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A Tandem Aldol-Diels-Alder Reaction Accelerated in Water: An Approach to the Catalyst-Free One-Pot Synthesis of Spiro Thio-Oxindoles

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Spiro thio-oxindoles are prepared *in situ* by the reaction of the corresponding aldehydes and thio-oxindoles in a straightforward, environmentally friendly, highly efficient and simple procedure. The reaction took place in water with no catalyst added. This one-pot reaction afforded regio- and diastereoselective products in high yields (61-93%).

Keywords: Spiro thio-oxindoles, Aldol-Diels-Alder reaction, Dimerization, α,β-Unsaturated thio-oxindole

INTRODUCTION

Organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most abundant, cheapest, and environmentally friendly solvents, but also because water exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents. Thus, the development of novel reactivity as well as selectivity that cannot be attained in conventional organic solvents is one of the challenging goals of aqueous chemistry [1].

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 [2]. Spirooxindole ring systems are the central skeleton for numerous alkaloids [3] such as Gelsemine, and mitraphylline. Interestingly enough, spiropyrrolidinyl-oxindole ring systems are also found in a number of alkaloids like horsifiline, spirotryprostatine A and B, elacomine *etc*. [4]. The derivatives of spirooxindole have found very wide biological applications [5] and recently the synthesis of some derivatives of spirooxidole have been reported [6]. 3,3-Disubstituted thio-oxindoles were declared to be effective in the treatment of skin disorders such as acne and hirsutism [7] and hormone related conditions including obesity, hair loss (alopsia), diabetes, Alzheimer's disease and a lot of other diseases [8]. In this respect, the utilization of the hetero Diels-Alder reaction undoubtedly represents one of the most attractive routes for preparing these heterocycles with maximum atom economy and high regio- and stereoselectivity [2].

Most notably, Diels-Alder cycloaddition of hydrophobic compounds have been found to be accelerated in dilute aqueous solution [9]. Water is a desirable solvent for chemical reactions for reasons of cost, safety and environmental concerns. The study of organic reactions in aqueous solvents has an intriguing history [10]. In recent years, Sharpless *et al*. have noticed that many organic reactions often proceed optimally in pure water [11], and particularly when the organic reactants are insoluble in aqueous phase [12]. They showed that the expression "substances do not interact unless

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dissolved" can be distinctly counterproductive and substantial rate acceleration can be achieved when insoluble reactants are stirred in aqueous suspension. Even when the rate of acceleration is negligible, the use of water as the only supporting medium has additional advantages including ease of product isolation, safety, high heat capacity and unique redox stability [13]. There are several examples of Diels-Alder reaction of α,β-unsaturated sulfur analogues. A novel tandem [4+2] cycloaddition-elimination reaction of 1,3-oxathianes as a synthetic equivalent of a highly reactive thiocinnamaldehyde, with olefins promoted by titanium tetrachloride to give 3,4-dihydro-2H-thiopyrans, has been developed [14]. The cycloaddition of 2- or 2,3-substituted 1-thia-4-dimethylamino-buta-1,3-dienes with various dienophiles in the presence of a Lewis acid has provided a rapid and diastereoselective access to the 3,4-dihydro-2H-thiopyran backbones [15]. Likewise an efficient one-pot synthesis of substituted 4H-thiopyrans has been accomplished from a three-component reaction of α,β-unsaturated ketones, Lawesson reagent and alkynes under microwave irradiation [16].

EXPERIMENTAL

General Procedure for Aldol-Diels-Alder Reaction

To a flask containing 1 mmol of thio-oxindole in Water (5 ml), 1.2 mmol of aldehyde was added. Progress of the reaction was followed up by thin layer chromatography (TLC) whose spots were visualized either with UV light or Iodine stabilized on silica gel. The reaction mixture was stirred for the set reaction time and the temperature is presented in Table 2. Then the product was extracted by acetone (3 × 7 ml), the solvent was removed under reduced pressure and the residue was purified by column chromatography eluted with hexane-ethyl acetate (3-7:1). In the case of compounds **3a**, **3k**, **3l**, **3n**, **3o**, after the reactions were completed, the solid product in the reaction mixture (water medium) was filtered and recrystalized from ethyl acetate. As for compounds **3c**, **3g**, **3h**, **3i** and **3j**, the solid products in water medium were filtered and dried without any further purification.

