A Novel, One-Pot Four-Component Route to 2′-Thioxo-2′,3′-dihydrospiro[indole-3,6′-[1,3]thiazin]-2-one Derivatives

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An efficient route to 2′,3′-dihydro-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one derivatives is described. It involves the reaction of isatine, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one, and different amines in the presence of CS_2 in dry MeOH at reflux (*Scheme 1*). The alkyl carbamodithioate, which results from the addition of the amine to CS_2, is added to the α,β-unsaturated ketone, resulting from the reaction between 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one and isatine, to produce the 3′-alkyl-2′,3′-dihydro-4′-phenyl-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one derivatives in excellent yields (*Scheme 2*). Their structures were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and by elemental analyses.

Introduction. – A wide range of advantages offered by multicomponent reactions (MCRs), such as high degree of atom economy, convergence, ease of execution, and access to complex molecules, has been recognized in the past decade. The utility of MCRs in preparing libraries to screen for biologically active compounds and potent drug candidates is well-appreciated [1]. Thus, the search and discovery of new MCRs is still of considerable current interest.

The indole ring system is probably the most ubiquitous heterocycle in nature. Because of the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents [2].

Furthermore, it has been reported that sharing C(3) of indoles in the formation of spiro-indole derivatives can highly enhance their biological activity [3]. The spiro-oxindole system is the core structure of several pharmacological agents and natural alkaloids [4]. For example, spirotryprostatin A and B, two natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, have been identified as novel inhibitors of microtubule assembly [4d], and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors [4a] (*Fig. 1*).

The dithiocarbamates and their cyclic derivatives show antibacterial [5], anthelmintic [6], fungicidal [7], herbicidal [8], antifouling [9], growth depressant [10], and algicidal activities [11]. They are also effective catalysts for photopolymerization [12] and vulcanization [13] (*Fig. 2*).

Considering the above reports, and as part of our program aimed at developing new methodologies for the preparation of heterocyclic compounds [14], here, we report the

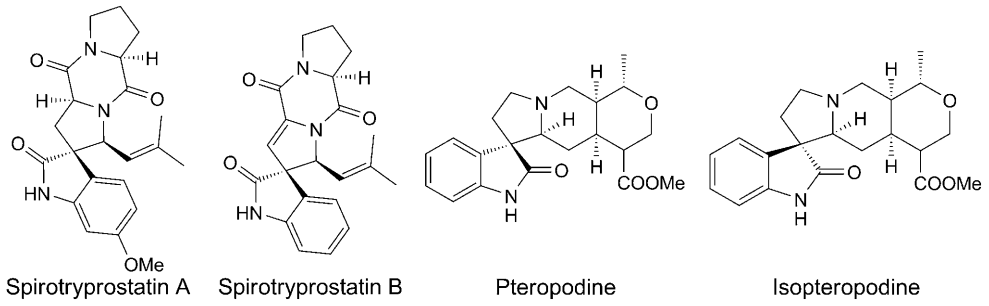


Fig. 1. *Representatives of important spiro-oxindoles*

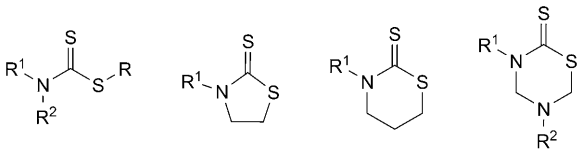
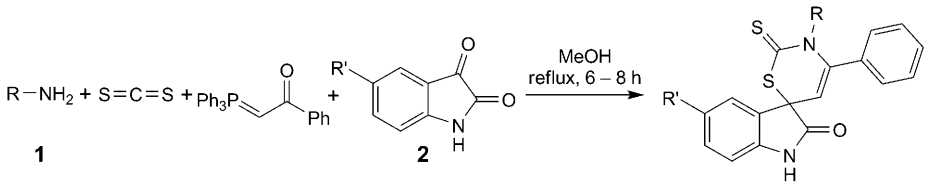


Fig. 2. *Representatives of substituted dithiocarbamates*

synthesis of 2′,3′-dihydro-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one derivatives through a condensation reaction in MeOH.

