1,3-Dipolar Cycloaddition Reaction of Nitrile Oxides to Isatin Imines

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ABSTRACT: *A simple and efficient one-pot route for the synthesis of novel spiro [indolin–oxadiazol] derivatives by 1,3-dipolar cycloaddition reaction of nitrile oxides and isatin imine under classical or microwave irradiation conditions is described. 4-amino-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione was synthesized by cyclization of thiocarbohydrazide and acetic acid. 3-((3-methyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)imino)indolin-2-one was prepared by condensation of primary amine of 4-amino-5-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thione with isatin through a single step and 4'-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 3'-(substituted phenyl)-4'-hydro spiro[indolin-3,5'[1,2,4]oxadiazol]-2-one were afforded by the reaction of corresponding Schiff base with hydroximinoyl chloride and their derivatives under basic conditions at room temperature. The products were obtained in good yields. Elemental analysis, IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data confirmed the structure of newly synthesized compounds.*

KEY WORDS: *Spiro indole; 1,3-dipolar cycloaddition; Microwave irradiation; Isatin imines; Schiff base; Nitrile oxides.*

INTRODUCTION

Spiro heterocyclic compounds are well known to possess varied pharmacological activities and hence their synthesis has always been a challenge and of attraction to organic chemists. These compounds, display pronounced antimicrobial [1], analgesic [2], anti-inflammatory [2], antimycobacterial [3], antifungal [4], antitumor [5,6] and antiviral [5,6] activities. Among these heterocycles, spiro indoles have been identified as privileged structures in medicinal chemistry and have attracted increasing interest in the recent years [7-10].

Also 1,2,4-Oxadiazole rings occur widely in biologically active synthetic compounds, and are often used in drug discovery as hydrolysis-resisting bioisosteric replacements for ester or amide functionalities [11-13]. Numerous 1,2,4-oxadiazoles have been suggested as potential agonists for cortical muscarinic [13,14], benzodiazepine [15], and 5-HT1D (5-hydroxytryptamine) receptors [16], and as antagonists for 5-HT3 [17], or histamine H3 receptors [18]. They show activity as antirhinoviral agents [12], growth hormone secretagogues [19], anti-inflammatory agents [20], and antitumor agents [21].

Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of spiro indole heterocycles containing 1,2,4-oxadiazoles ring fragments is therefore an interesting challenge. In continuation of our previous work

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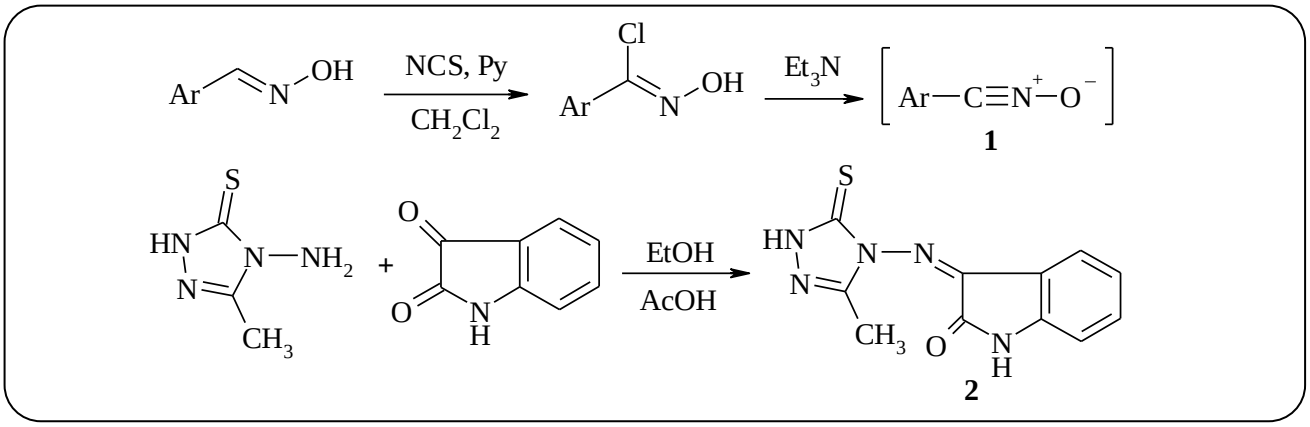


Scheme 1: Synthesis of Schiff bases.

on the synthesis of spiroindoles [22-24], we now describe a one-pot synthesis of new spiro [indolin– *oxadiazol*] derivatives **3** from 1,3-dipolar cycloaddition reaction of benzonitrile oxide derivatives **1** and isatin imine **2** in fairly good yields under classical or microwave irradiation conditions .

The benzonitrile oxide derivatives **1**, generated in situ from the corresponding oximes [25,26], according to *Larsen & Torssel's* method [27], and isatin imines **2** were synthesized according to previous work [28], by the reaction of isatin and heterocyclic primery amine in ethanol and acetic acid (Scheme 1).

EXPERIMENTAL SECTION

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heracus CHN-O-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer. Mass spectra were recorded on a Hewlett-Packard 5973 mass spectrometer operating at an ionization potential of 70 eV. Microwave reactions were carried out in microwave oven with a 2500 W power (Micro-Synth, Milestone). The chemicals used in this work purchased from fluka (Buchs, Switzerland) and were used without further purification.

