A facile synthesis of novel spiro indoline-based heterocycles through 1,3-dipolar cycloaddition reactions

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A simple and efficient one-pot route for the synthesis of novel spiro [indolin–3,3′-1,2,4-triazol] derivatives by 1,3-dipolar cycloaddition reaction of nitrilimines and isatin imines under classical or microwave irradiation conditions is described. Spiro heterocyclic compounds possess pharmacological properties such as antimicrobial, analgesic, anti-inflammatory, antimycobacterial, antifungal, antitumor and antiviral activities.

Keywords: spiro indole, 1,3-dipolar cycloaddition, nitrilimines, microwave irradiation, antimicrobial activity

Spiro heterocyclic compounds possess variious pharmacological properties and hence their synthesis is of interest to organic chemists. Such compounds display pronounced antimicrobial,[1] analgesic,[2] anti-inflammatory,[2] antimycobacterial,[3] antifungal,[4] antitumor[5,6] and antiviral[5,6] activities.

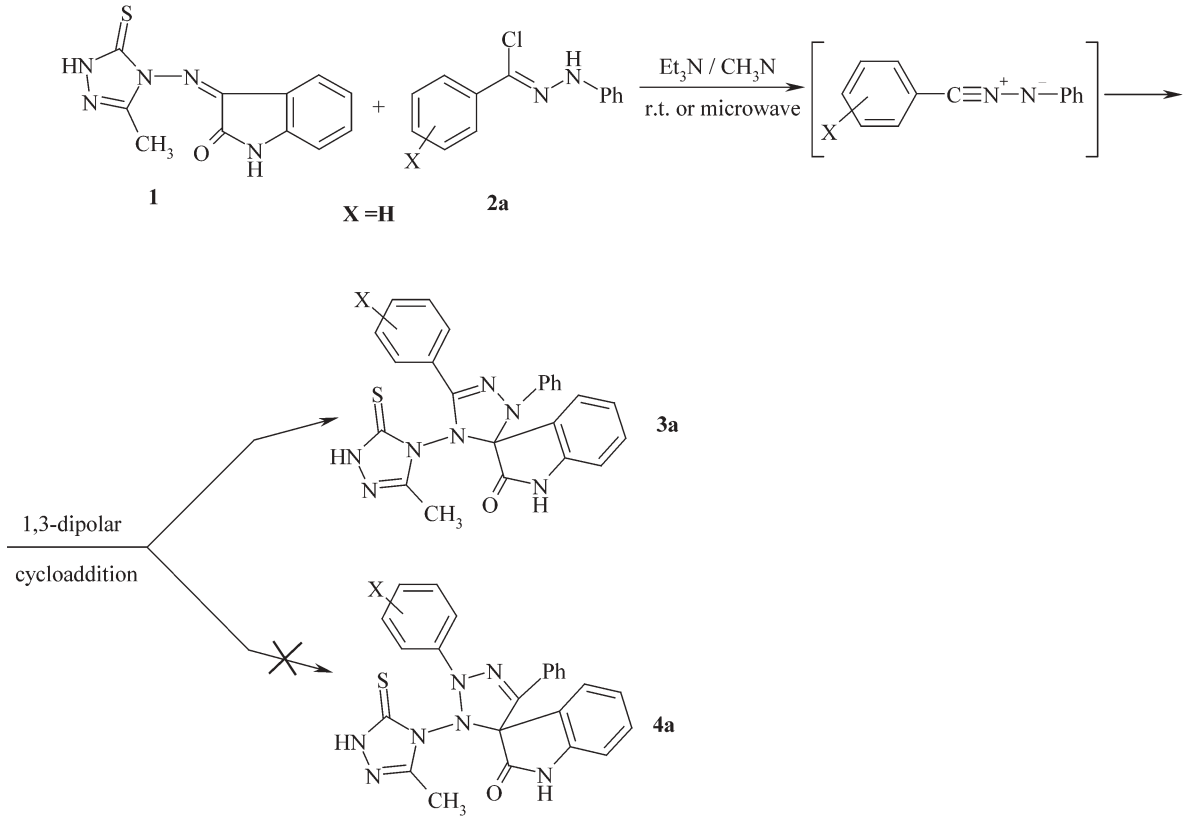
Among these heterocycles, spiro indoles have been identified as privileged structures in medicinal chemistry and have attracted increasing interest in the recent years.[7–10] Also 1,2,4-triazoles and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities[11–13] including antimicrobial[14,15] sedative, anticonvulsant [16] and anti-inflammatory properties.[17]