Spectra Data of Different Products

(3a). Yellow crystal; m.p.: 228-230 °C, IR (KBr) (ν_{max}/ cm^{-1}): 701, 746, 1094, 1177, 1371, 1461, 1603, 2929, 3039; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 3.04 (s, 3H), 3.83 (s, 3H), 5.30 (s, 1H), 5.50 (s, 1H), 6.21 (d, J = 8.00 Hz, 1H), 6.48 (d, J = 7.91 Hz, 1H), 6.60 (d, J = 7.82 Hz, 1H), 6.70 (t, J = 7.61 Hz, 1H), 6.78 (t, J = 7.61 Hz, 1H), 6.84 (d, J = 7.51 Hz, 2H), 7.01-7.05 (m, 3H), 7.12-7.21 (m, 4H), 7.28 (d, J = 7.80 Hz, 1H), 7.33 (d, J = 8.22 Hz, 1H), 7.54 (d, J = 7.62 Hz, 1H), 7.93 (d, J = 7.51 Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 30.5 (CH_3), 31.4 (CH_3), 52.3 (CH), 55.6 (CH), 66.4 (C_{spiro}), 108.4 (CH), 108.8 (C), 109.1 (CH), 119.3 (CH), 119.9 (CH), 121.1 (CH), 123.5 (CH), 126.9 (CH), 127.1 (CH), 127.5 (CH), 127.8 (C), 127.9 (2CH), 128.8 (CH), 128.9 (2CH), 129.9 (2CH), 130.7 (CH), 130.9 (C), 131.6 (CH), 131.9 (C), 135.2 (C), 137.7 (C), 138.1 (C), 146.3 (C), 204.3 (C); Crystal data: $C_{32}H_{26}N_2S_2$, M = 502.67, prismatic pale yellow crystal, dimensions 0.60 × 0.55 × 0.3 mm, monoclinic, space group $P2_1/a$, Z = 4, a = 11.9699 (13), b = 12.3375 (15), c = 107.8027 (18)Å , β = 100.192 (8)°, V = 2587.6 (5)Å^3, T = 298 (2) K, D_x = 1.290 g cm^{-3}, μ (Mo-K_α) = 0.230 mm^{-1}, $\theta_{(max)}$ = 26.75°, transmission factors (min; max) 0.865; 0.945, collected reflections 12356, unique reflections 5408, R_{int} = 0.0411, reflections used in refinement 5408, parameters refined 327; $R_1 = \Sigma \big| |F_o| - |F_c| / \Sigma |F_o| = 0.0528$, $wR_2 = [\Sigma (w(F_0^2 - F_c^2)^2) / \Sigma (w(F_0^2)^2]^{1/2} = 0.1212$ [2].

(3b). Pale yellow crystal; m.p.: 158-160 °C; IR (KBr) (ν_{max}/cm^{-1}): 746, 810, 1029, 1100, 1177, 1240, 1371, 1461, 1506, 1603, 1731, 2936; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 3.10 (s, 3H), 3.70 (s, 3H), 3.73 (s, 3H), 3.83 (s, 3H), 5.24 (s, 1H), 5.40 (s, 1H), 6.22 (dt, J = 7.71, 2.60 Hz, 2H), 6.35 (dd, J = 8.72, 1.80 Hz, 1H), 6.55 (d, J = 8.50 Hz, 2H), 6.63 (d, J = 7.83 Hz, 1H), 6.69 (dd, J = 8.51, 2.62 Hz, 1H), 6.74 (d, J = 8.42 Hz, 2H), 6.77 (t, J = 7.52 Hz, 1H), 7.10 (t, J = 7.81 Hz, 1H), 7.17 (t, J = 7.50 Hz, 1H), 7.28 (t, J = 7.53 Hz, 2H), 7.44 (dd, J = 8.51, 1.8 Hz, 1H), 7.89 (d, J = 7.52 Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 30.5 (CH_3), 31.6 (CH_3), 51.6 (CH), 54.9 (CH), 55.4 (OCH_3), 55.5 (OCH_3), 66.6 (C_{spiro}), 108.4 (CH), 109.0 (C), 109.3 (CH), 112.3 (CH), 112.8 (CH), 113.3 (2CH), 119.3 (CH), 120.0 (CH), 121.1 (CH), 123.6 (CH), 127.3 (C), 127.9 (C), 128.8 (CH), 128.9 (CH), 129.9 (C), 130.9 (C), 131.1 (2CH), 131.6 (CH), 132.1 (C), 132.6 (CH), 138.0 (C), 146.4 (C), 158.6 (C), 159.8 (C), 204.6 (C).

(3c). Orange powder; m.p.: 205 °C ; ^{1}H NMR ($CDC1_3$, 500

MHz) δ (ppm): ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 3.21 (s, 3H), 3.80 (s, 3H), 5.70 (br s, 1H), 5.60 (s, 1H), 6.31 (d, J = 7.52 Hz, 1H), 6.75 (m, 4H), 6.84 (t, J = 7.51 Hz, 1H), 6.95 (d, J = 4.53 Hz, 1H), 7.03 (d, J = 4.50 Hz, 1H), 7.14 (t, J = 7.52 Hz, 1H), 7.22 (t, J = 7.50 Hz, 1H), 7.32 (m, 2H), 7.39 (t, J = 7.01 Hz, 1H), 7.84 (d, J = 7.52 Hz, 1H), ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 30.53 (CH_3), 31.74 (CH_3), 48.29 (CH), 51.02 (CH), 66.18 (C), 108.57 (CH), 108.65 (CH), 109.33 (CH), 114.01 (C), 119.55 (C), 119.61 (CH), 121.36 (CH), 124.09 (CH), 125.01 (CH), 125.30 (CH), 126.26 (CH), 127.80 (CH), 128.50 (CH), 129.03 (CH), 129.60 (CH), 129.85 (C), 129.90 (C), 131.32 (C), 137.17 (C), 137.95 (C), 147.11 (C), 204.59 (C).

(3d). Yellow crystal; m.p.: 243-245 °C; IR (KBr) (ν_{max}/ cm^{-1}): 733, 1100, 1351, 1461, 1519, 1596, 2929, 3065; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 3.09 (s, 3H), 3.85 (s, 3H), 5.36 (s, 1H), 5.64 (s, 1H), 6.17 (d, J = 7.72 Hz, 1H), 6.66-6.70 (m, 2H), 6.83 (t, J = 7.13 Hz, 1H), 7.01 (d, J = 7.72 Hz, 2H), 7.19 (t, J = 7.30 Hz, 1H), 7.26 (t, J = 7.22 Hz, 1H), 7.34-7.39 (m, 2H), 7.57 (d, J = 8.00 Hz, 1H), 7.71 (d, J = 8.00 Hz, 1H), 7.91 (m, 3H), 8.04 (d, J = 7.61 Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 30.6 (CH_3), 31.7 (CH_3), 51.9 (CH), 54.9 (CH), 65.9 (C_{spiro}), 107.3 (C), 108.9 (CH), 109.8 (CH), 119.3 (CH), 119.9 (CH), 121.9 (CH), 122.1 (CH), 122.9 (CH), 123.1 (2CH), 124.2 (CH), 127.1 (C), 128.8 (CH), 130.1 (CH), 130.2 (C), 131.0 (2CH), 131.5 (CH), 132.1 (CH), 138.2 (C), 142.0 (C), 145.5 (C), 146.0 (C), 147.3 (C), 148.3 (C), 203.0 (C).