Results and Discussion. – Our new method leading to the formation of the title compounds is depicted in *Scheme 1*. Reaction between an isatine **2**, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one, and different benzyl and alkyl amines **1** in the presence of CS_2 in dry MeOH at reflux afforded the 3′-alkyl-2′,3′-dihydro-4′-phenyl-2′-thioxospiro[indoline-3,6′-[1,3]thiazin]-2(1*H*)-one derivatives **3** in 72–87% yields (*Scheme 1*).

Scheme 1

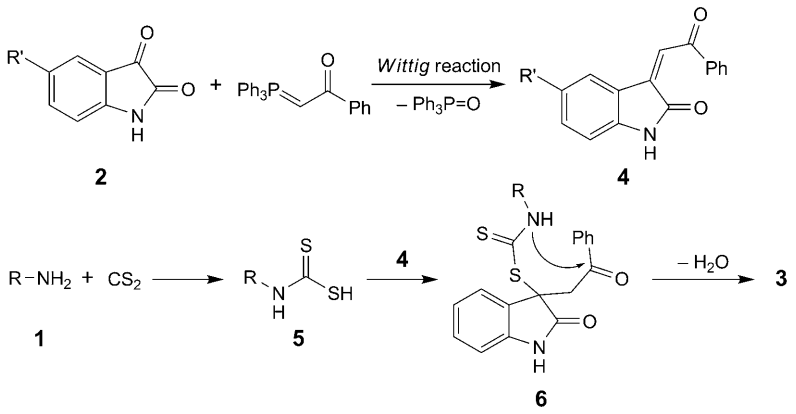


	R	R'	Time [h]	Yield [%]
3a	Bn	H	6	78
3b	2-Cl–$C_6H_4CH_2$	H	5	81
3c	4-Cl–$C_6H_4CH_2$	H	5	74
3d	4-Me–$C_6H_4CH_2$	H	6	79
3e	4-MeO–$C_6H_4CH_2$	H	5	86
3f	4-Cl–$C_6H_4CH_2$	Br	6	72
3g	Allyl	H	6	87

The structures of compounds **3a**–**3g** were deduced from their elemental analysis, and IR, and ^{1}H- and ^{13}C-NMR spectra. The mass spectrum of **3a** displayed the molecular-ion peak at *m*/*z* 414, which is in agreement with the proposed structure. The IR spectrum of **3a** showed absorption bands due to the NH group at 3170, the CO group at 1689, and CS group at 1175 cm^{-1}. The ^{1}H-NMR spectrum of **3a** showed two sharp *singlet*s for CH and NH groups (δ(H) 8.86 and 10.94 ppm), two *doublet*s at δ(H) 4.65, and 4.89 ($^2J = 15.0$) for the CH_2–N, and the Ar moieties gave rise to *multiplet*s in the aromatic region of the spectrum (6.71–7.61 ppm). The ^{1}H-decoupled ^{13}C-NMR spectrum of **3a** showed 20 distinct resonances in agreement with the suggested structure.

Although we have not established the mechanism of the reaction experimentally, a possible explanation is proposed in *Scheme 2*. Compound **3** could be resulted from the initial addition of the amine to CS_2 and subsequent attack of the resulting reactive alkyl carbamodithioate **5** on compound **4** to yield intermediate **6**. Cyclization of the intermediate **6** and subsequent loss of H_2O lead to compound **3**.

Scheme 2. *Proposed Mechanism of the Formation of* **3**



In conclusion, an efficient method for the preparation of 2′,3′-dihydro-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one derivatives using readily available starting materials is reported. These types of heterocycles contain a number of functional groups with possible biological activities. Prominent among the advantages of this new method are operational simplicity and high product yields.

