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Easy Access to Indole-based Bi-Sulfurylate-Heterocyclic Scaffolds

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Dedicated to the memory of Prof. Paolino Filippone, on the first anniversary of his death

Abstract: New and valuable indole based sulfurylated bi-heterocyclic systems such as 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles and 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazoles are regioselectively obtained under very mild conditions employing 1,2-diaza-1,3-dienes and not smelly indoline 2-thiones as starting materials.

Introduction

The heterocyclic compounds constitute the core of the majority of drugs and they are then relevant targets for drug discovery. Usually, the investigations involve only one heterocyclic scaffold, and the library diversity was achieved by means of derivatization of the common heterocyclic core with different groups.[1] However, several examples indicate as the functionalization of the heterocyclic core with a second one often produces a huge increment of the biological properties: not by change, numerous of the most common drugs contain a bi-heterocyclic structure (Omeprazole, Losartan, Amoxicillin, Alprazolam, Trazodone, Meloxicam, Clopidogrel).[2] Among heterocycles, the indole nucleus represents a privileged structure present in a variety of pharmaceutical derivatives, bioactive compounds and natural products.[3] In this context, aryl- or heterocyclic-sulfenylindole derivatives were displayed to possess relevant biological/pharmaceutical properties (Figure 1) that include anti-viral (HIV-1),[4] anti-allergic,[5] anti-cancer,[6] anti-atherothrombotic-[7] vasoconstrictor-activities,[8] as well as NTPase-,[9] renin-,[10] autotaxin-,[11] poxvirus-inhibitors,[12] or as treatment for respiratory diseases.[13]

Consequently, numerous efforts have been devoted to development of new methods for their synthesis. The 3-sulfenylindole are the most recurrent structures since the indole can be easily functionalized at the C3 position employing both carbon and heteroatomic electrophiles. In fact, several methods reported in literature allow to obtain the 3-sulfenylated derivatives directly using the indoles with thiols,[14] disulfides,[15] sulfenyl halides,[16] arylsulfonyl chlorides,[17] sulfonyl hydrazides,[18] *N*-thioimides,[19] just to mention the most common ones.

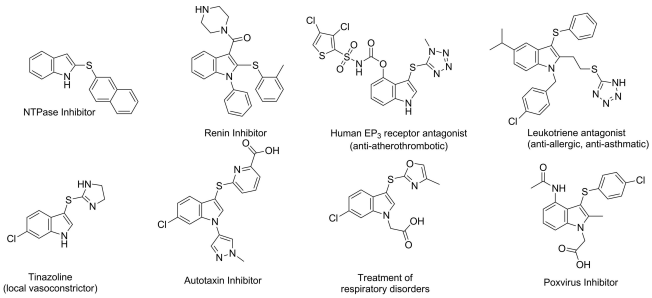

Figure 1. Some relevant examples of aryl- or heterocyclic-sulfenylindole derivatives.

The weak reactivity of the C2 position makes the synthesis of the 2-sulfenylindole more difficult, especially for *N*-unprotected heterocycles. Usually, the 2-sulfenylindoles were obtained by means of acid-catalyzed rearrangement of 3-sulfenylindole,[20] or through the sulfenylation of 2-lithioindoles.[21] Recently, some efficient methods have been developed: some examples include the TFA-,[22] or the Cp*CoIII[23] catalyzed cyclization of indoles and *N*-(thio)-succinimides, and the visible light induced radical process of ortho-substituted arylisocianides and thiols.[24] Nevertheless, these methods frequently require harsh reaction conditions, or suffer from use of strong acids or strong bases, incompatible with different functional groups, or require a high transition metal catalyst loading, and an excess of additives or oxidants to obviate their deactivation; some sulfenylating agents are moisture- and air- sensitive and often they are strong smelly compounds, difficult to prepare and not readily commercially available. Based on these considerations, the development of new, efficient, and simple approaches to 2-sulfenylindoles are of high appeal. On the other hand, the chemistry of pyrazolones is the subject of great attention in medicinal chemistry due to their multiple pharmacological properties, including anti-inflammatory, antitumor, antimicrobial, anticonvulsant, antidepres-