(3e). Pale yellow crystal; m.p.: 208-210 °C; IR (KBr) (ν_{max}/cm^{-1}): 700, 746, 1100, 1255, 1345, 1403, 1461, 1603, 2975, 3045; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 0.50 (t, J = 7.25 Hz, 3H), 1.55 (t, J = 7.10 Hz, 3H), 3.58 (m, 1H), 3.92 (m, 1H), 4.29 (m, 2H), 5.33 (s, 1H), 5.53 (s, 1H), 6.20 (d, J = 8.00 Hz, 1H), 6.50 (d, J = 7.92 Hz, 1H), 6.63 (d, J = 7.81 Hz, 1H), 6.72 (t, J = 7.54 Hz, 1H), 6.78 (t, J = 7.52 Hz, 1H), 6.85 (d, J = 7.50 Hz, 2H), 7.04 (t, J = 7.63 Hz, 3H), 7.12-7.21 (m, 4H), 7.31 (m, 1H), 7.36 (d, J = 8.25 Hz, 1H), 7.60 (d, J = 7.67 Hz, 1H), 7.90 (d, J = 7.51 Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 10.6 (CH_3), 15.8 (CH_3), 39.2 (CH_2), 39.3 (CH_2), 51.9 (CH), 55.6 (CH), 66.0 (C_{spiro}), 108.5 (CH), 108.9 (C), 109.3 (CH), 119.2 (CH), 120.0 (CH), 121.0 (CH), 123.4 (CH), 126.9 (CH), 127.1 (CH), 127.6 (CH), 127.9 (2CH), 128.1 (C), 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.9 (C), 130.2 (2CH), 130.8 (CH), 132.0 (CH), 132.1 (C), 135.1 (C), 136.9 (C), 137.8 (C), 145.4 (C), 203.1 (C).

(3f). Pale yellow crystal; m.p.: 187-189 °C; IR (KBr) (ν_{max}/cm^{-1}): 746, 817, 1029, 1107, 1177, 1248, 1454, 1506, 1603, 2934, 2972, 3046; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 0.55 (t, J = 7.10 Hz, 3H), 1.52 (t, J = 7.12 Hz, 3H), 3.63 (m, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 3.92 (m, 1H), 4.26 (m, 2H), 5.28 (s, 1H), 5.43 (s, 1H), 6.22 (d, J = 8.00 Hz, 2H), 6.26 (dd, J = 8.74, 2.4 Hz, 1H), 6.36 (dd, J = 8.72, 1.7 Hz, 1H), 6.56 (d, J = 8.63 Hz, 2H), 6.65 (d, J = 7.81 Hz, 1H), 6.71 (dd, J = 8.43, 2.4 Hz, 1H), 6.75 (d, J = 8.32 Hz, 2H), 6.78 (t, J = 7.73 Hz, 1H), 7.12 (t, J = 7.75 Hz, 1H), 7.17 (t, J = 7.51 Hz, 1H), 7.30 (t, J = 8.03 Hz, 1H), 7.34 (d, J = 8.22 Hz, 1H), 7.49 (dd, J = 8.41, 1.7 Hz, 1H), 7.84 (d, J = 7.53 Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 10.7 (CH_3), 15.8 (CH_3), 39.1 (CH_2), 39.3 (CH_2), 51.2 (CH), 54.8 (CH), 55.4 (OCH_3), 55.6 (OCH_3), 66.2 (C_{spiro}), 108.4 (CH), 109.1 (C), 109.3 (CH), 112.3 (CH), 112.9 (CH), 113.3 (2CH), 119.1 (CH), 120.0 (CH), 120.9 (CH), 123.4 (CH), 127.3 (C), 128.1 (C), 128.9 (CH), 129.0 (CH), 130.0 (CH), 131.2 (2CH), 131.6 (CH), 132.3 (C), 133.1 (CH), 136.9 (C), 145.5 (C), 158.6 (C), 160.0 (C), 203.5 (C).

(3g). Yellow powder; m.p.: 109-112 °C; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 0.93 (t, J = 7.16 Hz, 3H), 1.51 (t, J = 7.19 Hz, 3H), 3.91 (m, 1H), 4.1 (m, 1H), 4.24 (m, 2H), 5.5 (s, 1H), 5.54 (t, J = 3.05 Hz, 2H), 5.90 (d, J = 3.00 Hz, 1H), 6.06 (s, 1H), 6.09 (s, 1H), 6.38 (d, J = 7.92 Hz, 1H), 6.81 (d, J = 7.86 Hz, 1H), 6.89 (t, J = 7.01 Hz, 1H), 6.96 (s, 1H), 7.14 (m, 3H), 7.33 (m, 2H), 7.73 (d, J = 7.53 Hz, 1H), ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 11.29 (CH_3), 15.75 (CH_3), 39.21 (CH_2), 39.68 (CH_2), 46.18 (CH), 48.67 (CH), 63.23 (C), 106.77 (C), 108.68 (CH), 108.97 (CH), 109.53 (CH), 110.09 (CH), 110.73 (CH), 118.76 (CH), 119.78 (CH), 121.30 (CH), 123.85 (CH), 128.09 (C), 128.39(C), 128.74 (CH), 128.91 (CH), 132.29 (CH), 136.87 (C), 141.57 (CH), 142.48 (CH), 145.05 (C), 146.67 (CH), 149.04 (C), 151.84 (C), 204.06 (C).

