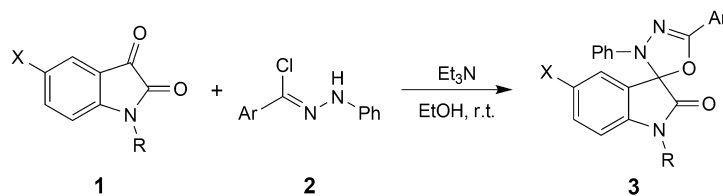


Fig. 2. Synthesis of nitrile imine from hydrazonoyl chloride.

Scheme 1. Convenient synthesis of spirooxindoles **3**.

## Results and Discussion

Reaction of isatin **1a** (X, R = H) with nitrile imine **A** (generated *in situ* from the corresponding hydrazonoyl chloride **2a** (Ar = Ph) and Et<sub>3</sub>N) in EtOH proceeds at room temperature for 5 h to afford 3',5'-diphenyl-3'H-spiro[indoline-3,2'-[1,3,4]oxadiazol]-2-one (**3a**) in 83% yield.

The IR spectrum of **3a** displayed absorption peaks at 3432 and 1736 cm<sup>-1</sup> for NH and C=O groups, respectively. The <sup>1</sup>H-NMR spectrum of **3a** consists of one singlet at 11.14 ppm due to the NH group and characteristic signals for 14 aromatic H-atoms, which is consistent with the proposed structure. The proton-decoupled <sup>13</sup>C-NMR spectrum of **3a** showed 17 distinct resonances in agreement with the proposed structure. The characteristic signals for the spiro-C-atom and the C=O group were observed at 95.5 and 169.8 ppm, respectively.

We extended the scope of this reaction to different isatins **1** and hydrazonoyl chlorides **2** under the same condition. The corresponding spirooxindoles **3** were synthesized in high yields (Table).

1,3-Dipolar cycloaddition reactions of various 1,3-dipoles, such as nitrile ylide and nitrile oxide, with acenaphthoquinone (**4**) and 9,10-phenanthraquinone (**6**) have been reported [30][31]. In the present study, a nitrile imine was used as 1,3-dipole and reacted with **4** and **6**. As

expected, spirocompounds **5** and **7** were obtained in high yields (Scheme 2).

The mechanism of this reaction involves formation of nitrile imine **A** from the reaction of hydrazonoyl chloride and Et<sub>3</sub>N. 1,3-Dipolar cycloaddition reaction of intermediate **A** onto the C=O group of isatin (**1a**) generates product **3a** (Scheme 3). Analogously, the reaction of **A** with a C=O group of **4** and **6** leads to the spirocompounds **5** and **7**, respectively.

In brief, we have developed an efficient method for the synthesis of spiro[indoline-3,2'-[1,3,4]oxadiazol]-2-one derivatives by treatment of various isatins with hydrazonoyl chlorides in the presence of Et<sub>3</sub>N. This protocol has some advantages compared to previous method [25] like using available starting materials, mild reaction condition, relatively short reaction time, and high yields of product.

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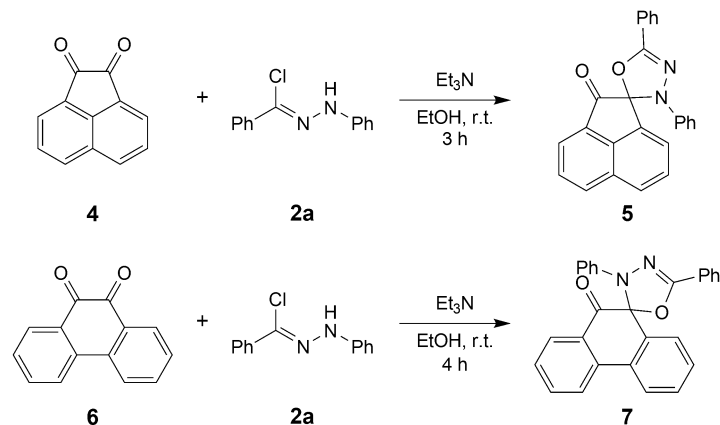
## Experimental Part

