

## An Efficient Synthesis of Fused Polycyclic Indole Derivatives via Aldol-Hetero Diels-Alder Reaction of $\alpha,\beta$ -Unsaturated Thio-oxindoles with Various Dienophiles

F. Matloubi Moghaddam\*, S. Taheri, L. Hojabri, P. Pirani and S. Maktabian

Laboratory of Organic Synthesis & Natural Products, Department of Chemistry, Sharif University of Technology, P. O. Box 11155-9516, Tehran, Iran

(Received 26 May 2010, Accepted 13 August 2010)

An efficient and one-pot synthesis of thiopyrano[2,3-*b*]indole derivatives via Hetero Diels-Alder reaction of  $\alpha,\beta$ -Unsaturated thio-oxindoles with electron poor acetylenes and Cyclic Dienophiles is described. In the proposed method the reaction is performed under neutral and one-pot reaction conditions, and also the substances can be mixed without any activation or modification and without using any catalysts.

**Keywords:** Hetero-Diels-Alder reaction, Aldol reaction, Thiooxindoles, Dialkylacetylenedicsters

### INTRODUCTION

Heterocyclic compounds containing nitrogen or sulfur (or both) are common features incorporated in the structures of numerous natural products and pharmaceutical compounds and the development of simple and effective methods for their preparation is a point of major concern in medicinal chemistry [1]. The hetero Diels-Alder reaction is a very powerful method for the preparation of six-membered heterocyclic compounds and has been applied to natural product synthesis [2].

Many dienes and dienophiles involving heteroatoms such as phosphorus, silicon, oxygen, sulfur and selenium have been investigated [3]. Among the members of this family,  $\alpha,\beta$ -unsaturated thioaldehydes and thioketones and their behavior in the Diels-Alder reaction have been investigated by Hall, *et al.* [4]. In their report, compounds  $R_1CH=CH-C(=S)R_2$  function as hetero-dienes and/or dienophiles in (4+2) dimerization reactions to afford different types of dimeric products depending on  $R_1$  and  $R_2$ . However, the monomeric forms of the  $\alpha,\beta$ -unsaturated thioaldehydes and thioketones are

inaccessible because of their tendency to dimerize easily, even at low temperature [4].

### EXPERIMENTAL

#### General Procedure for Aldol-Hetero Diels-Alder Reaction

To a flask containing 1 mmol of thio-oxindole in toluene (5 ml), 1.2 mmol of heteroaromatic aldehyde was added in refluxing temperature, After the starting thio-oxindole was consumed, acetylenedicster (or cyclic dienophiles) was added to the reaction mixture to produce the thiopyrano[2,3-*b*]indole derivatives. Progress of the reaction was followed up by thin layer chromatography (TLC) whose spots were visualized either with UV light or with Iodine stabilized on silica gel. Reaction mixture was stirred for a given reaction time and then the solvent was removed under reduced pressure and the residue was purified by column chromatography eluted with hexane-ethyl acetate (3-7:1).

#### Spectra Data of the Products (Tables 1 and 2)

**11a.** Yellow crystal (hexane/ethyl acetate), m.p.: 169-171

\*Corresponding author. E-mail: matloubi@sharif.edu.

°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.75 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 5.89 (s, 1H), 6.16 (d,  $J = 3.1$  Hz, 1H), 6.27 (d,  $J = 1.9$  Hz, 1H), 7.14 (t,  $J = 7.5$  Hz, 1H), 7.24 (t,  $J = 7.6$  Hz, 1H), 7.29-7.31 (m, 2H), 7.49 (d,  $J = 7.9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  30.7, 37.5, 53.1, 53.8, 105.4, 107.0, 109.0, 110.7, 118.3, 120.4, 122.4, 125.0, 126.1, 130.4, 130.7, 138.8, 142.6, 154.1, 165.2, 167.2.

**11b.** Brown oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.83 (s, 3H), 3.88 (s, 3H), 5.97 (s, 1H), 6.25 (d,  $J = 3.2$  Hz, 1H), 6.32 (dd,  $J = 3.2, 1.3$  Hz, 1H), 7.19-7.21 (m, 2H), 7.28-7.29 (m, 1H), 7.37 (d,  $J = 1.3$  Hz, 1H), 7.50-7.53 (m, 3H), 7.59-7.62 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  37.4, 53.2, 53.7, 107.17, 107.23, 110.2, 110.8, 118.4, 121.3, 123.1, 125.1, 126.6, 127.3, 128.8, 129.4, 130.3, 131.7, 136.8, 139.1, 142.7, 154.0, 165.2, 167.1.