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sant, anti-amyotrophic lateral sclerosis, anti-Alzheimer's, antioxidant, anti-tuberculosis antiviral, lipid-lowering, antihyperglycemic activities.[25] Recently, we proposed a metal-free strategy aimed to the preparation of not easily accessible 2-carboxylated thieno[2,3-*b*]indole derivatives that requires as starting materials 1,2-diaza-1,3-dienes (DDs) **1** and non-smelly indoline 2-thiones **2** (Figure 2).[26] The assembly of the new condensed thiophene structure takes place in acid reaction environment. Based on our previous experience,[27] we have supposed that a change of the reaction conditions can induce a different ring closure process that leads to unknown heterobicyclic scaffolds such as the 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles **4**. Furthermore, the study of the mechanistic aspects involved in the synthesis of derivatives **A** suggested that a structural modification of the starting indoline 2-thiones **2** could trigger a different cyclization that leads to the formation of new and interesting 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazol derivatives **5** (Figure 2). Spiro compounds represent an important class of organic frameworks and natural products manifesting numerous pharmacological activities; among them, the anticancer properties of spiro compounds have prompted medicinal chemists to investigate new spiro-derivatives with significantly improved pharmacodynamic and pharmacokinetic profile.[28] Then, also the development of new and simply strategies devoted to their preparation are topics of great relevance. Here, the investigations on the synthesis of both unprecedented 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles **4** and 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazole derivatives **5** are described (Figure 2).

Results and Discussion

Our research begins with the attempt to obtain new and interesting indol-pyrazol-sulfide systems **4** (Figure 2). Recently, we have observed that, although not commonly used,[29] indoline-2-thiones **2** are efficient and odorless sulfenylating agents that can be successfully employed in the preparation of thieno[2,3-*b*]indoles by reaction with DDs **1**.[26] The one-pot procedure developed can be divided in two steps, namely the thia-Michael addition of the indoline 2-thiones **2** to the azo-ene system of DDs **1** that produces the hydrazones **3**, and the acidic promoted cyclization that leads to the thieno[2,3-*b*]indoles **A** (Figure 2).[26] Based on our previous findings,[27] we have then supposed that derivatives **3** could be valuable intermediates also for the preparation of new heterobicyclic scaffolds such as the 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles **4**.

To investigate this synthesis, the DD **1a** and the indoline 2-thione **2a** were chosen as representative model (Scheme 1).

Several solvents, such as acetonitrile (ACN), ethanol (EtOH), methanol (MeOH) have proved to be effective in the reaction between DD **1a** and **2a** furnishing the corresponding α-thiohydrazone **3a** in quantitative yields after few minutes.[26] The thia-Michael addition to the terminal carbon atom of the azo-ene system of the DD **1** occurs as a result of the induced sulphur nucleophilicity from the indoline-2-thione **2a**/1*H*-indole-2-thiol **2a'** tautomerism (Step a, Scheme 1). Clearly, the driving force of the reaction is related to the aromaticity of the formed 1*H*-indole-2-thiol. Starting from the 4-ethoxy carbonyl-DD **1a**, the corresponding hydrazone **3a** is generated, which in turn, can trigger an intramolecular cyclization exploiting the nucleophilic nitrogen (highlighted in red) and the carboxylic carbon (highlighted in yellow, Step b, Scheme 1). To enhance the nitrogen reactivity, different bases such as sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), sodium bicarbonate ($NaHCO_3$), sodium acetate (NaOAc), potassium acetate (KOAc), sodium methoxide (NaOMe), potassium *tert*-butoxide (KO*t*Bu), *N*,*N*-diisopropylethylamine (DIPEA), 1,8-diazabicyclo 5.4.0 undec-7-ene (DBU), and sodium hydride (NaH) were tested (Entries 1–11, Table 1).