### General

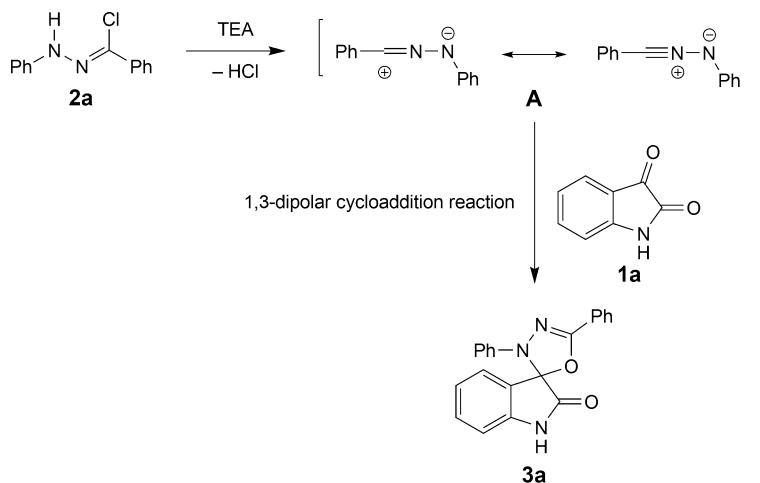
Isatin, acenaphthoquinone, and 9,10-phenanthraquinone were obtained from *Merck* (Darmstadt, Germany) and *Fluka* (Buchs, Switzerland) and were used without further

Table. Results of the synthesis of **3**

Entry	X	R	Ar	Time [h]	Yield of <b>3</b> [%]
<b>a</b>	H	H	Ph	5	83
<b>b</b>	H	Me	<i>p</i> -Cl-Ph	3	87
<b>c</b>	H	Et	<i>p</i> -Cl-Ph	5	85
<b>d</b>	Br	H	<i>p</i> -Cl-Ph	3	88
<b>e</b>	Br	Me	Ph	4	83

Scheme 2. Synthesis of spirocompounds **5** and **7**.

Scheme 3. Mechanism of the reaction.



purification. M.p.: *Electrothermal 9100* instrument (*Bibby Scientific Ltd.*, Stone, UK). IR Spectra: as KBr pellets on a *NICOLET FT-IR 100* spectrometer (*Thermo Fisher*, Waltham, MA, USA); in  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz, 300 MHz) and  $^{13}\text{C-NMR}$  (100 MHz, 75 MHz) spectra: *Bruker DRX-400* and *Bruker DRX-300 AVANCE* spectrometers (*Bruker*, Bremen, Germany). MS: *FINNIGAN-MAT 8430* mass spectrometer (*FINNIGAN*, Nevada, USA) operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

**Synthesis of Compounds 2** (exemplified for **2a**). Compound **2** was synthesized according to previous reports [21][32]. To a stirred soln. of 2.16 g (20 mmol) phenylhydrazine in 20 ml pyridine was slowly added dropwise benzoyl chloride (2.8 g, 20 mmol) under the ice bath over a period of 20 min. Upon completion of addition, ice bath was taken away, and the stirring was continued for another 15 h at the r.t. After this time,  $\text{H}_2\text{O}$  (15 ml) was added to the above mixture and the precipitate was collected by filtration, washed with  $\text{H}_2\text{O}$ , dried, and recrystallized with MeOH to give benzoyl phenylhydrazine in

80% yield. Then a mixture of  $\text{CCl}_4$  (1.46 ml, 15 mmol),  $\text{Ph}_3\text{P}$  (4.91 g, 18.75 mmol), and benzoyl phenylhydrazine (3.18 g, 15 mmol) in MeCN (40 ml) was stirred at r.t. for 6 h. After completion of reaction, the solid was filtered and washed with  $\text{Et}_2\text{O}$  to afford hydrazonoyl chloride **2a** in 50% yield.