**11c.** Yellow crystal (hexane/ethyl acetate), m.p.: 125-127 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.43 (t,  $J = 7.2$  Hz, 3H), 3.83 (s, 3H), 3.94 (s, 3H), 4.18 (m, 2H), 5.90 (s, 1H), 6.17 (d,  $J = 3.0$  Hz, 1H), 6.29 (dd,  $J = 3.0, 1.9$  Hz, 1H), 7.14 (t,  $J = 7.5$  Hz, 1H), 7.24 (t,  $J = 7.6$  Hz, 1H), 7.32-7.34 (m, 2H), 7.51 (d,  $J = 7.9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  15.7, 37.5, 39.6, 53.3, 53.9, 105.2, 107.1, 109.1, 110.8, 118.4, 120.3, 122.3, 123.9, 126.3, 130.4, 130.4, 137.6, 142.7, 154.0, 165.2, 167.4.

**11d.** Yellow crystal (hexane/ethyl acetate), m.p.: 158-160 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.74 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 5.89 (s, 1H), 6.16 (d,  $J = 3.1$  Hz, 1H), 6.27 (dd,  $J = 3.1, 1.8$  Hz, 1H), 7.12-7.16 (m, 1H), 7.22-7.26 (m, 1H), 7.30 (d,  $J = 7.9$  Hz, 1H), 7.32 (dd,  $J = 1.8, 0.6$  Hz, 1H), 7.49 (d,  $J = 7.9$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  30.8, 37.5, 53.2, 53.8, 105.3, 107.0, 109.0, 110.7, 118.3, 120.4, 122.4, 125.0, 126.1, 130.4, 130.6, 138.8, 142.7, 154.0, 165.2, 167.3.

**11e.** Brown oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.83 (s, 3H), 3.90 (s, 3H), 6.05 (s, 1H), 6.32 (d,  $J = 3.1$  Hz, 1H), 6.36 (dd,  $J = 3.1, 1.8$  Hz, 1H), 7.22-7.24 (m, 2H), 7.30-7.33 (m, 1H), 7.41 (dd,  $J = 1.8, 0.6$  Hz, 1H), 7.50-7.53 (m, 3H), 7.59-7.62 (m, 2H), 7.65-7.67 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  37.5, 53.2, 53.8, 107.2, 107.3, 110.3, 110.9, 118.4, 121.4, 123.2, 125.1, 126.7, 127.3, 128.8, 129.5, 130.3, 131.8, 136.8, 139.1, 142.8, 154.1, 165.3, 167.2.

**11f.** Yellow crystal (hexane/ethyl acetate), m.p.: 132-133 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44 (t,  $J = 7.2$  Hz, 3H), 3.82 (s, 3H), 3.94 (s, 3H), 4.18 (m, 2H), 5.89 (s, 1H), 6.16 (d,  $J = 3.1$  Hz, 1H), 6.28 (dd,  $J = 3.1, 1.8$  Hz, 1H), 7.14 (t,  $J = 7.5$  Hz, 1H), 7.23 (t,  $J = 8.0$  Hz, 1H), 7.31-7.33 (m, 2H), 7.51 (d,  $J = 7.9$

Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  15.6, 37.5, 39.6, 53.2, 53.8, 105.4, 107.0, 109.1, 110.7, 118.4, 120.3, 122.3, 123.9, 126.3, 130.4, 130.5, 137.7, 142.6, 154.1, 165.2, 167.3.

**11g.** Yellow crystal (hexane/ethyl acetate), m.p.: 133 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.16 (t,  $J = 7.1$  Hz, 3H), 1.20 (t,  $J = 7.1$  Hz, 3H), 3.80 (s, 3H), 4.12-4.22 (m, 4H), 5.13 (s, 1H), 6.46 (d,  $J = 8.1$  Hz, 1H), 6.50 (d,  $J = 3.2$  Hz, 1H), 6.62 (dd,  $J = 3.2, 1.8$  Hz, 1H), 7.01 (t,  $J = 7.6$  Hz, 1H), 7.19 (t,  $J = 7.6$  Hz, 1H), 7.28 (d,  $J = 8.2$  Hz, 1H), 7.64 (d,  $J = 1$  Hz, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  14.4, 14.5, 31.5, 44.9, 61.1, 62.6, 108.7, 109.4, 111.2, 111.6, 112.8, 119.5, 121.6, 122.5, 126.6, 136.3, 137.0, 138.8, 142.6, 150.5, 167.1, 170.4.