From the set of the data collected, we noted that the heterogeneous promotion of weakly bases such as sodium carbonate, potassium carbonate, sodium bicarbonate, sodium acetate, potassium acetate, is more effective in term of yields (Table 1 entries 1–5), than that obtained with stronger bases, such as NaOMe, KO*t*Bu or NaH (Table 1 entries 6, 7, and 11), or with nitrogenous bases (DIPEA, DBU, Table 1 entries 8–10). This can be explained by considering the acidity of N(1)-H, whose conjugate base is stabilized by the carbamic moiety, allowing this proton to easily react even with weaker bases which have the advantage of not triggering other side reactions. From this preliminary screening, we decided to continue the tests by focusing our attention on sodium acetate, which is the base that gave the best result, by changing solvent, temperature, and molar ratio (Table 1 entries 8–17). The solvents were chosen which quantitatively supplied the hydrazone **3a**, so as to be able to carry out a one-pot synthesis of the desired derivatives **4** (Table 1 entries 12–14). In methanol, after 12.0 the starting hydrazone **3** is completely converted, but from the isolation of the two main spots, we noted as also a concomitant transesterification that produces the corresponding methyl-ester hydrazone **3a'** occurs (Table 1, entry 12).[30] By prolonging the

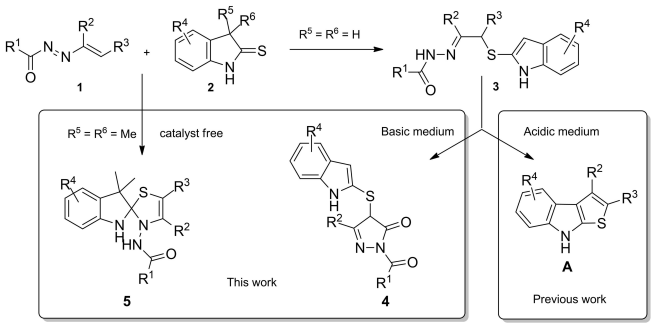
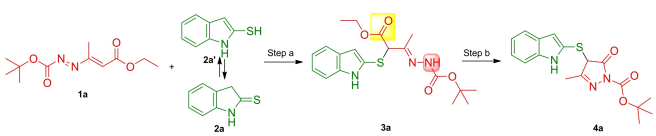


Figure 2. Reactions between 1,2-diaza-1,3-dienes **1** and indoline 2-thiones **2**: state of the art and perspectives.



Scheme 1. Representative model for the optimization of the synthesis of 4-((1*H*-indol-2-yl)thio)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole **4a**.

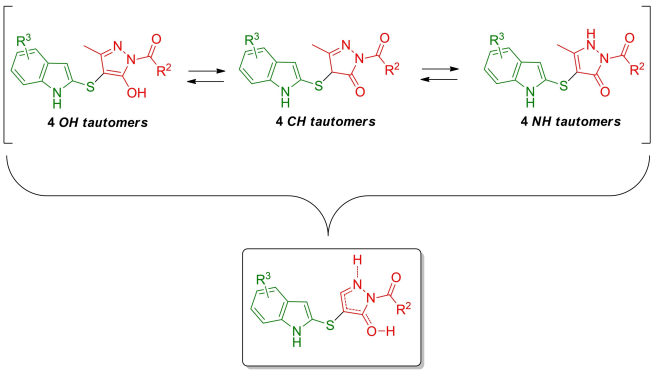
Table 1. Tuning of the cyclization conditions for the synthesis of the 4-((1*H*-indol-2-yl)thio)-1*H*-pyrazol-5-ole **4a**.

Entry[a]	Temp. [C°]	Solvent	Promoter	Amount of promoter [equiv.]	Time [h]	Yield **4a** [%][b]
1	r.t.	ACN	Na_2CO_3	2	18	88
2	r.t.	ACN	K_2CO_3	2	18	73
3	r.t.	ACN	$NaHCO_3$	2	24	85
4	r.t.	ACN	NaOAc	2	14	92
5	r.t.	ACN	KOAc	2	14	89
6	r.t.	ACN	NaOMe	0.2	2	32
7	r.t.	ACN	KO*t*Bu	0.2	3.5	41
8	r.t.	ACN	DIPEA	2	10	65
9	r.t.	ACN	DBU	1	3	-[c]
10	r.t.	ACN	DBU	0.2	12	32
11	r.t.	ACN	NaH	0.1	0.5	-[c]
12	r.t.	MeOH	NaOAc	2	12	67[d]
13	r.t.	MeOH	NaOAc	2	20	81
14	r.t.	EtOH	NaOAc	2	16	84
15	r.t.	ACN	NaOAc	1	48	58
16	r.t.	ACN	NaOAc	4	8	77
17	50	ACN	NaOAc	2	3.5	54[e]