**Synthesis of Compounds 3** (exemplified for **3a**). A mixture of isatin (**1a**; 1 mmol), hydrazonoyl chloride (**2a**; 1 mmol), and  $\text{Et}_3\text{N}$  (1 mmol) in EtOH (5 ml) was stirred at r.t. for the time given in *Table*. After completion of the reaction (TLC), the mixture was filtered and the precipitate washed with EtOH to afford the pure product **3a** in 83% yield.

**Synthesis of Compound 5**. A mixture of acenaphthoquinone (**4**; 1 mmol), hydrazonoyl chloride (**2a**; 1 mmol), and  $\text{Et}_3\text{N}$  (1 mmol) in EtOH (5 ml) was stirred at r.t. for 3 h. After completion of the reaction (TLC), the mixture was filtered and the precipitate was washed with EtOH (4 ml) to afford the pure product **5**.

**Synthesis of Compound 7**. A mixture of 9,10-phenanthraquinone (**6**; 1 mmol), hydrazonoyl chloride (**2a**;

1 mmol), and Et<sub>3</sub>N (1 mmol) in EtOH (5 ml) was stirred at r.t. for 4 h. After completion of the reaction (TLC), the mixture was filtered and the precipitate was washed with EtOH (4 ml) to afford the pure product **7**.

**3',5'-Diphenyl-3'H-spiro[indole-3,2'-[1,3,4]oxadiazol]-2(1H)-one (3a)**. Yield: 0.283 g (83%). Yellow powder. M.p. 227–229 °C. IR: 3432 (NH), 1736 (C=O), 1599, 1486 (Ar), 1129 (C–O). <sup>1</sup>H-NMR (400 MHz, (D<sub>6</sub>)DMSO): 6.75 (*d*, <sup>3</sup>*J* = 7.6, 2 H); 6.83 (*t*, <sup>3</sup>*J* = 7.2, 1 H); 7.06 (*d*, <sup>3</sup>*J* = 8.0, 1 H); 7.10 (*t*, <sup>3</sup>*J* = 7.6, 1 H); 7.19 (*d*, <sup>3</sup>*J* = 8.4, 2 H); 7.47–7.56 (*m*, 5 H); 7.82 (*d*, <sup>3</sup>*J* = 8.0, 2 H); 11.14 (*s*, 1 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 95.5; 111.5; 113.3; 120.6; 122.9; 123.4; 124.0; 125.95; 125.98; 129.1; 129.3; 131.1; 132.9; 141.8; 143.7; 151.5; 169.8. EI-MS (70 eV): 341 (*M*<sup>+</sup>, 80), 313 (100), 208 (49), 105 (69), 91 (65), 77 (96). Anal. calc. for C<sub>21</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> (341.36): C 73.89, H 4.43, N 12.31; found: C 73.96, H 4.39, N 12.36.

**5'-(4-Chlorophenyl)-1-methyl-3'-phenyl-3'H-spiro[indole-3,2'-[1,3,4]oxadiazol]-2(1H)-one (3b)**. Yield: 0.339 g (87%). Orange powder. M.p. 215–217 °C. IR: 1731 (C=O), 1605 and 1486 (Ar), 1120 (C–O). <sup>1</sup>H-NMR (300 MHz, (D<sub>6</sub>)DMSO): 3.22 (*s*, 3 H); 6.70 (*d*, <sup>3</sup>*J* = 7.6, 2 H); 6.82 (*t*, <sup>3</sup>*J* = 7.2, 1 H); 7.15–7.27 (*m*, 4 H); 7.50–7.57 (*m*, 4 H); 7.81 (*d*, <sup>3</sup>*J* = 8.0, 2 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 26.9; 95.2; 111.0; 113.9; 121.4; 122.8; 123.3; 124.5; 126.1; 128.2; 129.7; 129.8; 133.5; 136.1; 141.9; 144.4; 151.2; 169.7. Anal. calc. for C<sub>22</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub> (389.83): C 67.78, H 4.14, N 10.78; found: C 67.83, H 4.18, N 10.73.

