

## Spiro Cyclohexadienones from the Reaction of Phenolic Enaminone Derivatives with Hypervalent Iodine Reagents

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**Abstract:** Phenolic enamino compounds, prepared from 2-(4-hydroxyphenyl)-ethylamine and the corresponding  $\beta$ -keto carbonyl compounds, afford spiro cyclohexadienone derivatives on reaction with hypervalent iodine reagents.

**Keywords:** Spiro cyclohexadienones, hypervalent iodine, enamino esters.

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### Introduction

The action of hypervalent iodine compounds on phenols gives rise to a variety of products depending on the nature of the phenol and the reaction conditions. The most interesting reaction pathway is oxidation of the phenolic moiety with simultaneous nucleophilic attack on the *para* position of the phenolic ring. When this attack occurs place intramolecularly, a variety of spirodienone derivatives are formed with considerable synthetic possibilities [1-3]. Especially noteworthy is the oxidative coupling of phenolic derivatives of  $\beta$ -phenylethylamine, studied extensively by Kita and coworkers [4]. This coupling, outlined below, offers an easy access to pharmacologically interesting natural products, when the substituent on nitrogen is an aromatic or a quinone ring.

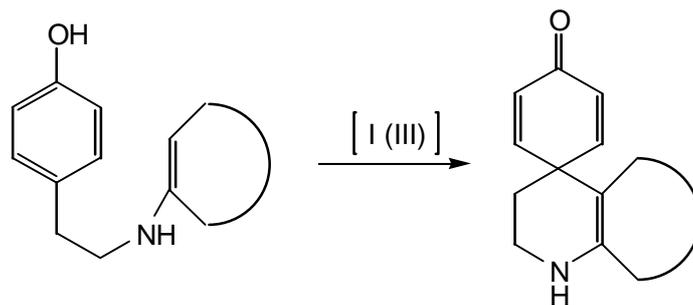


Figure 1.

## Results and Discussion

Continuing the exploration of the chemistry of hypervalent iodine reagents [5], we investigated the possibility of analogous cyclization reactions using enamino carbonyl systems of type **I**. Recently we reported the isolation of stable iodonium salts of type **II**, resulting from enamino carbonyl compounds such as amino quinones [6], aminocrotonates [7] and cyclic enamines [8] (in the last case the Ph of the iodonium salt group had been replaced by the  $\text{CF}_3\text{CH}_2$  group). We have also reported the oxidative cyclization of analogous enamino carbonyl compounds with an indole ring, resulting into the formation of tetrahydro- $\beta$ -carbolines [9].

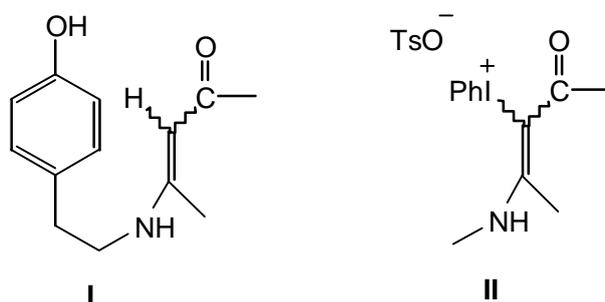
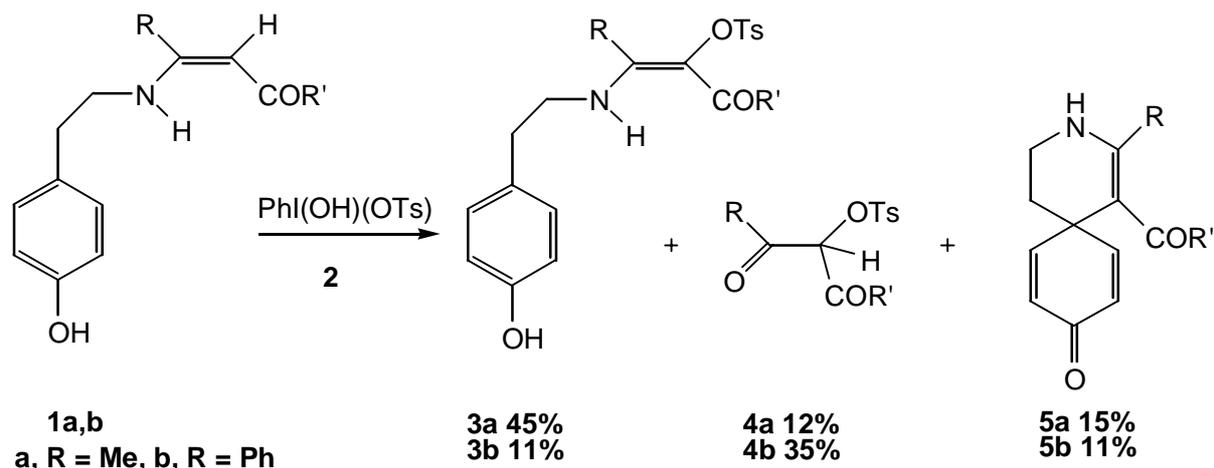


Figure 2.