Experimental Part

General. The reagents, including 5-bromoisatine, and solvents were obtained from *Fluka* (Buchs) and used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra (KBr): *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded at 500 and 125 MHz, respectively, on a *BRUKER DRX 500-AVANCE* FT-NMR instrument with (D_6)DMSO as solvent. MS: *FINNIGAN-MAT 8430* mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

General Procedure. Formation of **3a**. A soln. of 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-ethan-1-one (0.38 g, 1 mmol) and isatin (0.15 g, 1 mmol) was magnetically stirred in MeOH (3 ml) for

20 min. Then, $BnNH_2$ (0.11 g, 1 mmol) and CS_2 (1.2 mmol) were added simultaneously. The mixture was stirred for 6 h at reflux temp. The progress of the reaction was followed by means of TLC. After completion, the solvent was removed under reduced pressure, and the residue was purified by CC (hexane/AcOEt, 4:1).

*3′-Benzyl-2′,3′-dihydro-4′-phenyl-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3a**). Yield: 0.32 g (78%). Yellow crystals. M.p. 212° (dec.). IR: 3170 (NH), 1689 (NCO), 1462, 1447 (Ar), 1175 (C=S). ^{1}H-NMR: 4.65 (*d*, *J* = 15.0, 1 H); 4.89 (*d*, *J* = 15.0, 1 H); 6.71 (*t*, *J* = 7.0, 1 H); 6.78 (*d*, *J* = 7.7, 1 H); 7.05–7.10 (*m*, 6 H); 7.22 (*t*, *J* = 7.6, 1 H); 7.28 (*t*, *J* = 7.5, 2 H); 7.53 (*d*, *J* = 7.8, 1 H); 7.61 (*d*, *J* = 7.4, 2 H); 8.86 (*s*, 1 H); 10.94 (*s*, 1 H). ^{13}C-NMR: 47.9; 102.0; 110.2; 118.6; 119.8; 121.4; 126.4; 126.4; 127.0; 127.8; 128.0; 128.9; 129.7; 129.8; 136.2; 137.9; 142.1; 150.0; 168.5; 190.9. EI-MS (70 eV): 415 (10, $[M+1]^+$), 341 (9), 327 (17), 281 (57), 207 (27), 147 (36), 73 (76), 43 (100). Anal. calc. for $C_{24}H_{18}N_2OS_2$ (414.54): C 69.54, H 4.38, N 6.76; found: C 69.49, H 4.30, N 6.65.

*3′-(2-Chlorobenzyl)-2′,3′-dihydro-4′-phenyl-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3b**). Yield: 0.38 g (86 %). Yellow crystals. M.p. 220° (dec.). IR: 3211 (NH), 1690 (NCO), 1595, 1462 (Ar), 1171 (C=S). ^{1}H-NMR: 4.73 (*d*, *J* = 16.1, 1 H); 4.96 (*d*, *J* = 16.1, 1 H); 6.69 (*t*, *J* = 7.2, 1 H); 6.79 (*t*, *J* = 7.3, 2 H); 6.97–7.29 (*m*, 7 H); 7.45 (*d*, *J* = 7.8, 1 H); 7.60 (*d*, *J* = 9.1, 2 H); 8.95 (*s*, 1 H); 10.98 (*s*, 1 H). ^{13}C-NMR: 45.3; 101.7; 110.3; 119.8; 120.8; 121.5; 126.0; 126.4; 126.8; 128.0; 128.2; 129.0; 129.5; 129.8; 131.4; 132.6; 137.6; 142.2; 149.4; 168.5; 191.5. EI-MS (70 eV): 448 (1, M^+), 429 (40), 355 (28), 281 (21), 221 (28), 147 (38), 73 (100), 43 (17). Anal. calc. for $C_{24}H_{17}ClN_2OS_2$ (448.98): C 64.20, H 3.82, N 6.24; found: C 64.14, H 3.75, N 6.18.