(3h). Yellow powder; m.p.: 175-177 °C ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 664 (t, J = 6.34 Hz, 3H), 1.51 (t, J = 7.14 Hz, 3H), 3.74 (m, 1H), 4 (m, 1H), 4.24 (m, 2H), 5.60 (s, 1H), 5.80 (br s, 1H), 6.30 (d, J = 7.17 Hz, 1H), 6.76 (m, 4H), 6.83 (t, J = 7.55 Hz, 1H), 6.96 (d, J = 4.49 Hz, 1H), 7.02 (d, J = 4.92.Hz, 1H), 7.12 (t, J = 7.53.Hz, 1H), 7.21 (t, J = 7.46 Hz, 1H), 7.32 (m, 2H), 7.41 (t, J = 7.46 Hz, 1H), 7.79 (d, J = 7.47 Hz, 1H), ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 10.84 (CH_3),

15.72 (CH_3), 39.21 (CH_2), 39.51 (CH_2), 48.10 (CH), 50.92 (CH), 65.60 (C), 108.61 (CH), 108.67 (CH), 109.44 (C), 119.45 (CH), 119.50 (CH), 121.22 (C), 123.95 (CH), 125.50 (CH), 125.60 (CH), 126.16 (CH), 126.24 (CH), 128.07 (CH), 128.68 (CH), 128.70 (C), 128.90 (CH), 129.00 (C), 129.17 (CH), 129.61 (C), 131.53 (C), 136.83 (C), 137.15 (C), 146.29 (C), 203.47 (C).

(3i). Yellow powder; m.p.:145 °C; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 0.713 (t, J = 6.24 Hz, 3H), 1.53 (t, J = 7.22 Hz, 3H), 3.72 (m, 1H), 3.95 (m, 1H), 4.28 (d, J = 7.28 Hz, 2H), 5.47 (s, 1H), 5.79 (s, 1H), 6.24 (br s, 1H), 6.56 (d, J = 7.59 Hz, 1H), 6.79 (t, J = 7.35 Hz, 1H), 6.88 (t, J = 5.55 Hz, 1H), 7.05 (t, J = 6.01 Hz, 1H), 7.10-7.30 (m, 5H), 7.36 (d, J = 7.96 Hz, 1H), 7.46 (t, J = 7.23 Hz, 1H), 7.95 (s, 1H), 8.2 (s, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 211.66 (CH_3), 15.83 (CH_3), 15.83 (CH_3), 39.73 (CH_2), 57.73 (CH), 53.1 (CH), 65.18 (C), 108.55 (CH), 108.77 (CH), 110.03 (CH), 119.37 (CH), 121.18 (CH), 121.93 (CH), 123.46 (CH), 123.65 (CH), 124.14 (C), 124.24 (C), 124.39 (C), 124.58 (CH), 125.44 (CH), 127.85(C), 128.35 (CH), 128.83 (C), 132.26 (C), 135.11 (CH), 136.03 (CH), 137.11 (C), 148.54 (CH), 148.95 (CH), 154.71 (C), 158.39 (C), 203.25 (C).

(3j). Orange powder; m.p.: 158-160.5 °C ^{1}H NMR ($CDCl_3$/DMSO d_6): 0.53 (t, J = 3.56 Hz, 6H), 1.55 (t, J = 3.567 Hz, 6H), 3.6 (m, 2H), 3.9 (m, 2H), 4.25-4.31 (m, 3H), 5.30 (s, 1H), 5.32 (s, 1H), 5.54 (s, 1H), 6.17 (d, J = 5.00 Hz, 1H), 6.66 (d, J = 7.88 Hz, 1H), 6.7-7.17 (m, 8H), 7.21 (t, J = 7.40 Hz, 1H), 7.26 (t, J = 7.40, 1H), 7.33 (t, J = 4.28 Hz, 1H), 7.37 (d, J = 9.44 Hz, 1H), 7.68 (d, J = 1.82 Hz, 1H), 7.83 (d, J = 7.4 Hz, 1H), 7.89 (t, J = 5.71 Hz, 1H), 8.09 (d, J = 1.50 Hz, 1H), 8.12 (d, J = 1.50 Hz, 1H), 8.29 (dd, J = 6.50 Hz, J = 1.50 Hz, 1H), 8.35 (dd, J = 6.00 Hz, J = 1.50 Hz, 1H), 8.42 (d, J = 1.03 Hz, 1H), 8.74 (d, J = 1.82 Hz, 1H), ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 10.67 (CH_3), 10.79 (CH_3), 14.62 (C), 15.76 (CH_3), 21.47 (CH_3), 39.34 (CH_2), 39.35 (CH_2), 39.51 (CH_2), 39.57 (CH_2), 49.06 (CH), 50.05 (CH), 52.79 (CH), 65.38 (C), 65.55 (C), 107.14 (C), 107.33 (C), 108.87 (CH), 108.90 (CH), 109.72 (CH), 119.32 (CH), 119.63 (CH), 119.68 (CH), 119.81 (CH), 121.53 (CH), 121.59 (CH), 122.33 (CH), 122.98 (C), 123.021 (CH), 123.86 (C), 124.42 (CH), 127.39 (C), 127.49 (C), 128.80 (CH), 128.93 (CH), 129.17 (C), 129.74 (C), 129.88 (CH), 130.09 (CH), 130.36 (C), 130.53 (C), 131.06 (C), 131.125 (C), 133.63 (C), 138.83 (C), 137.03 (C), 137.78 (C), 138.02 (CH), 138.56 (CH), 139.94 (CH), 145.08 (C), 145.38 (C), 147.55 (CH), 148.34 (CH), 149.75 (CH), 150.76 (CH), 150.84 (C), 151.12 (CH), 151.53 (CH), 175.22 (C), 202.07 (C), 202.10 (C).