**11h.** Brown oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.33 (t,  $J = 7.2$  Hz, 3H), 1.38 (t,  $J = 7.2$  Hz, 3H), 4.26-4.38 (m, 4H), 6.01 (s, 1H), 6.29 (d,  $J = 3.2$  Hz, 1H), 6.35 (dd,  $J = 3.2, 1.8$  Hz, 1H), 7.20-7.23 (m, 2H), 7.29-7.31 (m, 1H), 7.40 (dd,  $J = 1.8, 0.7$  Hz, 1H), 7.50-7.53 (m, 3H), 7.59-7.63 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  14.4 (2CH<sub>3</sub>), 37.6, 62.2, 63.1, 107.2, 107.3, 110.2, 110.9, 118.4, 121.3, 123.1, 125.3, 126.7, 127.4, 128.8, 129.7, 130.3, 131.3, 136.9, 139.1, 142.6, 154.2, 164.8, 166.8.

**12a.** m.p.: 212-217 °C,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.42 (t,  $J = 7.18$  Hz, 3H), 3.65 (dd,  $J = 3.37$  Hz,  $J = 5.33$  Hz, 1H), 4.62 (q,  $J = 4.84$  Hz, 2H), 4.63 (d,  $J = 8.95$  Hz, 1H), 5.05 (d,  $J = 5.22$  Hz, 1H), 6.33 (dd,  $J = 2.86$  Hz,  $J = 15.33$  Hz, 2H), 7.11-7.36 (m, 7H), 8.2 (s, 1H),  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 15.7 (CH), 35.3 (CH), 39.3 (CH<sub>2</sub>), 46.0 (CH), 48.9 (CH), 109.3 (CH), 110.0 (C), 111.0 (CH), 117.6 (CH), 120.2 (CH), 121.8 (CH), 125.9 (C), 127.6 (C), 136.7 (C), 142.1 (CH), 152.1 (C), 175.8 (C), 176.1 (C),

**12b.** m.p.: 92-95 °C,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 3.65 (q,  $J = 5.54$  Hz, 1H), 4.59 (d,  $J = 8.93$  Hz, 1H), 5.17 (d,  $J = 5.54$  Hz, 1H), 6.32 (m, 1H), 6.39 (d,  $J = 3.19$  Hz, 1H), 7.18-7.37 (m, 5H), 7.39 (dd,  $J = 2.09$  Hz,  $J = 9.05$  Hz, 3H), 7.48 (t,  $J = 4.18$  Hz, 2H), 7.96 (s, 1H),  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 34.9 (CH), 45.5 (CH), 48.9 (CH), 109.7 (CH), 110.5 (CH), 110.9 (C), 111.1 (CH), 117.4 (CH), 121.3 (CH), 122.7 (CH), 126.3 (C), 127.2 (CH), 128.5 (CH), 128.8 (C), 130.1 (CH), 137.0 (C), 138.1 (C), 142.5 (CH), 151.5 (C), 175.2 (C), 175.8 (C).

**12c.** m.p.: 150.8-152.3,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.22 (t,  $J = 7.18$  Hz, 3H), 3.72 (q,  $J = 4.23$  Hz, 1H), 4.05 (m, 2H), 4.82 (t,  $J = 5.13$  Hz, 1H), 4.85 (s, 1H), 6.14 (d,  $J = 2.92$  Hz, 1H), 6.16 (d,  $J = 1.37$  Hz, 1H), 6.90 (t,  $J = 7.47$ , 1H), 7.02 (t,  $J = 7.07$ , 2H), 7.17 (d,  $J = 8.33$  Hz, 1H), 7.23 (s, 1H),  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 15.5 (CH<sub>3</sub>), 35.0 (CH), 39.3 (CH<sub>2</sub>), 44.0 (CH), 48.2 (CH),

108.8 (C), 109.7 (CH), 111.0 (CH), 117.5 (CH), 120.3 (CH), 122.0 (CH), 125.7 (C), 126.5 (C), 136.6 (C), 142.6 (CH), 150.8 (C), 169.5 (C), 170.2 (C).