**5'-(4-Chlorophenyl)-1-ethyl-3'-phenyl-3'H-spiro[indole-3,2'-[1,3,4]oxadiazol]-2(1H)-one (3c)**. Yield: 0.343 g (85%). Orange powder. M.p. 220–222 °C. IR: 1732 (C=O), 1641 (C=N), 1602, 1535 and 1484 (Ar), 1122 (C–O). <sup>1</sup>H-NMR (300 MHz, (D<sub>6</sub>)DMSO): 1.18 (*t*, <sup>3</sup>*J* = 6.9, 3 H); 3.77 (*m*, 2 H); 6.71 (*d*, <sup>3</sup>*J* = 8.0, 2 H); 6.80 (*t*, <sup>3</sup>*J* = 8.7, 1 H); 6.83 (*t*, <sup>3</sup>*J* = 6.9, 1 H); 7.16 (*t*, <sup>3</sup>*J* = 8.0, 2 H); 7.33 (*d*, <sup>3</sup>*J* = 8.4, 1 H); 7.55–7.57 (*m*, 1 H); 7.59 (*d*, <sup>3</sup>*J* = 8.1, 2 H); 7.83 (*d*, <sup>3</sup>*J* = 8.4, 2 H); 7.94 (*d*, <sup>3</sup>*J* = 8.1, 1 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 12.6; 35.1; 95.3; 111.0; 114.0; 121.5; 123.1; 123.4; 124.4; 126.4; 128.2; 129.7; 129.8; 133.6; 136.2; 142.1; 143.4; 151.3; 169.3. Anal. calc. for C<sub>23</sub>H<sub>18</sub>ClN<sub>3</sub>O<sub>2</sub> (403.86): C 68.40, H 4.49, N 10.40; found: C 68.32, H 4.54, N 10.46.

**5-Bromo-5'-(4-chlorophenyl)-3'-phenyl-3'H-spiro[indole-3,2'-[1,3,4]oxadiazol]-2(1H)-one (3d)**. Yield: 0.400 g (88%). Yellow powder. M.p. 134–135 °C. IR: 3438 (NH), 1743 (C=O), 1600 and 1487 (Ar), 1137 (C–O). <sup>1</sup>H-NMR (300 MHz, (D<sub>6</sub>)DMSO): 6.75 (*d*, <sup>3</sup>*J* = 8.1, 2 H); 6.87 (*t*, <sup>3</sup>*J* = 7.5, 1 H); 7.03 (*d*, <sup>3</sup>*J* = 7.1, 1 H); 7.22 (*t*, <sup>3</sup>*J* = 7.8, 2 H); 7.60 (*d*, <sup>3</sup>*J* = 8.4, 2 H); 7.68 (*d*, <sup>3</sup>*J* = 8.4, 1 H); 7.79 (*s*, 1 H); 7.83 (*d*, <sup>3</sup>*J* = 8.4, 2 H); 11.3 (*s*, 1 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 95.0; 113.8; 114.5; 115.5; 121.5; 123.4; 125.6; 128.3; 129.4; 129.7; 129.9; 136.1; 136.2; 141.8; 142.3; 151.3; 171.0. Anal. calc. for C<sub>21</sub>H<sub>13</sub>BrClN<sub>3</sub>O<sub>2</sub> (454.70): C 55.47, H 2.88, N 9.24; found: C 55.51, H 2.82, N 9.16.