(3k). Yellow crystal; m.p.: 216-217 °C; IR (KBr) (ν_{max}/cm^{-1}): 694, 733, 1139, 1222, 1338, 1442, 1493, 1615, 1693, 3277; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 5.16 (s, 1H), 5.23 (s, 1H), 5.92 (d, J = 8.00 Hz, 1H), 6.31 (d, J = 8.01 Hz, 1H), 6.50 (d, J = 7.72 Hz, 1H), 6.57 (m, 2H), 6.76 (d, J = 7.50 Hz, 2H), 6.87-6.92 (m, 4H), 6.97 (t, J = 7.62 Hz, 1H), 7.01 (d, J = 7.31 Hz, 1H), 7.04-7.08 (m, 2H), 7.22 (d, J = 8.02 Hz, 1H), 7.52 (d, J = 7.71 Hz, 1H), 7.74 (d, J = 7.52 Hz, 1H), 10.21 (s, 1H), 11.39 (s, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 51.8 (CH), 55.2 (CH), 66.3 (C_{spiro}), 109.0 (C), 110.3 (CH), 110.6 (CH), 118.9 (CH), 119.3 (CH), 120.9 (CH), 122.8 (CH), 26.9 (CH), 127.0 (CH), 127.5 (CH), 127.9 (2CH), 128.0 (C), 128.4 (C), 128.6 (CH), 128.8 (CH), 128.9 (CH), 130.2 (2CH), 130.7 (CH), 132.1 (CH), 132.2 (C), 135.6 (C), 137.0 (C),137.9 (C), 144.7 (C), 205.7 (C).

(3l). Yellow crystal; m.p.: 187-189 °C; IR (KBr) (ν_{max}/cm^1): 553, 739, 1023, 1171, 1242, 1435, 1499, 1603, 1712, 3251, 3361; ^{1}H NMR ($CDCl_3$/$DMSOd_6$) δ = 3.71 (s, 3H), 3.73 (s, 3H), 5.27 (s, 1H), 5.30 (s, 1H), 6.17 (d, J = 8.00 Hz, 1H), 6.28 (dd, J = 8.72, 2.7 Hz, 1H), 6.35 (dd, J = 8.71, 2.3 Hz, 1H), 6.57-6.60 (m, 3H), 6.75 (dd, J = 8.50, 2.73 Hz, 1H), 6.77-6.81 (m, 3H), 7.08 (t, J = 8.00 Hz, 1H), 7.15 (t, J = 7.61 Hz, 1H), 7.23 (t, J = 7.63 Hz, 1H), 7.32 (d, J = 8.12 Hz, 1H), 7.55 (dd, J = 8.51, 2.30 Hz, 1H), 7.88 (d, J = 7.65 Hz, 1H), 8.12 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): δ = 51.3 (CH), 54.7 (CH), 55.3 (OCH_3), 55.4 (OCH_3), 66.8 (C_{spiro}), 109.6 (C), 110.3 (CH), 110.6 (CH), 112.6 (CH), 112.8 (CH), 113.3 (2CH), 119.2 (CH), 119.6 (CH), 121.0 (CH), 122.9 (CH), 127.7 (C), 128.2 (C), 128.5 (C), 128.8 (CH), 128.9 (CH), 130.1 (C), 131.3 (2CH), 131.6 (CH), 132.4 (C), 133.1 (CH), 137.1 (C), 144.6 (C), 158.6 (C), 159.8 (C), 206.3 (C).

(3m). Yellow crystal; m.p.: 217-219 °C [18]; IR (KBr) (ν_{max}/cm^{-1}): 733, 1132, 1352, 1441, 1506, 1615, 3193, 3380; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 0.75 (d, J = 6.72 Hz, 3H), 0.85 (d, J = 6.90 Hz, 3H), 3.77-3.80 (m, 2H), 6.81-6.86 (m, 2H), 6.92 (t, J = 7.21 Hz, 1H), 6.96 (d, J = 7.63 Hz, 1H), 7.06 (d, J = 7.62 Hz, 1H), 7.11 (t, J = 7.60 Hz, 1H), 7.20 (d, J = 7.91 Hz, 1H), 7.39 (d, J = 8.00 Hz, 1H), 10.06 (s, 1H),

12.29 (s, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 14.9 (CH_3), 15.5 (CH_3), 40.0 (CH), 44.9 (CH), 66.5 (C_{spiro}), 110.1 (C), 110.3 (CH), 110.9 (CH), 119.0 (CH), 119.1 (CH), 120.6 (CH), 123.3 (CH), 126.7 (C), 128.0 (CH), 128.3 (C), 128.5 (CH), 131.4 (C), 137.2 (C), 144.8 (C), 210.0 (C).