Considering the above reports, the development of new and simple synthetic methods for the efficient preparation of spiro indole heterocycles containing 1,2,4-triazole ring fragments is therefore an interesting challenge. In continuation of our previous work on the synthesis of spiroindoles,[18,19] we now describe a one-pot synthesis of new spiro [indolin–triazol] derivatives **3** from 1,3-dipolar cycloaddition reactions of isatin imines **1** and nitrilimines **2** (generated *in situ* from the corresponding hydrazonyl chlorides[20,21]) in fairly good yields under classical or microwave irradiation conditions (Scheme 1).

Initially, we studied the reaction of isatin imine **1** and 1-(chloro(phenyl)methylen)-2-phenylhydrazine **2a** in the presence of triethylamine in MeCN at room temperature.

The reaction was complete after 18 h (reaction progress was monitored by TLC) and 2′,5′-diphenyl-4′-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)-2′,4′-dihydrospiro[indolin-3,3′[1,2,4] triazol]-2-one (**3a**) was obtained in 82% yield.

In order to improve the yields, we examined the reaction under different conditions including refluxing in various solvents (EtOH, THF, MeCN 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



Scheme 1

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Table 1 Comparison of preparation methods

3	X	Time/h[a]	Yield/%[b]	Time/min[c]	Yield/%[d]
a	H	18	82	3	87
b	4-Br	18	80	3	86
c	4-Cl	18	77	3	84
d	2,3-di NO_2	19	70	4	78

[a] Time for reactions based on Method A.
[b] Pure isolated yields of products **3** from Method A.
[a] Time for reactions based on Method B.
[b] Pure isolated yields of products **3** from Method B.

from 18 hours to 3 min and the yield of the reaction was enhanced by 5% compared to the classical method (Table 1).

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 3240–3278 (NH), at 1715–1752(C=O) and at 1568–1658 cm^{-1} (C=N).

In the ^{13}C NMR spectra, the carbonyl absorption at 167–169 ppm, imine carbon (C=N) at 149–153 ppm, and a signal at 89–90 ppm attributable to the spiro carbon atom, are in agreement with proposed structure **3**, but not with structure **4.**

In conclusion, 1,3-dipolar cycloaddition of isatin imine **1** and nitrilimines **2** by microwave irradiation provides a facile, high yielding, rapid method, for the synthesis of a number of interesting spiro [indolin-3,3′-1,2,4-triazol] derivatives **3**.

Experimental

CAUTION: Results may not be reproducible and there can be hazards in using a domestic microwave oven for chemical purposes.

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 Bomem FT-IR-MB100 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 irradiations were carried out in a National Oven, Model 5250 (Japan) at 2450 MHz. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

The imine of isatin **1** was prepared by the treatment of isatin and amino triazole in ethanol and acetic acid.[22]

General procedure

Method A: To a magnetically stirred solution of hydrazonyl chloride (5 mmol) and isatin imine (5 mmol) in MeCN (15 mL), a mixture of triethylamine (5 mmol) in MeCN (5 mL) at room temperature was added dropwise over 15 min. The reaction mixture was stirred for 19 h, it was then filtered to remove triethylamine hydrochloride, washed with water, dried, and the solvent was removed under reduced pressure to yield the crude product.

Method B: A mixture of isatin imin (5 mmol), triethylamine (5 mmol), and hydrazonyl chloride (5 mmol) in dimethylformamide (DMF) (1 mL) was placed in an Erlenmeyer flask covered with a watch glass and irradiated in the microwave oven at 360W for 3 min. After completion of the reaction (monitored by TLC), EtOH (10 mL) and ice water (5mL) were added to the reaction mixture and kept at room temperature. The resulting crystalline product was filtered and washed with light petroleum. Analytical samples were obtained by recrystallisation twice from ethanol/water.