**12d.** m.p.: 184.6-186.2 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.80 (q, J = 4.04 Hz, 1H), 4.71 (d, J = 9.47 Hz, 1H), 5.21 (d, J = 5.38 Hz, 1H), 6.35 (s, 2H), 7.21 (m, 2H), 7.32 (d, J = 4.08 Hz, 1H), 7.40 (t, J = 4.49, 1H), 7.43 (s, 1H), 7.48 (d, J = 7.74 Hz, 2H), 7.54 (t, J = 7.41 Hz, 1H), 7.62 (t, J = 7.65 Hz, 2H), <sup>13</sup>C NMR(CDCl<sub>3</sub>): 34.7 (CH), 43.6 (CH), 47.9 (CH), 109.4 (C), 110.3 (CH), 110.6 (CH), 111.2 (CH), 117.3 (CH), 121.4 (CH), 123.0 (CH), 126.2 (C), 127.2 (CH), 127.9 (C), 128.9 (CH), 130.2 (CH), 136.7 (C), 138.2 (C), 143.3 (CH), 150.1 (C), 169.1 (C), 169.2 (C).

**12e.** m.p.: 213-214 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>): 0.98 (t, J = 7.02, 3H), 3.66 (dd, J = 3.23, J = 5.45, 1H), 3.88 (q, J = 7.17, 2H), 4.17 (t, J = 8.34, 2H), 5.84 (d, J = 8.24, 2H), 6.03 (d, J = 7.52, 1H), 6.33 (s, 1H), 6.54 (t, J = 7.77, 2H), 6.74 (t, J = 7.38, 1H), 6.94 (d, J = 8.22, 1H), 10.46 (s, 1H), 10.94 (s, 1H), <sup>13</sup>C NMR (CDCl<sub>3</sub>): 15.3 (CH<sub>3</sub>), 36.4 (CH), 38.9 (CH<sub>2</sub>), 47.4 (CH), 50.97 (CH), 108.2 (CH), 108.7 (CH), 109.1 (CH), 114.3 (C), 117.5 (CH), 118.6 (CH), 119.7 (CH), 121.4 (CH), 125.4 (C), 125.5 (C), 128.3 (C), 135.0 (CH), 136.5 (C), 176.4 (C), 179.1 (C)

**12f.** m.p.: 209.1-211.2 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.77 (dd, J = 3.49 Hz, J = 5.25 Hz, 1H), 4.21 (d, J = 8.71 Hz, 1H), 4.41 (d, J = 3.47 Hz, 1H), 5.98 (s, 2H), 6.23 (d, J = 8.01, 1H), 6.67 (d, J = 2.17, 1H), 6.71 (t, J = 10.06, 1H), 6.84 (t, J = 3.98, 1H), 7.01 (d, J = 8.28, 1H), 7.15 (d, J = 7.33, 2H), 7.23 (t, J = 7.46, 1H), 7.34 (d, J = 7.61, 2H), 10.50 (s, 1H), 11.04 (s, 1H), <sup>13</sup>C NMR (CDCl<sub>3</sub>): 36.3 (CH), 47.3 (CH), 51.1 (CH), 108.4 (CH), 109.0 (CH), 110.2 (CH), 115.6 (C), 117.8 (CH), 118.6 (CH), 120.9 (CH), 122.3 (CH), 125.8 (C), 126.7 (C), 126.9 (CH), 128.0 (C), 128.1 (CH), 129.8 (CH), 136.2 (C), 137.9 (C), 176.3 (C), 179.1 (C).