[a] The reactions were conducted on 0.5 mmol of **3a**, in 6 mL of solvents. [b] Yield of isolated **4a** referred to **3a**. [c] The TLC profile is very complicated, both **3a** and **4a** were not detected in the reaction mixture. [d] The methyl ester derivative **3a'** was isolated in 11% yields.[30] [e] The N(1) unprotected pyrazole **4a'** was isolated in 21% yield.

reaction times, also the conversion of **3a'** is complete, but in this case, as well as for the reaction carried out in ethanol, the yields obtained are lower (Table 1, entries 13, and 14). Then, the amount of the promoter was changed: by reducing the molar ratio of the base to 1 equivalent, the yield decreases to 58%, while to an increment until 4 equiv. corresponds a reduction of the reaction time but associated to a lower yield (Table1, entries 15, and 16). Finally, increasing the temperature to 50 °C, the reaction is faster, but also the hydrolysis of the carbamic moiety on the N(1) of the formed pyrazole ring occurs, and the desired 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazole **4a** was isolated only in 54% (Table 1, entry 17).[31]

The individual reaction conditions identified were applied to a one-pot procedure: in a solution in acetonitrile of DD **1a** one equivalent of indoline-2-thione **2a** was added. After 5 minutes, the typical red coloration of the solution due to the conjugation of the azo-ene system of DDs **1** disappeared, a sign that the hydrazone intermediate **3a** is formed, as also verified by TLC analysis. Then, directly to the reaction medium, two equivalents of sodium acetate were added; after further 14.0 hours, the conversion of **3a** is complete and the desired 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazole **4a** was obtained in 90% yield, in accordance with the overall values found in the step by step approach. Then different DDs **1a–d** and substituted indoline-2-thiones **2a–g** were tested under these optimized one-pot reaction conditions. As summarized in Table 2, several 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles **4a–o** were easily obtained in good yields. As well known, for compounds **4** in solution, three tautomeric forms, that can be named as OH-, CH-, and NH-tautomers, are in equilibrium (Scheme 2).[32] Due to the aromaticity of the pyrazole nucleus, the most recurrent one is the OH-form, but the other two

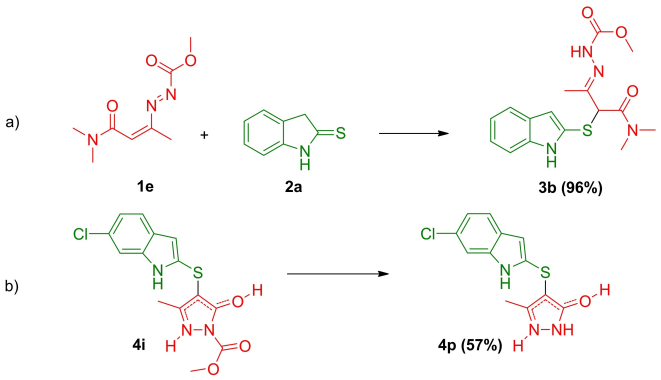


Scheme 2. Possible tautomeric forms of 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles **4**.

tautomers are also present to a lesser extent. Furthermore, the NH- and OH- forms can be involved in intramolecular hydrogen bonds, determining two different *syn-anti* conformations whose formation is influenced mainly by the nature of the solvent and/or by the substituent steric hindrance present on the N(1) of the pyrazole core. The combination of all these factors sometimes makes the characterization of these compounds quite complicated, due to the presence of multiple signals.[33]