Interesting results were obtained from the reaction of amino crotonic esters **1** with [(hydroxy)(tosyloxy)iodo]benzene, **2**. These esters, easily prepared from the reaction of 2-(4-hydroxyphenyl)-ethylamine with the corresponding  $\beta$ -keto acetate according to the literature method [10], react with **2** under mild conditions ( $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ) to give the products indicated in the scheme below. All new compounds have spectral and analytical data consistent with their structure.



Scheme 1.

The first step of the reaction involves probably the formation of an iodonium intermediate, **6**. This affords the tosyloxy derivative **3** through an internal nucleophilic displacement of the phenyliodonio group by the tosylate. This displacement takes place with retention of the configuration and was observed in analogous isolable iodonium salts [7]. Enamino tosylates **3** were partially hydrolyzed to keto tosylates **4** during work-up.

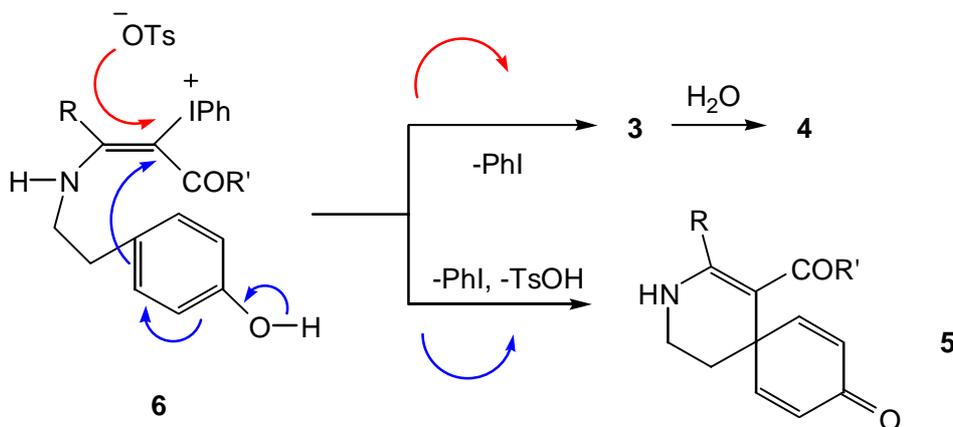
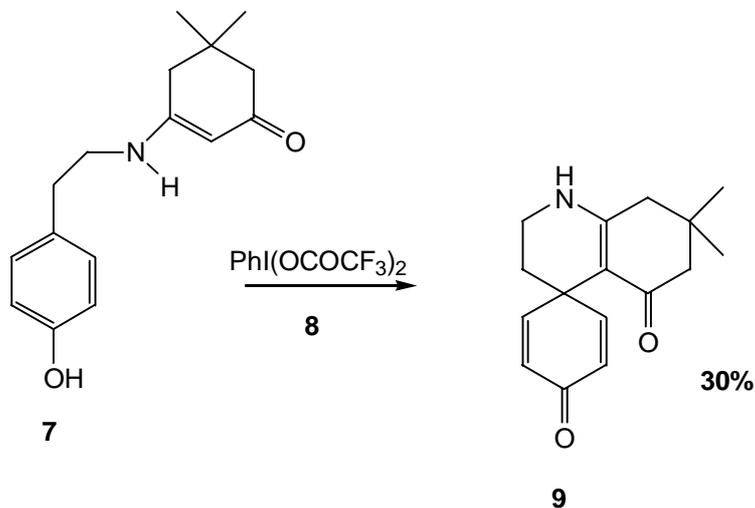


Figure 3.

A second reaction pathway leads to the formation of spiro cyclohexadienone derivatives **5**, by attack of the electron rich aromatic ring on the electrophilic carbon bearing the phenyliodonio group, with the simultaneous elimination of *p*-toluenesulfonic acid.

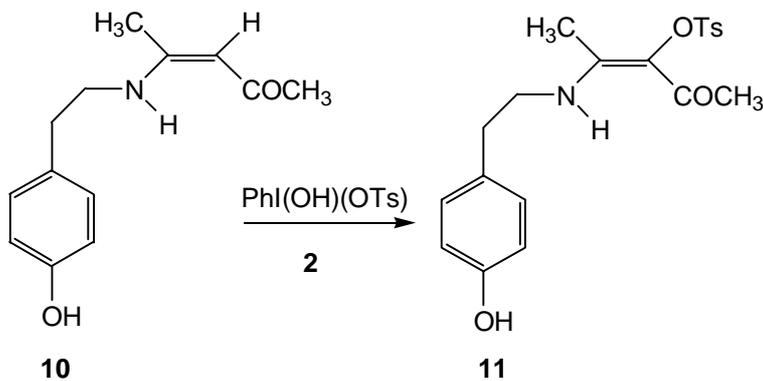
The same reaction was tried using the trimethyl silyl ethers of the phenolic derivatives **1**. Under conditions described by Kita [4], ( $\text{CF}_3\text{CH}_2\text{OH}$  as solvent,  $\text{PhI(OCOCF}_3)_2$  as oxidant) the reaction afforded a complicated mixture of products and no spiro cyclohexadienone derivatives were detected among them.