(3n). Yellow crystal; m.p.: 252-254 °C; IR (KBr) (ν_{max}/ cm^{-1}): 695, 746, 1023, 1313, 1377, 1448, 1494, 1590, 3058; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 5.35 (s, 1H), 5.69 (s, 1H), 5.97 (d, J = 7.60 Hz, 1H), 6.17 (d, J = 7.81 Hz, 1H), 6.40 (d, J = 8.00 Hz, 1H), 6.72 (d, J = 7.92 Hz, 1H), 6.85 (d, J = 8.90 Hz, 1H), 6.84-6.90 (m, 4H), 7.08 (t, J = 7.73 Hz, 2H), 7.11-7.26 (m, 5H), 7.30-7.36 (m, 3H), 7.40 (t, J = 7.42 Hz, 1H), 7.45 (t, J = 7.50 Hz, 1H), 7.52 (t, J = 7.33 Hz, 1H), 7.64 (t, J = 8.00 Hz, 2H), 7.69 (d, J = 7.31 Hz, 2H), 7.75 (d, J = 7.71 Hz, 1H), 8.09 (d, J = 7.32 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 52.2 (CH), 56.0 (CH), 66.7 (C_{spiro}), 109.8 (CH), 110.3 (CH), 110.7 (C), 120.1 (CH), 120.2 (CH), 121.9 (CH), 123.7 (CH), 127.2 (CH), 127.4 (CH), 127.6 (2CH), 127.7 (CH), 127.7 (2CH), 128.0 (2CH), 128.3 (C), 128.5 (CH), 128.9 (CH), 129.0 (CH), 129.0 (CH), 129.5 (CH), 130.1 (CH), 130.2 (C), 130.3 (C), 130.4 (2CH), 130.9 (CH), 131.1 (C), 131.6 (C), 132.1 (CH), 135.1 (C), 137.0 (C), 137.4 (C), 137.7 (C), 138.3 (C), 147.6 (C), 205.7 (C).

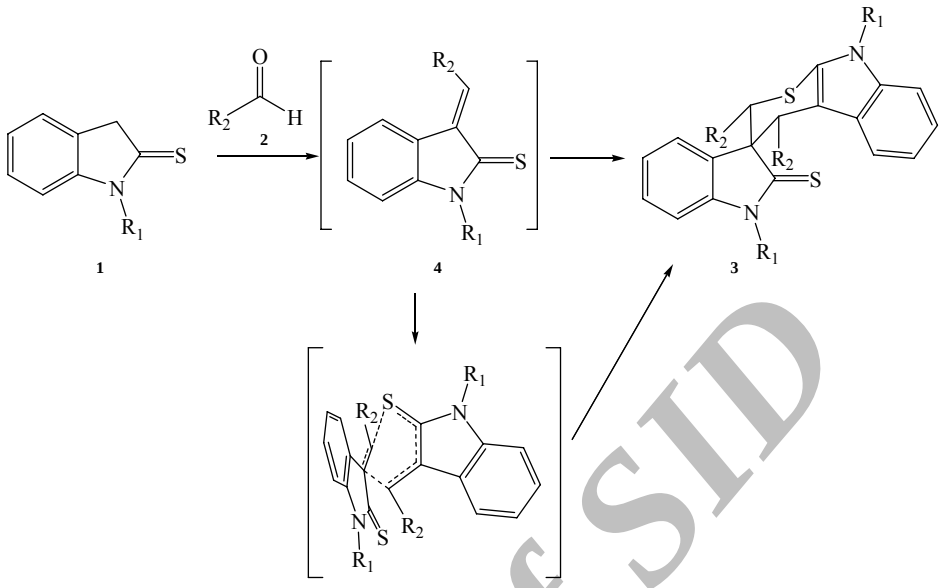
(3o). Yellow crystal; m.p.: 160-162 °C; IR (KBr) (ν_{max}/ cm^{-1}): 694, 739, 1029, 1174, 1240, 1448, 1506, 1609, 3058; ^{1}H NMR ($CDC1_3$, 500 MHz) δ (ppm): 3.75 (s, 3H), 3.77 (s, 3H), 5.31 (s, 1H), 5.61 (s, 1H), 6.11 (d, J = 7.30 Hz, 1H), 6.22 (d, J = 7.81 Hz, 1H), 6.38 (dd, J = 8.72, 2.7 Hz, 1H), 6.41 (d, J = 8.12 Hz, 1H), 6.59 (d, J = 8.73 Hz, 1H), 6.60 (d, J = 8.70 Hz, 2H), 6.69 (d, J = 7.31 Hz, 1H), 6.80 (d, J = 8.42 Hz, 2H), 6.84 (dd, J = 8.70, 2.9 Hz, 1H), 6.88 (t, J = 7.33 Hz, 1H), 7.11 (t, J = 7.71 Hz, 1H), 7.19 (t, J = 7.60 Hz, 1H), 7.24 (t, J = 7.52 Hz, 1H), 7.33 (d, J = 8.21 Hz, 1H), 7.36 (d, J = 7.63 Hz, 1H), 7.40 (t, J = 7.30 Hz, 1H), 7.45 (t, J = 7.20 Hz, 1H), 7.51 (t, J = 7.34 Hz, 1H), 7.61-7.69 (m, 5H), 8.06 (d, J = 7.42 Hz, 1H); ^{13}C NMR ($CDC1_3$, 125 MHz) δ (ppm): 51.6 (CH), 55.4 (CH), 55.6 (OCH_3), 55.7 (OCH_3), 67.0 (C_{spiro}), 109.8 (CH), 110.4 (CH), 110.9 (C), 112.5 (CH), 113.1 (CH), 113.4 (2CH), 120.2 (2CH), 121.8 (CH), 123.7 (CH), 127.3 (CH), 127.7 (2CH), 127.8 (C), 128.4 (CH), 128.5 (CH), 128.9 (CH), 129.0 CH), 129.4 (2CH), 129.9 (CH), 130.11 (2CH), 130.2 (C), 130.3 (C), 131.1 (C), 131.5 (2CH), 131.8 (C), 131.9 (CH), 133.1 (CH), 137.1 (C), 137.5 (C), 138.4 (C), 147.7 (C), 158.9 (C), 160.1 (C), 206.1 (C).