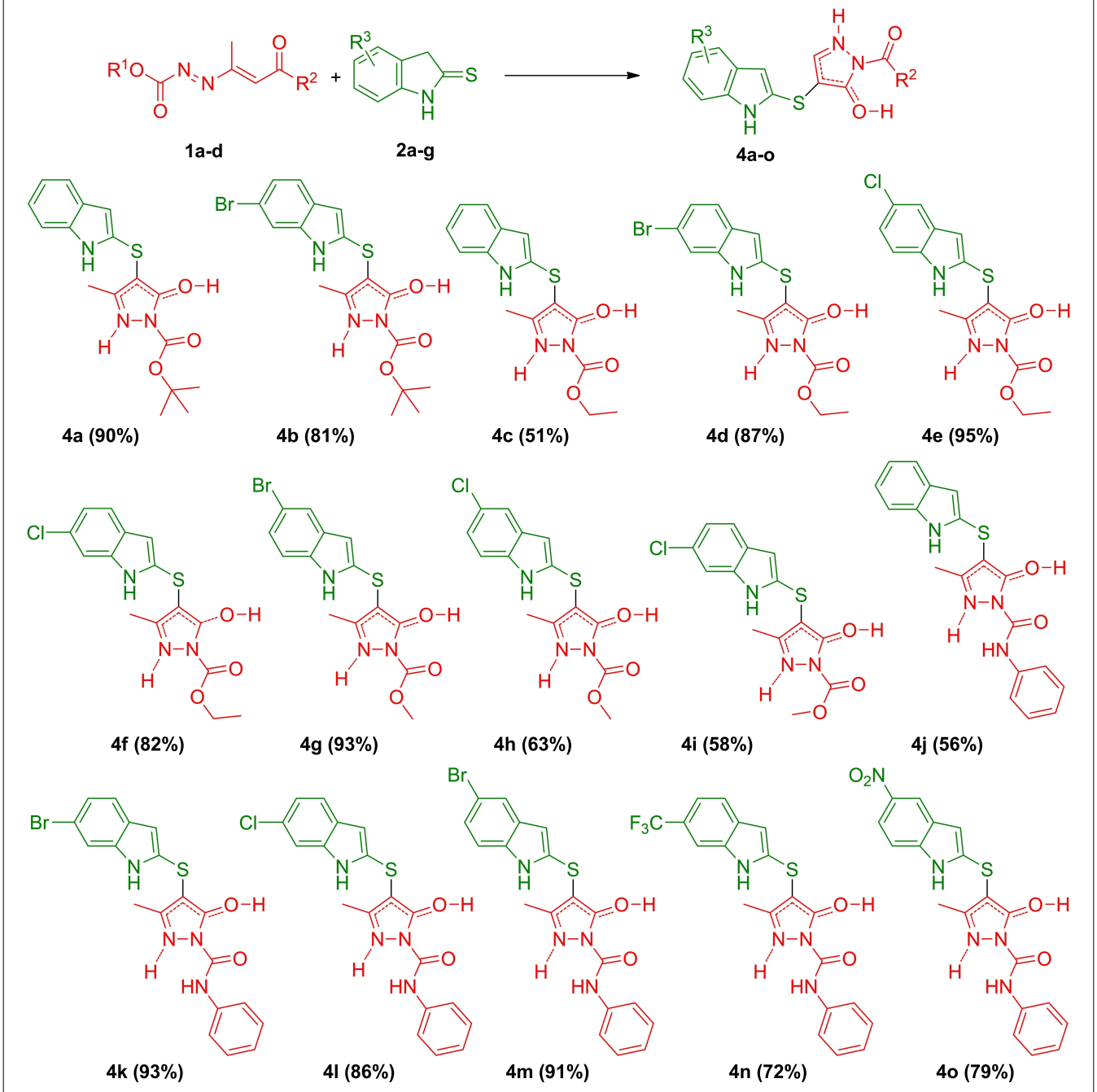
To describe in a coherent and faithful way the real situation observed in the NMR analyses, the compounds **4** are represented as the result of the possible tautomeric forms as indicated in Scheme 2 and reported in Table 2.

Albeit treated under the optimized reaction conditions, the 4-aminocarbonyl DD **1e** furnishes exclusively the corresponding hydrazonic adduct **3b** (Scheme 3a). In this case, the lower reactivity of the amide function prevents the final intramolecular cyclization reaction. Based on the results found in the optimization tests (Table 1, entry 17), compound **4i**, chosen as representative example, was subjected to prolonged basic treatment at higher temperatures. Under these conditions, hydrolysis of the carbamic moiety takes place with consequent deprotection of the N(1) nitrogen of pyrazole, leading to the unsubstituted indol pyrazol sulfide derivative **4p** (Scheme 3b).



Scheme 3. Further investigations: reaction of 4-aminocarbonyl DD **1e** with indoline-2-thione **2a**, and deprotection of the N(1) pyrazole nitrogen of compound **4i**.