This cyclization reaction was extended to other enamino carbonyl systems. Thus, enamino compound **7**, prepared from the condensation reaction of dimedone with 2-(4-hydroxyphenyl)-ethylamine, afforded spiro cyclohexadienedione **9** as the sole isolable product. This time the cyclization was effected by [bis(trifluoroacetoxy)iodo]benzene **8** in  $\text{CH}_2\text{Cl}_2$  at room temperature in 12 hours.



Scheme 2.

In contrast, enaminone **10**, prepared analogously from acetylacetone, afforded a complex mixture of products with [bis(trifluoroacetoxy)iodo]benzene. However, it reacted smoothly with [(hydroxy)(tosyloxy)iodo]benzene to afford the tosyloxy enaminone **11** in 45% yield, but no cyclization product was isolated.



Scheme 3.

## Conclusion

The reported oxidative cyclization offers an interesting entry to spiro cyclohexadienones; research will be continued to explore the scope of the reaction with other enamino carbonyl systems.

## Experimental

### Typical procedure for the preparation of **5** and **9**

[(Hydroxy)(tosyloxy)iodo]benzene (1 mmol) was added to a stirred solution of enamino carbonyl derivative **1** (1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C under argon. The reaction mixture was allowed to reach room temperature and, after all enamino ester was consumed (5 h), it was concentrated and chromatographed on column (SiO<sub>2</sub>, hexanes-ethyl acetate) to afford, after iodobenzene, **3** and **4** as oils; Finally spiro cyclohexadienones **5a** and **5b** were eluted as light-yellow crystals.

### *2-Methyl-3-carboxyethyl-1,4,5,6-tetrahydropyridino-4-spiro-4'-cyclohexa-2',5'-dien-1'-one 5a*

Mp 180-182 °C (dec.). IR (Nujol): 3320, 1645, 1710, 1605, 1115 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.07 (t, J = 7 Hz, 3H), 1.83 (t, J = 5 Hz, 2H) 2.32 (s, 3H), 3.33 (m, 2H), 3.95 (q, J = 7 Hz, 2H), 4.65 (s, br, 1H), 6.21 (d, J = 10 Hz, 2H), 6.94 (d, J = 10 Hz, 2H); MS m/z 247 (M<sup>+</sup>, 50), 202 (45), 174 (93), 146 (100), 91 (60). Anal. Calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>3</sub>: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.42; H, 7.03; N, 5.31.

### *2-Phenyl-3-carboxyethyl-1,4,5,6-tetrahydropyridino-4-spiro-4'-cyclohexa-2',5'-dien-1'-one 5b*

Mp 199-201 °C. IR (Nujol): 3310, 1650 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 0.73 (t, J = 7 Hz, 3H), 1.94 (t, J = 5 Hz, 2H), 3.47 (m, 2H), 3.69 (q, J = 7 Hz, 2H), 4.70 (s, br, 1H), 6.27 (d, J = 10 Hz, 2H), 7.05 (d, J = 10 Hz, 2H), 7.27-7.38 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>/DMSO-d<sub>6</sub>): δ 13.39, 34.73, 38.54, 41.22, 58.99, 94.63, 127.32, 127.52, 128.12, 128.80, 139.26, 155.63, 156.12, 166.92, 186.15 ; MS m/z 309 (M<sup>+</sup>, 7), 236 (31), 208 (100), 105 (50), 77 (47). Anal. Calcd for C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.57; H, 5.94; N, 4.22.

### *7,7-Dimethyl-1,2,3,4,5,6,7,8-octahydro-quinoline-5-one-4-spiro-4'-cyclohexa-2',5'-dien-1'-one 9*

Mp 130-135 °C. IR (Nujol): 3320, 1660 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>/DMSO-d<sub>6</sub>): δ 1.03 (s, 6H), 1.74 (t, J = 5 Hz, 2H), 2.04 (s, 2H), 2.29 (s, 2H), 3.33 (m, 2H), 6.12 (d, J = 10 Hz, 2H), 6.88 (d, J = 10 Hz, 2H), 7.52 (s, br, 1H) ; <sup>13</sup>C NMR (CDCl<sub>3</sub>/DMSO-d<sub>6</sub>): δ 27.60, 31.18, 33.76, 37.05, 38.07, 42.24, 50.40, 100.82, 126.02, 155.70, 159.15, 185.37, 190.26 ; MS m/z 257 (M<sup>+</sup>, 24). Anal. Calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub>: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.59; H, 7.17; N, 5.63.

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*Samples Availability:* Not available.