RESULTS AND DISCUSSION

The behavior of linear α,β-unsaturated thioaldehydes and thioketones in Diels-Alder cycloadditions has been investigated previously [17]. Most of the sulfur analogues undergo [4π+2π] dimerization reaction in which C=S serves as the 2π dienophiles. A survey of litrature shows that there is only one report on the synthesis of spiro thiooxindole. In this experiment, Spiro thio-oxindoles were prepared in ethanolic solution in the presence of pipiridine as the catalyst. It should be noted that the electronic effect of substrates and the generality of the reaction are not described in this report [18].

There has been a long-standing interest in heterocycles incorporating sulfur and nitrogen in our laboratory [19]. As part of our continuing program for the synthesis of potentially pharmacologically active heterocycles, we have now investigated the synthesis of highly functionalized spiro dihydrothiopyrane compounds from corresponding aldehydes and thio-oxindoles in one step procedure *via* a tandem catalyst free Aldol-Diels-Alder reaction accelerated in water without the isolation of intermediates (Scheme 1). The thio-oxindole 1 (R1 = H, Me, Et, Ph) underwent aldol condensation with aldehyde 2 (R2 = Me, Ph, 4-MeOPhenyl, 2-pyridyl, 3-pyridyl, 4-nitrophenyl, 2-furyl, 2-thienyl) at 3-position to afford α,β-unsaturated thio-oxindoles. The monomeric form of this kind of α,β-unsaturated thio-oxindole is inaccessible in water because it undergoes fast [4π+2π] dimerization reaction with one molecule as the diene partner (4π) and the other as the dienophile (2π). The C=C bond of one molecule acted as the 2π dienophile while the C=S was not involved in the reaction. The C=S was greatly stabilized by the resonance effect with nitrogen lone pair electrons. Similarly the C=C bond was activated by the PhC=S group, so that not C=S but C=C participated in the reaction as the 2π dienophile.

The structure of product 3a-o was characterized by spectroscopic analysis (^{1}H NMR, ^{13}C NMR, DEPT experiments). The two protons attached to C10 and C18 were resonated as a singlet at δ 5.50 and 5.30 by 1H NMR, respectively. Also, thio carbonyl group and spiro carbon displayed ^{13}C resonance signal at δ 204.3 and 66.4 ppm, respectively. Extra peaks in ^{13}C NMR showed that one of the



Scheme 1

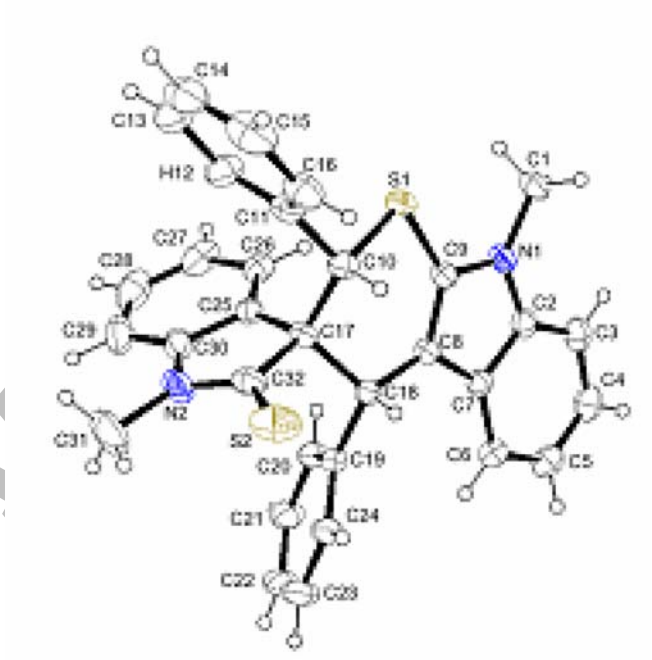


Fig. 1. Crystal structure of compound [20] **3a**.

phenyl rings had a steric hindrance to rotate.

The stereochemistry and final conformation of 3a was obtained from single-crystal X-ray diffraction. As it is shown in Fig. 1, the dihydrothiopyran moiety in 3a adopts a half-chair conformation, and the phenyl group on C (10) is in a cis relationship with the phenyl on C (18). There are three chiral centers in compound 3a and the other diastereomers have not been produced in this reaction. This is supported by the ^{1}H NMR measurement for the reaction mixture prior to separation and purification. Initially, we set out to investigate the solvent

Table 1. Investigation of Solvent Effect on the Reaction of **1a** and Benzaldehyde **2a**[a]

Entry	Solvent	Time (h)	Yield (%)[b]
1	CH_2Cl_2	6	95
2	CH_3CN	24	96
3	CH_3OH	2	80
4	Toluene	2	95
5	DMF	2	17
6	Solvent free	2	74
7	H_2O	2	91

[a]All reaction were carried out with 0.2 mmol of 2a and 0.24 mmol of benzaldehyde in room temperature (30 °C). [b]Isolated products.

effect in the reaction of N-methyl thio-oxindole 1a and benzaldehyde (Table 1). Among the organic solvents used, toluene was found to be the best in terms of higher yield and shortest reaction time (Table 1, entry 4). As it can be observed from Table 1, the reaction also took place in aqueous medium. Although the thio-oxindole 2a was insoluble in water, excellent yield was produced (Table 1, entry 7).