**5-Bromo-5'-(4-chlorophenyl)-1-methyl-3'-phenyl-3'H-spiro[indole-3,2'-[1,3,4]oxadiazol]-2(1H)-one (3e)**. Yield: 0.389 g (83%). Yellow powder. M.p. 232–235 °C. IR: 1741

(C=O), 1602 and 1488 (Ar). <sup>1</sup>H-NMR (300 MHz, (D<sub>6</sub>)DMSO): 3.2 (*s*, 3 H); 6.68 (*d*, <sup>3</sup>*J* = 7.3, 2 H); 6.82 (*t*, <sup>3</sup>*J* = 7.1, 1 H); 7.17 (*t*, <sup>3</sup>*J* = 7.8, 2 H) 7.55–7.78 (*m*, 7 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 27.0; 94.6; 113.1; 113.8; 116.2; 121.5; 123.2; 124.9; 128.2; 128.9; 129.6; 129.7; 129.8; 136.1; 141.7; 143.6; 151.1; 169.3. Anal. calc. for C<sub>22</sub>H<sub>15</sub>BrClN<sub>3</sub>O<sub>2</sub> (468.73): C 56.37, H 3.23, N 8.96; found: C 56.31, H 3.18, N 8.89.

**3',5'-Diphenyl-2H,3'H-spiro[acenaphthylene-1,2'-[1,3,4]oxadiazol]-2-one (5)**. Yield: 0.338 g (90%). Gray powder. M.p. 190–192 °C. IR: 1732 (C=O), 1594, 1493 (Ar), 1196 (C–O). <sup>1</sup>H-NMR (300 MHz, (D<sub>6</sub>)DMSO): 6.52 (*d*, <sup>3</sup>*J* = 5.7, 2 H); 6.71 (*t*, <sup>3</sup>*J* = 8.1, 1 H); 7.00 (*t*, <sup>3</sup>*J* = 8.1, 2 H); 7.51–7.53 (*m*, 3 H); 7.81–7.83 (*m*, 3 H); 7.91 (*d*, <sup>3</sup>*J* = 8.1, 1 H); 8.01 (*t*, <sup>3</sup>*J* = 8.9, 1 H); 8.17 (*d*, <sup>3</sup>*J* = 4.8, 1 H); 8.28 (*d*, <sup>3</sup>*J* = 7.2, 1 H); 8.54 (*d*, <sup>3</sup>*J* = 6.9, 1 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 97.6; 113.9; 121.1; 123.4; 123.7; 124.5; 126.5; 128.4; 128.9; 129.5; 129.7; 129.90; 129.95; 130.8; 131.6; 131.9; 134.4; 141.9; 142.2; 151.9; 192.1. Anal. calc. for C<sub>25</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> (376.41): C 79.77, H 4.28, N 7.44; found: C 79.72, H 4.36, N 7.48.

**3,5-Diphenyl-3H,10'H-spiro[1,3,4-oxadiazole-2,9'-phenanthren]-10'-one (7)**. Yield: 0.354 g (88%). Orange powder. M.p. 226–227 °C. IR: 1699 (C=O), 1595, 1495 (Ar), 1162 (C–O). <sup>1</sup>H-NMR (300 MHz, (D<sub>6</sub>)DMSO): 6.67 (*d*, <sup>3</sup>*J* = 7.2, 2 H); 6.72 (*t*, <sup>3</sup>*J* = 5.2, 1 H); 7.08 (*t*, <sup>3</sup>*J* = 6.9, 2 H); 7.46–7.49 (*m*, 3 H); 7.56–7.65 (*m*, 3 H); 7.76 (*d*, <sup>3</sup>*J* = 5.4, 2 H); 7.94 (*t*, <sup>3</sup>*J* = 6.0, 1 H); 7.99 (*d*, <sup>3</sup>*J* = 7.8, 2 H); 8.42 (*d*, <sup>3</sup>*J* = 7.2, 2 H). <sup>13</sup>C-NMR (75 MHz, (D<sub>6</sub>)DMSO): 93.0; 114.0; 120.4; 124.6; 125.1; 125.6; 126.3; 127.7; 128.6; 129.5; 129.6; 129.9; 130.2; 130.9; 131.4; 131.6; 132.3; 133.4; 136.5; 137.5; 142.0; 150.6; 191.0. Anal. calc. for C<sub>27</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> (402.44): C 80.58, H 4.51, N 6.96; found: C 80.65, H 4.56, N 6.90.

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