**12g.** m.p.: 228-231 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.37 (t, J = 7.19 Hz, 3H), 3.53 (dd, J = 5.34 Hz, J = 3.7 Hz, 1H), 4.20 (m, 2H), 4.64 (d, J = 9.19 Hz, 1H), 5.28 (d, J = 5.93 Hz, 1H), 6.83 (t, J = 4.28 Hz, 1H), 7.04 (t, J = 6.25 Hz, 2H), 7.11 (t, J = 3.57 Hz, 1H), 7.14 (d, J = 7.29 Hz, 1H), 7.29 (t, J = 7.01 Hz, 1H), 7.35 (d, J = 7.86 Hz, 1H), 10.52 (s, 1H), <sup>13</sup>C NMR (CDCl<sub>3</sub>): 15.7 (CH<sub>3</sub>), 35.8 (CH), 39.2 (CH<sub>2</sub>), 45.1 (CH), 50.0 (CH), 109.3 (CH), 112.3 (C), 117.3 (CH), 120.1 (CH), 121.8 (CH), 125.3 (CH), 126.0 (C), 127.0 (CH), 127.1 (C), 127.7 (CH), 136.6 (C), 141.6 (C), 176.1 (C), 176.7 (C).

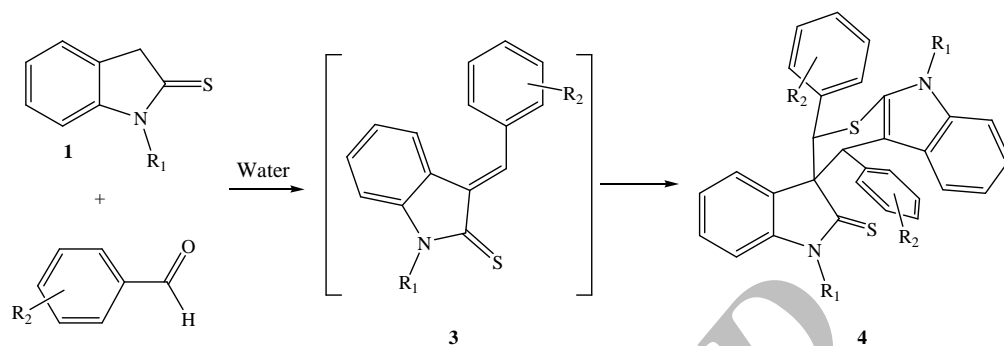
**12h.** m.p.: 93-96 °C, <sup>1</sup>H NMR (CDCl<sub>3</sub>): 3.68 (dd, J = 6.01 Hz, J = 3.14 Hz, 1H), 4.66 (d, J = 9.16 Hz, 1H), 5.42 (d, J = 6.01 Hz, 1H), 6.91 (q, J = 1.54 Hz, 1H), 7.14 (dd, J = 1.04 Hz, J = 4.06 Hz, 1H), 7.17-7.22 (m, 3H), 7.31 (m, 1H), 7.48-7.54 (m, 4H), 7.62 (t, J = 7.8 Hz, 2H), 7.89 (s, 1H), <sup>13</sup>C NMR (CDCl<sub>3</sub>): 35.7 (CH), 44.7 (CH), 50.1 (CH), 110.5 (CH), 113.2 (CH), 117.2 (CH), 121.2 (CH), 122.8 (CH), 125.8 (CH), 126.4 (C), 127.2 (CH), 127.3 (CH), 127.9 (CH), 128.0 (C), 128.6 (CH), 130.1 (CH), 130.1 (CH), 136.9 (C), 138.1 (C), 140.7 (C), 174.6 (C), 175.4 (C).

## RESULTS AND DISCUSSION

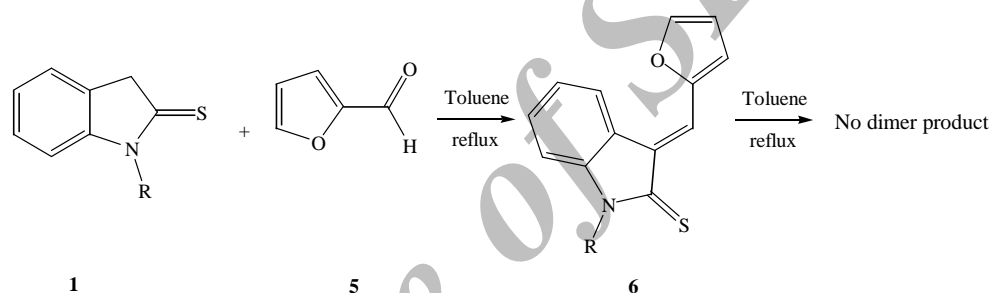
We have earlier demonstrated an efficient synthesis of highly functionalized spirodihydrothiopyrane **4** compounds from corresponding aldehydes **2** and thio-oxindoles **1** in water via one-pot procedure [5]. Initially, thiooxindole **1** underwent a condensation reaction with aldehyde **2** at position 3 to afford  $\alpha,\beta$ -unsaturated thio-oxindole **3** which self-dimerized via hetero Diels-Alder reaction and produced spirodihydrothio-oxindole **4** (Scheme 1).