*3′-(4-Chlorobenzyl)-2′,3′-dihydro-4′-phenyl-2′-thioxo-spiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3c**). Yield: 0.35 g (79%). Yellow crystals. M.p. 240° (dec.). IR: 3205 (NH), 1691 (NCO), 1463 (Ar), 1171 (C=S). ^{1}H-NMR: 4.66 (*d*, *J* = 16.1, 1 H); 4.88 (*d*, *J* = 16.1, 1 H); 6.71 (*t*, *J* = 8.1, 1 H); 6.78 (*d*, *J* = 8.7, 1 H); 7.06–7.09 (*m*, 3 H); 7.15 (*d*, *J* = 8.4, 2 H); 7.24 (*t*, *J* = 6.0, 1 H); 7.29 (*t*, *J* = 7.9, 2 H); 7.52 (*d*, *J* = 8.0, 1 H); 7.60 (*d*, *J* = 7.5, 2 H); 8.89 (*s*, 1 H); 10.95 (*s*, 1 H). ^{13}C-NMR: 47.2; 101.9; 110.2; 118.7; 119.8; 121.4; 126.4; 126.4; 128.0; 129.0; 129.7; 129.8; 131.6; 135.3; 137.8; 142.1; 149.8; 168.5; 191.0. EI-MS (70 eV): 448 (1, M^+), 207 (9), 182 (8), 125 (100), 116 (9), 89 (20), 73 (5), 43 (32). Anal. calc. for $C_{24}H_{17}ClN_2OS_2$ (448.98): C 64.20, H 3.82, N 6.24; found: C 64.16, H 3.77, N 6.19.

*2′,3′-Dihydro-3′-(4-methylbenzyl)-4′-phenyl-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3d**). Yield: 0.35 g (81%). Yellow crystals. M.p. 232° (dec.). IR: 3188 (NH), 1683 (NCO), 1455 (Ar), 1175 (C=S). ^{1}H-NMR: 2.17 (*s*, 3 H); 4.54 (*d*, *J* = 16.0, 1 H); 4.85 (*d*, *J* = 16.0, 1 H); 6.71 (*t*, *J* = 7.3, 1 H); 6.78 (*d*, *J* = 8.0, 1 H); 6.91 (*d*, *J* = 7.8, H); 6.95 (*d*, *J* = 7.8, 2 H); 7.08 (*t*, *J* = 7.3, 1 H); 7.25 (*t*, *J* = 7.6, 1 H); 7.31 (*t*, *J* = 7.4, 2 H); 7.54 (*d*, *J* = 8.0, 1 H); 7.61 (*d*, *J* = 7.5, 2 H); 8.85 (*s*, 1 H); 10.94 (*s*, 1 H). ^{13}C-NMR: 20.5; 47.2; 101.5; 109.7; 118.0; 119.4; 120.9; 125.9; 125.9; 127.5; 128.1; 128.5; 129.1; 129.3; 132.7; 135.5; 137.4; 141.6; 149.6; 168.0; 190.2. EI-MS (70 eV): 429 (1, $[M+1]^+$), 207 (12), 162 (8), 116 (4), 105 (100), 91 (8), 73 (16), 43 (28). Anal. calc. for $C_{25}H_{20}N_2OS_2$ (428.56): C 70.07, H 4.70, N 6.54; found: C 70.01, H 4.66, N 6.52.

*2′,3′-Dihydro-3′-(4-methoxybenzyl)-4′-phenyl-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3e**). Yield: 0.33 g (74%). Yellow crystals. M.p. 184°. IR: 3215 (NH), 1677 (NCO), 1542, 1444 (Ar), 1237 (C=S). ^{1}H-NMR: 3.71 (*s*, 3 H); 4.56 (*d*, *J* = 15.2, 1 H); 4.82 (*d*, *J* = 15.2, 1 H); 6.72 (*t*, *J* = 7.8, 1 H); 6.78 (*d*, *J* = 7.7, 1 H); 6.86 (*d*, *J* = 7.7, 2 H); 7.08 (*t*, *J* = 7.7, 1 H); 7.19 (*d*, *J* = 8.1, 2 H); 7.25 (*t*, *J* = 6.6, 1 H); 7.30 (*t*, *J* = 7.7, 2 H); 7.56 (*d*, *J* = 7.8, 1 H); 7.62 (*d*, *J* = 8.12, 2 H); 8.81 (*s*, 1 H); 10.92 (*s*, 1 H). ^{13}C-NMR: 47.4; 55.4; 102.0; 110.2; 113.6; 114.1; 118.5; 119.8; 121.4; 126.4; 128.3; 129.0; 129.7; 129.8; 137.9; 142.0; 150.2; 158.7; 168.5; 190.6. EI-MS (70 eV): 444 (1, $[M+1]^+$), 179 (4), 121 (100), 91 (5), 77 (10), 63 (2), 51 (4), 57 (14). Anal. calc. for $C_{25}H_{20}N_2O_2S_2$ (444.56): C 67.54, H 4.53, N 6.30; found: C 67.50, H 4.48, N 6.28.