General procedure

Method A

To a magnetically stirred solution of *N*-Chlorosuccinimide (NCS, 5 mmol) and pyridine (0.1 mL) in CH_2Cl_2 (15 mL), was added oximes (5 mmol) at 20-30°C in one portion and after 10 min, isatin imine (5 mmol) was added. Triethylamine (7 mmol in 5ml CH_2Cl_2) was added dropwise over the course of 15 min and the temperature rose to 35–40°C. The reaction mixture was stirred for approximately 2h. Then the reaction mixture was filtrated and then washed with water (2*20 mL) to remove triethylamine hydrochloride. The analytical sample was obtained by recrystallization in methanol.

Method B

In a high pressure Teflon reactor equipped with a magnetic stir bar and an optical fiber (for controlling the reaction temperature), a mixture of isatin imine (5 mmol), oximes (5 mmol) and with 4–5 drops of DMSO exposed to microwave irradiation at 80°C (400W) for the appropriate time (see Table 1) using a Micro-Synth lab station reactor. Then, the reaction mixture was allowed to cool down, 20 mL water was added, and the resulting solid was filtered off, washed with 10 mL of hot water, and recrystallized in metanol.

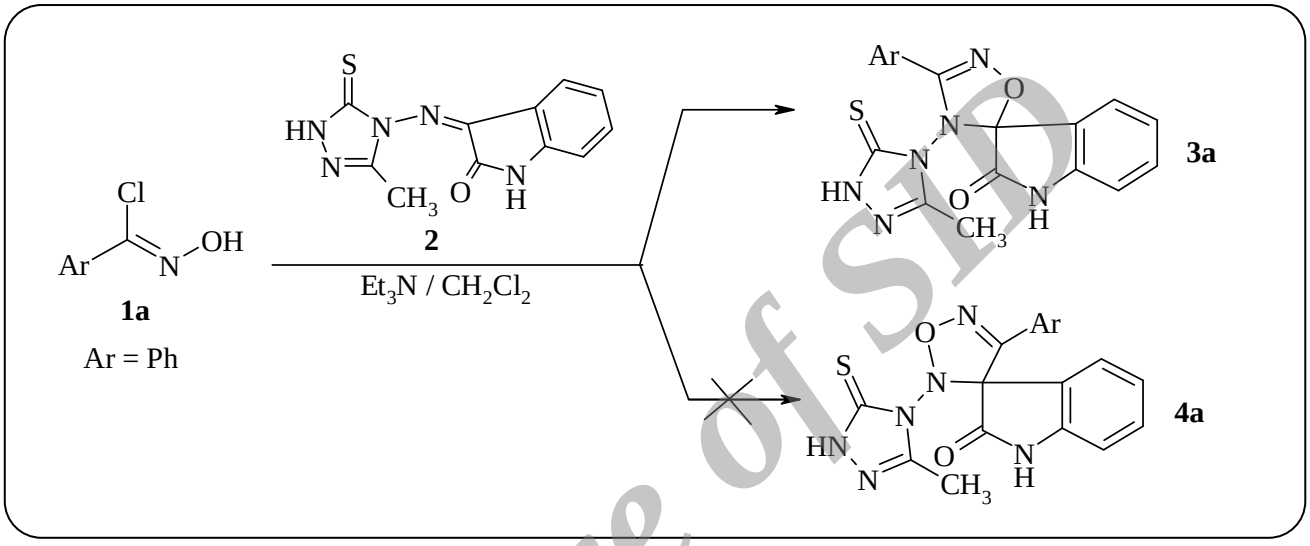
4'-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 3'-phenyl -4'-hydro spiro[indolin-3,5'[1,2,4]oxadiazol]-2-one **(3a).**

Yellow crystal, yield 89% (conventional 67%), m.p. 257-260°C, IR (KBr) (ν_{max}, cm^{-1}): 3275 (NH), 1747, 1608 (C=O, C=N, ester), Anal. Calcd (%) for $C_{18}H_{14}N_6O_2S$: C, 57.13; H, 3.73; N, 22.21; S, 8.47 Found: : C, 57.34; H, 3.61; N, 22.50; S, 8.22 ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (3 H, s, CH_3), 6.82-7.60 (aromatic), 10.32(H, NH), 10.88 (H, NH), ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 17.34 (CH_3), 92.08 (spiro carbon), 120.93-142.25 (aromatic), 154.00, 163.70 (2C=N), 168.27 (C=O), 185.12 (C=S), Mass, *m/z* (%) = 378 [M$^+$,9].

Table 1: Physical constants of the synthesized compounds.

3	Ar	Time (h)[a]	Yield (%)[b]	Time (h)[c]	Yield (%)[d]
a	Phenyl	3	67	3	89
b	p-Cl-phenyl	3	83	3	96
c	P-Br-phenyl	3	76	3	92
d	p-NO_2-phenyl	3	87	3	90

a) Time for reaction based on method A , b) Pure isolated yields of products 3 from method A
c) Time for reaction based on method B , d) Pure isolated yields of products 3 from method B



Scheme 2: Synthesis of final products.