In the context of our interest in exploring convenient access to heterocyclic systems by using thiooxindoles [5], we wish to report here the convenient process for the synthesis of thiopyrano[2,3-b]indole derivatives via condensation reaction of thio-oxindoles and heteroaromatic aldehydes followed by hetero Diels-Alder reaction with dialkylacetylenedicarbonyl and cyclic dienophiles. The reaction generally involves the initial condensation of indoline-2-thione **1** with five-member heteroaromatic aldehydes **5** to form  $\alpha,\beta$ -unsaturated thiooxindole intermediate **6**. In contrast to the obtained results in our previous report [5] (Scheme 1), the  $\alpha,\beta$ -unsaturated thio-oxindole **6** was very stable even at reflux condition in Toluene for one day, preventing the dimerization reaction and no dimerized product was observed (Scheme 2).

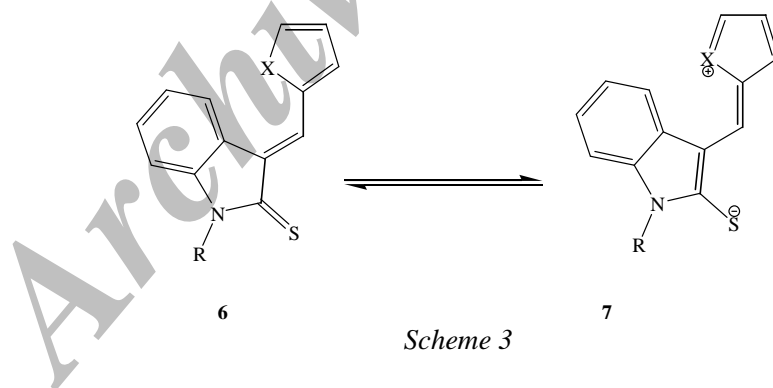
The deep red compound **6** was isolated and characterized on the basis of its NMR spectroscopic data. The <sup>1</sup>H NMR spectra displayed a signal as a single resonance at 8.2 ppm for the olefinic proton and the <sup>13</sup>C NMR showed the presence of quaternary C=S in compound **6**. It seems that the nature of the aromatic ring in starting aldehyde compound is the basic reason behind the observed difference in the chemical behavior of  $\alpha,\beta$ -unsaturated thio-oxindole. An important



Scheme 1



Scheme 2



Scheme 3

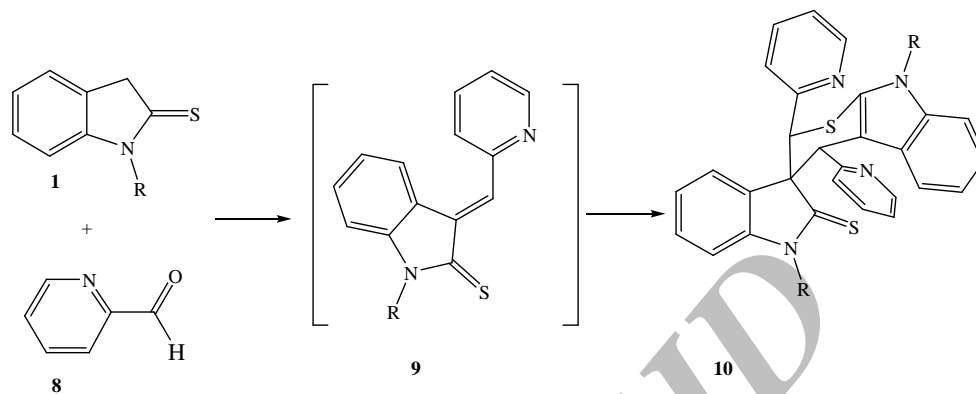
explanation is that the existence of heteroatom in 5-membered aromatic ring in compound **6** led to the resonance of lone pair electron in aromatic system (Scheme 3). This increases HOMO energy level and helps the compound to play the role of diene successfully, but it is doubtful that it is a suitable dienophile to dimerize.