Table 2. Substrate scope of 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles **4a-o** obtained through the one-pot approach.[a],[b]



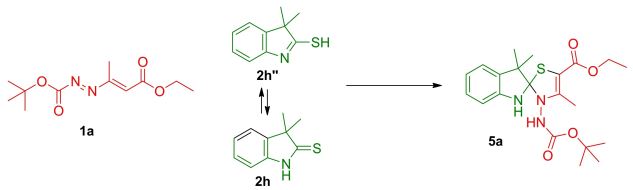
[a] Reaction conditions: DDs **1** (1 mmol), indoline-2-thiones **2** (1 mmol), ACN (12 mL), room temperature (0.1-0.5 h), then to the disappearance of the typical red coloration of the solution, to the crude sodium acetate (2 mmol) was added and the reaction was magnetically stirred for 13–17 h. [b] The isolated yields are shown in the brackets.

It is well known that the breaking of the carbamic bond in pyrazole structures occurs very easily.[27,33]

Aware of the importance of spiro-indole systems, on the basis of the results obtained in this and in the previous work,[26] we have designed a different synthetic approach targeted to their preparation, that involves the same DD **1a** and the indoline-2-thione with substituents blocking the C3 position such as the 3,3-dimethyl indoline-2-thione **2h** in which the only possible tautomerism concerns the indoline-2-thione **2h**/3*H*-indole-2-thiol **2h''** forms (Table 3).

With our great pleasure, we have observed that the reaction in acetonitrile at room temperature between **2h** and DD **1a**, chosen as representative example, furnishes directly the desired 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazol derivative **5a** without the need of any catalyst (Table 3, entry 1).

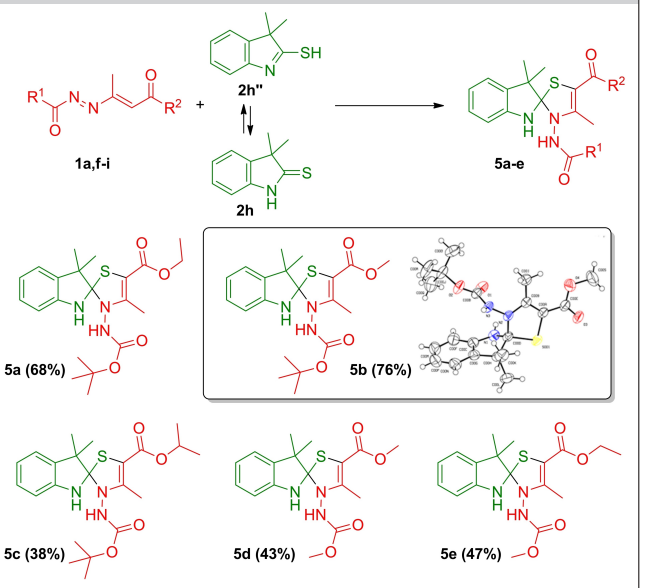
Table 3. Screening of different conditions in the reaction between DD **1 a** and 3,3-dimethylindoline-2-thione **2 h**.



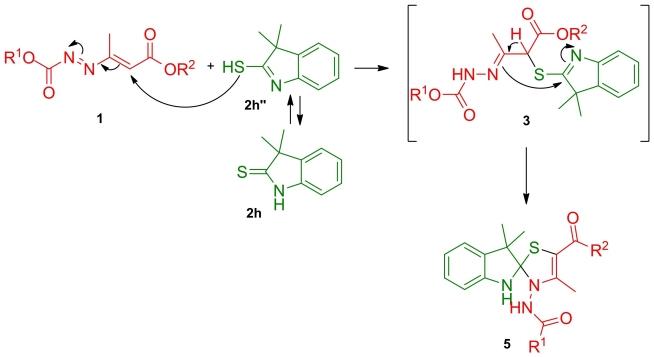
Entry[a]	Temp. [C°]	Solvent	Molar Ratio **1 a**/**2 h**	Time [h][b]
1	r.t.	ACN	1/1	4.5[b]
2	r.t.	MeOH	1/1	3.5[b]
3	r.t.	EtOH	1/1	3.5[b]
4	r.t.	DCM	1/1	4.5[b]
5	r.t.	$CHCl_3$	1/1	4.0[b]
6	r.t.	THF	1/1	4.0[b]
7	r.t.	$CHCl_3$	1/1.2	4,0[b]
8	r.t.	$CHCl_3$	1/0.8	4.0[c]
9	50	$CHCl_3$	1/1	2.5[b]

[a] The reactions were conducted on 0.5 mmol of **1 a**, in 3 mL of solvents. [b] Yield of isolated **5 a** referred to DD **1 a**. [c] Yield of isolated **5 a** referred to 3,3-dimethylindoline-2-thione **2 h**.