3'-(4clorophenyl)-4'-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)-4'-hydro spiro[indolin-3,5'[1,2,4]oxadiazol]-2-one **(3b).**

Yellow crystal, yield 96% (conventional 83%), m.p. 289-290°C, IR (KBr) (ν_{max}, cm^{-1}): 3174 (NH), 1735, 16760 (C=O, C=N, ester), Anal. Calcd (%) for $C_{18}H_{13}ClN_6O_2S$: C, 52.37; H, 3.17; N, 20.36; S, 7.77 Found: C, 52.15; H, 3.33; N, 20.61; S, 7.45 ^{1}H NMR (500 MH_Z, $CDCl_3$): δ = 1.91 (3 H, s, CH_3), 6.89-7.63 (aromatic), 10.13 (2H, br, 2NH), ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 15.34 (CH_3), 93.69 (spiro carbon), 122.96-142.96 (aromatic), 156.66, 160.05 (2C=N), 168.96 (C=O), 186.05 (C=S), Mass, *m/z* (%) = 412 [M^+,10].

3'-(4-bromophenyl)-4'-(3-methyl-5-thioxo-1H- 1,2,4-triazol-4(5H)-yl)-4'-hydro spiro[indolin-3,5'[1,2,4]oxadiazol]-2-one **(3c).**

Yellow crystal, yield 92% (conventional 76%), m.p. 285-288°C, IR (KBr) (ν_{max}, cm^{-1}): 3242 (NH), 1736, 1570 (C=O, C=N, ester), Anal. Calcd (%) for $C_{18}H_{13}BrN_6O_2S$: C, 47.28; H, 2.87; N, 18.38; S, 7.01 Found: C, 47.41; H, 2.67; N, 18.12; S, 7.31^{1}H NMR (500 MH_Z, $CDCl_3$): δ = 1.99 (3 H, s, CH_3), 6.89-7.58 (aromatic), 10.13 (br, 2H, 2NH), ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 16.12 (CH_3), 92,11 (spiro carbon), 116.21-144.11 (aromatic), 152.19, 161.77 (2C=N), 169.64 (C=O), 187.12 (C=S), Mass, *m/z* (%) = 456 [M^+,11].

4'-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 3'-4-nitrophenyl-4'-hydro spiro[indolin-3,5'[1,2,4]oxadiazol]-2-one **(3d).**

Yellow crystal, yield 90% (conventional 87%), 269-272 °C, IR (KBr) (ν_{max}, cm^{-1}): 3278 (NH), 1752, 1658 (C=O, C=N, ester), Anal. Calcd (%) for $C_{18}H_{13}N_7O_4S$: C, 51.06; H, 3.09; N, 23.16; S, 7.57 Found: C, 51.22; H, 3.31; N, 22.92; S, 7.37 ^{1}H NMR (500 MH_Z, $CDCl_3$): δ = 2.42(3 H, s, CH_3), 7.11- 8.16 (aromatic), 10.32 (br, 2H, 2NH), ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 17.06 (CH_3),

91.88 (spiro carbon), 120.90-149.49 (aromatic), 155.11, 161.40 (2C=N), 168.44 (C=O), 186.97 (C=S), Mass, *m/z* (%) = 423 [M^+,10].

RESULTS AND DISCUSSION

Initially, we studied the reaction of benzonitrile oxide **1a** and isatin imines **2** in the presence of triethylamine in dichloromethane at room temperature. The reaction was completed after 3h (the reaction progress was monitored by TLC) and *4'-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 3'-phenyl -4'-hydro spiro[indolin-3,5'[1,2,4] oxadiazol]-2-one* (**3a**) was obtained in 67 % yield.

In order to improve the yield of reaction, we examined the reaction under different conditions including refluxing in various solvents (EtOH, THF, CH_3CN and toluene) and also under microwave irradiation. In refluxing solvents, after 48 h, the yields of products were low (<40%). We found that the best results were obtained under microwave irradiation. By using microwave irradiation, the reaction time was reduced greatly from 3 hours to 3 min and the yield of the reaction was enhanced by 3-22% compared to the classical method (Table1).

The structures of compounds **3a**–**d** were deduced from their mass spectra, elemental analyses, and high-field ^{1}H and ^{13}C NMR spectra, as well as the IR spectra, which displayed NH at 3174-3278 cm^{-1}, C=O at 1735–1752 and C=N at 1570–1676 cm^{-1}.

In the ^{13}CNMR spectra, the carbonyl absorption at about 168-169 ppm, imine carbon (C=N) at 152-163 ppm, and a signal at 91-93 ppm attributable to the spiro carbon atom, are in agreement with proposed structure **3**, but not with structure **4.**

COCLUSIONS

In conclusion, 1,3-dipolar cycloaddition of benzonitrile oxide derivatives and isatin imines by microwave irradiation, provides a facile, high yield, and rapid method, which can be used as a path for synthesis a number of interesting spiro [indolin– *oxadiazol*] derivatives.

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