To find out more about the behavior of these compounds, we tried to investigate the reaction of thio-oxindole **1** and 2-pyridinecarbaldehyde **8**. As expected, it afforded the dimer

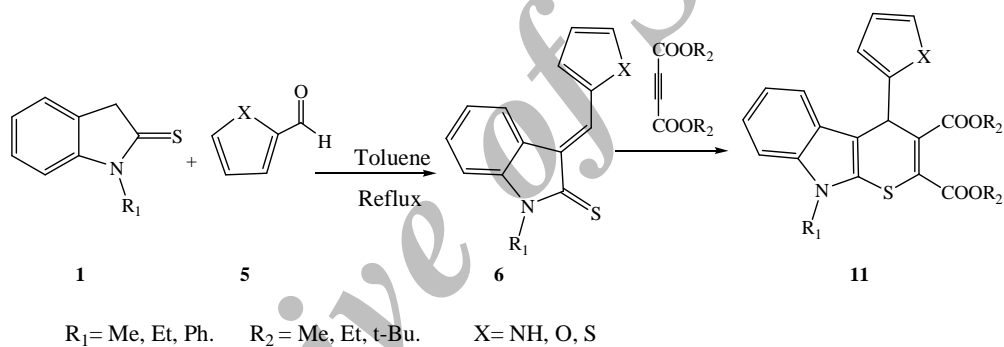
product **10**, the lone pair electron of nitrogen in pyridine ring which does not take part in the conjugation system and has the same effect as phenyl group in intermediate **3**.

We then performed cycloaddition of the hetero diene **6** and the reactive dienophile DMAD in one-pot Diels-Alder reaction. The reaction of **6a** with DMAD in refluxing toluene for 2 h gave a fused product **11a** as the only reaction product (Scheme 5). The structure of the products was determined on the basis of their  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, 2DNMR (H-H COSY,

## An Efficient Synthesis of Fused Polycyclic Indole Derivatives



Scheme 4



Scheme 5

HMQC, HMBC) spectra. For example, the <sup>1</sup>H NMR spectrum of **11a** consists of three distinct singlets at 3.75, 3.82 and 3.93 ppm for three methyl groups attached to heteroatom and the aliphatic CH group of thiopyran ring in 5.89 ppm. The <sup>13</sup>C NMR displayed two carbonyl groups, seven quaternary carbons and an aliphatic CH group. Further evidence for the fused structure was provided by the 2DNMR spectrum.

In view of the success of the above reaction, we explored the scope of this reaction by varying the structure of indolin-2-thiones **1**, 5-membered ring heteroaromatic aldehydes **5** and dialkylacetylenedicarboxylate components to obtain the corresponding products **11a-k**. The results are summarized in Table 1. The reaction was triggered with 1 mmol of thioindole and 1.2 mmol of heteroaromatic aldehyde **5** in refluxing toluene to access the isolable  $\alpha,\beta$ -unsaturated thioindole derivatives. After the starting thio-indole was

consumed, acetylenic diester was added to the reaction mixture to produce the thiopyrano[2,3-*b*]indole derivatives.

Then, we investigated the scope of the reaction with cyclic dienophiles under the same reaction condition to obtain the fused tetracyclic indole derivatives **12a-h** (Table 2). The reaction proceeded under mild conditions and no undesirable side reactions were observed under these reaction conditions. Stereochemical relevant (NOE and NMR coupling constant) showed that H<sub>a</sub>, H<sub>b</sub> and H<sub>c</sub> are *cis*. In all the cases the stereochemistry of the ring juncture protons was found to be the same.