2′,5′-Diphenyl- 4′-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)-2′,4′-dihydro spiro[indolin-3,3′[1,2,4]triazol]-2-one (**3a**): Yellow crystals, yield 87% (conventional 82%), m.p. 302–303 °C; IR (KBr) (ν_{max}, cm^{-1}): 3275 (NH), 1747, 1608 (C=O, C=N, ester); ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 2.18 (3 H, s, CH_3), 6.68–7.71 (aromatic), 9.92 (H, NH); 10.92 (H, NH), ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.8 (CH_3), 89.2 (spiro carbon), 117.1–143.2 (aromatic), 149.3, 152.7 (2C=N), 168.4 (C=O), 186.2 (C=S), mass, *m/z* (%) = 453 [M^+,9]. Anal. Calcd for $C_{24}H_{19}N_7OS$: C, 63.56; H, 4.22; N, 21.62; S,7.07. Found: C, 63.72; H, 4.42; N, 21.51; S, 7.31%.

5′-(4-Bromophenyl)-4′-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 2′-phenyl- 2′,4′-dihydro spiro[indolin-3,3′[1,2,4]triazol]-2-one (**3b**): Yellow crystals, yield 86% (conventional 80%), m.p. 292–294 °C; IR (KBr) (ν_{max}, cm^{-1}): 3242 (NH), 1736, 1568 (C=O, C=N, ester); S, 6.35^{1}H NMR (500 MH_Z, $CDCl_3$): δ 2.3 (3 H, s, CH_3), 6.6–7.6 (aromatic), 9.8 (H, NH), 10.7 (H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 16.1 (CH_3), 89.7 (spiro carbon), 116.2–144.1 (aromatic), 150.2, 151.8 (2C=N), 169.6 (C=O), 187.1 (C=S); mass, *m/z* (%) = 531 [M^+,11]. Anal. Calcd for $C_{24}H_{18}BrN_7OS$: C, 54.14; H, 3.41; N, 18.42; S, 6.02. Found: C, 54.34; H, 3.31; N, 18.16%.

5′-(4-Chlorophenyl)-diphenyl- 4′-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 2′-phenyl- 2′,4′-dihydro spiro[indolin-3,3′[1,2,4]triazol]-2-one (**3c**): Yellow crystals,yield 84% (conventional 77%), m.p. 298–300 °C; IR (KBr) (ν_{max}, cm^{-1}): 3242 (NH), 1715, 1560 (C=O, C=N, ester); ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 2.2 (3 H, s, CH_3), 6.6–7.8 (aromatic), 9.80 (H, NH), 10.85 (H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.7 (CH_3), 89.4 (spiro carbon), 115.8–144.3 (aromatic), 150. 9, 152.3 (2C=N), 167.3 (C=O), 185.8 (C=S); mass, *m/z* (%) = 487 [M^+,11]. Anal. Calcd for $C_{24}H_{18}ClN_7OS$: C, 59.07; H, 3.72; N, 20.09; S,6.57. Found: C, 59.27; H, 3.62; N, 20.22; S,6.32%.

5′-(3,5-Dinitrophenyl)-diphenyl- 4′-(3-methyl-5-thioxo-1H-1,2,4-triazol-4(5H)-yl)- 2′-phenyl- 2′,4′-dihydro spiro[indolin-3,3′[1,2,4]triazol]-2-one (**3d**): Yellow crystals, yield 78% (conventional 70%), 295–296 °C; IR (KBr) (ν_{max}, cm^{-1}): 3278 (NH), 1752, 1658 (C=O, C=N, ester); ^{1}H NMR (500 MH_Z, $CDCl_3$): δ 2.2 (3 H, s, CH_3), 6.5–8.8 (aromatic), 10.7 (H, NH), 10.9 (H, NH); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 15.8 (CH_3), 90.1 (spiro carbon), 115.1–149.2 (aromatic), 152.2, 153.1 (2C=N), 169.3 (C=O), 186.2 (C=S), Mass, *m/z* (%) = 543 [M^+,10]. Anal. Calcd for $C_{24}H_{17}N_9O_5S$: C, 53.04; H, 3.15; N, 23.19; S, 5.90 Found: C, 53.34; H, 3.25; N, 23.27; S, 5.62%.

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