*5-Bromo-3′-(4-chlorobenzyl)-2′,3′-dihydro-4′-phenyl-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3f**). Yield: 0.38 g (72%). Yellow crystals. M.p. 210° (dec.). IR: 3239 (NH), 1696 (NCO), 1592, 1460 (Ar), 1171 (C=S). ^{1}H-NMR: 4.68 (*d*, *J* = 15.6, 1 H); 4.90 (*d*, *J* = 15.6, 1 H); 6.75 (*d*, *J* = 8.4, 1 H); 7.07 (*d*, *J* = 8.4, 2 H); 7.15 (*d*, *J* = 8.2, 2 H); 7.25–7.32 (*m*, 4 H); 7.58 (*d*, *J* = 8.1, 2 H); 7.64 (*d*, *J* = 4.6, 1 H); 9.02 (*s*, 1 H); 11.12 (*s*, 1 H). ^{13}C-NMR: 54.9; 101.4; 111.6; 112.7; 117.0; 121.0; 125.9; 127.5; 128.1; 128.6; 129.3; 129.6; 131.1; 131.4; 134.7; 136.8; 140.6; 151.8; 167.6; 190.0. EI-MS (70 eV): 527 (2, M^+), 183 (9), 125 (100), 116 (5), 99 (6), 89 (16), 75 (4), 63 (8), 43 (1). Anal. calc. for $C_{24}H_{16}BrClN_2OS_2$ (527.88): C 54.61, H 3.05, N 5.31; found: C 54.58, H 3.02, N 5.28.

*2′,3′-Dihydro-4′-phenyl-3′-(prop-2-en-1-yl)-2′-thioxospiro[indole-3,6′-[1,3]thiazin]-2(1*H*)-one* (**3g**). Yield: 0.32 g (87%). Yellow crystals. M.p. 172°. IR: 3153 (NH), 2927 (aliphatic CH), 1640 (C=C), 1706 (NCO), 1452 (Ar), 1223 (C=S). ^{1}H-NMR: 4.08–4.13 (*m*, 2 H); 5.23 (*d*, *J* = 10.2, 1 H); 5.28 (*d*, *J* = 10.2, 1 H); 5.85–5.89 (*m*, 1 H); 6.88 (*d*, *J* = 7.7, 1 H); 7.02 (*t*, *J* = 7.6, 1 H); 7.32 (*t*, *J* = 7.6, 2 H); 7.54 (*t*, *J* = 7.7, 2 H); 7.64 (*t*, *J* = 7.2, 1 H); 7.87 (*s*, 1 H); 8.12 (*d*, *J* = 7.6, 2 H); 8.23 (*s*, 1 H); 8.31 (*d*, *J* = 7.8, 1 H). ^{13}C-NMR: 47.0; 110.0; 117.6; 120.7; 122.9; 126.5; 128.0; 128.8; 128.9; 132.7; 133.1; 133.8; 136.7; 137.6; 143.2; 169.3; 191.1. EI-MS (70 eV): 365 (1, $[M+1]^+$), 281 (25), 221 (30), 147 (37), 73 (100), 44 (20). Anal. calc. for $C_{20}H_{16}N_2OS_2$ (364.48): C 65.91, H 4.42, N 7.69; found: C 65.80, H 4.39, N 7.65.

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