In conclusion, we have reported a convenient aldol hetero diels-alder reaction involving thio-oxindole derivatives, five-membered heteroaromatic aldehydes with dialkyl acetylenic diesters and cyclic dienophiles for the synthesis of fused polycyclic thiopyrano[2,3-*b*]indole derivatives. The present

**Table 1.** The Synthesis of Thiopyrano[2,3-*b*]indole Derivatives

Entry	R <sub>1</sub>	X	R <sub>2</sub>	Product	Yield (%) <sup>a</sup>
1	Me	O	Me	<b>11a</b>	77
2	Ph	O	Me	<b>11b</b>	88
3	Et	O	Me	<b>11c</b>	69
4	Me	S	Me	<b>11d</b>	57
5	Ph	S	Me	<b>11e</b>	69
6	Et	S	Me	<b>11f</b>	63
7	Me	O	Et	<b>11g</b>	36
8	Ph	O	Et	<b>11h</b>	54
9	Me	S	t-Bu	<b>11i</b>	52
10	Ph	S	Et	<b>11j</b>	34
11	Me	O	t-Bu	<b>11k</b>	64
12	Me	NH	t-Bu	<b>11l</b>	37

<sup>a</sup>Isolated yield.**Table 2.** The Synthesis of Fused Tetracyclic Indole Derivatives

Entry	X <sub>1</sub>	X <sub>2</sub>	R	Time	Product	Yield (%) <sup>a</sup>
1	O	NH	Et	3	<b>12a</b>	65
2	O	NH	Ph	2.5	<b>12b</b>	82
3	O	O	Et	2	<b>12c</b>	69
4	O	O	Ph	1	<b>12d</b>	88
5	NH	NH	Et	4	<b>12e</b>	59
6	NH	NH	Ph	3	<b>12f</b>	73
7	S	NH	Et	3	<b>12g</b>	62
8	S	NH	Ph	2.5	<b>12h</b>	75

<sup>a</sup>Isolated yield.

method enjoys the advantage that, not only the reaction is performed under neutral and one-pot reaction conditions, but also the substances can be mixed without any activation or modification and without using any catalysts.

## ACKNOWLEDGMENTS

We would like to acknowledge the financial support from Islamic Development Bank (IDB) to purchase a 500 MHz NMR spectrometer. We also gratefully acknowledge financial support from the Research Council of Sharif University of Technology.

## REFERENCES

- [1] For recent reviews on the enantioselective (hetero) Diels-Alder reaction, see: a) E.J. Corey, *Angew. Chem. Int. Ed.* 41 (2002) 1650; b) K.C. Nicolaou, S.A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* 41 (2002) 1668; c) L.F. Tietze, G. Kettischau, In *Topics in Current Chemistry*, Vol. 189, Springer, Berlin, 1997; d) D.L. Boger, in: B.M. Trost, I. Fleming, L.A. Paquette (Eds.), *Comprehensive Organic Synthesis*, Vol. 5, Pergamon, Oxford, 1991, pp. 451-512.
- [2] a) D.L. Boger, S.M. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, CA, 1987; b) F. Fringuelli, A. Taticchi, *Dienes in the Diels-Alder Reaction*, Wiley, New York, 1990.
- [3] F. Duss, in: D.H.R. Barton, W.D. Ollis (Eds.), *Comprehensive Organic Chemistry*, Vol. 3, Pergamon, Oxford, UK, 1979, pp. 373-487; b) P.D. Magnas, E.J. Corey, *Angew. Chem. Int. Ed.* 41 (2002) 491; c) C. Paulmier, in: J.E. Baldwin (Ed.), *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon, Oxford, UK, 1986, pp. 58-83; d) F.S. Guziec, *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2, Wiley, New York, 1987, pp. 215-273.
- [4] K. Tanaka, T. Nakajima, R.A. Zingaro, J.H. Reibenspies, M.B. Hall, *J. Org. Chem.* 65 (2000) 6601.
- [5] F.M. Moghaddam, L. Hojabri, S. Taheri, P. Pirani, *J. Iran. Chem. Soc.* 7 (2010) 1.
- [6] a) F.M. Moghaddam, Z. Mirjafary, H. Saeidian, S. Taheri, M. Doulabi, M. Kiamehr, *Tetrahedron* 66 (2010) 134; b) F.M. Moghaddam, S. Taheri, Z. Mirjafary, H. Saeidian, *Synlett* (2010) 123; c) F.M. Moghaddam, M. Kiamehr, S. Taheri, Z. Mirjafary, *Helv. Chim. Acta* 93 (2010) 964; d) F.M. Moghaddam, H. Saeidian, Z. Mirjafary, S. Taheri, S. Kheirjou, *Synlett* (2009) 1047; e) M. Kiamehr, F.M. Moghaddam, *Tetrahedron Lett.* 50 (2009) 6723.