A series of different thio-oxindoles and aldehydes were employed in this reaction. In the presence of electron donating substituent on the phenyl ring of benzaldehyde the temperature of reaction was required (Table 2, entries 1, 2, 6, 7, 11, 13). Occurrence of the reaction in toluene led to obtaining better yields in the cases of entries 2, 7 in Table 2. Surprisingly, the use of nitro-substituted benzaldehyde, which would be expected to accelerate the reaction, led to a decrease of isolated yield (Table 2, entry 4). The use of the aliphatic substrate acetaldehyde resulted in moderate yield (Table 2, entry 14). There were no products when bulky and long chain aliphatic substrates of 2-methyl propanal and heptanal were used as substrates. Concerning the mechanism of this reaction, it seems that the self-dimerization of diene is extremely rapid and rate determining step is the formation of intermediate 4 (Scheme 1).

In this respect, entrapping the intermediate with the exploitation of steric hindrance as a restricting factor in dimerization reaction seemed quite interesting. Namely, 2-anthraldehyde 2e was employed as a substrate and the reaction ceased in α,β-unsaturated thio-oxindole step (Scheme 2). The possible mechanism concerning the compound 4k is proposed in Scheme 1. Probably, one molecule playing the role of dienophile is set vertically between two double-bonds of heterodyne and cycloadditon takes place from two different faces of dienophile, thus two phenyl groups are cis to each other.

In summary, spiro thio-oxindoles were prepared *in situ* by the reaction of the corresponding aldehydes and thio-oxindoles in a straightforward, environmentally friendly condition in water, without any catalyst. The short reaction times, good to excellent yields, extremely facile and single step and ease of work-up are the advantages of this reaction.

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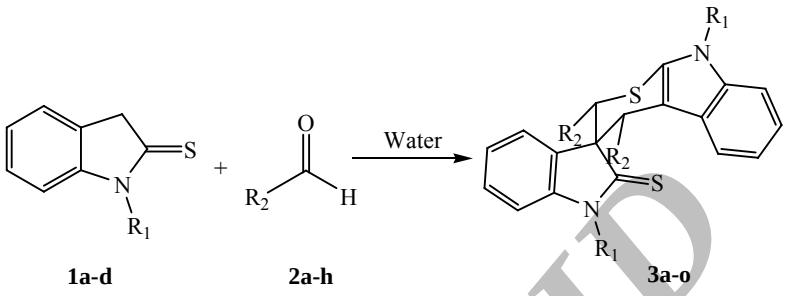
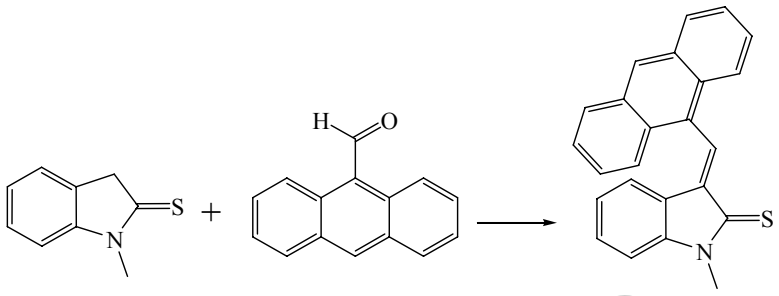
Table 2. The Condensation of Thio-Oxinoles **1a-d** with Aldehydes **2a-h** and Self Dimerization of Corresponding Diene[a]



1a-d **2a-h** **3a-o**

Entry	R_1	R_2	Product	T (°C)	Time (h)	Yield (%)[b]
1	Me	4-OMephenyl	3b	70	5	67
2[c]	Me	4-OMephenyl	3b	60	3	83
3	Me	Thiophen-2-yl	3c	rt	1	86
4	Me	4-Nitrophenyl	3d	rt[e]	2	61
5	Et	Phenyl	3e	rt[e]	3	76
6	Et	4-OMephenyl	3f	70	5	63
7[c]	Et	4-OMephenyl	3f	60	3	70
8	Et	2-Furyl	3g	rt	2	67
9	Et	Thiophen-2-yl	3h	rt	3	89
10	Et	2-Pyridyl	3i	rt	3	54[f]
11	Et	3-Pyridyl	3j	rt	3	72[f]
12	H	Phenyl	3k	rt[e]	3	93
13	H	4-OMephenyl	3l	60	1.5	85
14[c]	H	Methyl	3m	rt[e]	5	61
15	Ph	Phenyl	3n	rt[e]	3	85
16	Ph	4-OMephenyl	3o	70	4	84

[a]All reaction were carried out with 1 mmol of thio-oxindole and 1.2 mmol of aldehyde in water (4 ml), for a detailed experimental operation, see Supporting Information. [b]Isolated products. [c]Reactions was performed in toluene (2 ml). [d]Acetaldehyde (8 eq) was added portionwise in four steps. [e]Room temperature was 30 °C. [f]A 50:50 mixture of two diastereomers were observed.



1a **2e** **4k**

Scheme 2

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