Table 4. Substrate scope of 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazoles **5**.[a],[b]



[a] Reaction conditions: DDs **1** (1 mmol), 3,3-dimethylindoline-2-thione **2 h** (1 mmol), $CHCl_3$ (6 mL), room temperature (3–4.5 h). [b] The isolated yields are shown in the brackets.



Scheme 4. Plausible mechanism of the formation of 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazoles **5**.

Several other solvents such as, methanol, ethanol, dichloromethane (DCM), chloroform, tetrahydrofuran (THF) were also tested (Table 3, entries 2–6), noting as the best results were obtained in chloroform. No improvement in the reaction corresponds to the variation of the molar ratios between the reactants **1 a** and **2 h** (Table 3, entries 7, and 8), as well as to the increase in temperature (Table 3, entry 9).

With these optimized reaction conditions, the scope of the reaction was enlarged employing different DDs **1 a,f–i**. The corresponding spiro derivatives **5 a**–**e** were obtained in discrete yields in 3–4.5 hours (Table 4).

The ^{13}C-NMR signals at 87.8-88.8 ppm are diagnostic for the quaternary spiro-carbon atom; however, the structure of compound **5 b** was unequivocally confirmed by X-ray spectroscopy (Table 2).[34] Importantly, this cyclization generates an unusual spirocyclic thio-aminal quaternary centre that, to the best of our knowledge, is very poorly represented in literature.[35]

The plausible mechanism involves an initial thia-Michael addition of the sulphur deriving from the 3,3-dimethyl-3*H*-indole-2-thiol **2 h''** to the terminal carbon atom of the azo-ene system of the DDs **1** with formation of the non-isolable hydrazone intermediate **3**. The subsequent spontaneous elimination of the activated proton originally located in position 4 of the azo-enic system of the DDs **1** activates the nitrogen nucleophilicity, promoting the attack on the carbon of the imidothioate function deriving from 3,3-dimethylindoline-2-thione **2 h** thus completing the cyclization process (Scheme 4).

Conclusion

In conclusion, here is demonstrated as the indolin-2-thiones are effectively, inexpensive, odorless and safe sulfenylating agents able of overcoming the classic poor reactivity of the C2-indole position, and it is also confirmed the versatility and usefulness of 1,2-diaza-1,3-dienes in the construction of heterocyclic structures under mild conditions. In detail, with simple work-up, without metal catalysts, anhydrous environments, or controlled atmospheres it was possible to prepare new and fascinating bi-heterocyclic structures such as the 4-((1*H*-indol-2-yl)thio)-5-oxo-4,5-dihydro-1*H*-pyrazoles and the 3′*H*-spiro-indoline-2,2′-thiazoles, that represent interesting indole-based scaffolds with valuable potential biological properties, not easily obtainable in any other way.

Experimental Section

General procedure for the synthesis of *tert*-butyl 2-(3-((1*H*-indol-2-yl)thio)-4-ethoxy-4-oxobutan-2-ylidene)-hydrazinecarboxylate 3 a and methyl 2-(3-((1*H*-indol-2-yl)thio)-4-(dimethylamino)-4-oxobutan-2-ylidene)hydrazinecarboxylate 3 b.

To a solution of 1,2-diaza-1,3-dienes **1 a,e**[37] (1 mmol) in acetonitrile (6 mL) at room temperature, indoline-2-thione **2 a**[38] (1 mmol) dissolved in acetonitrile (6 mL) was added and the reaction mixture was stirred at room temperature until the disappearance of the reagents (TLC monitoring, 0.1-0.5 h) as also evidenced by the colour change from red, typical of DDs, to pale yellow. Then, the solvent was evaporated under reduced pressure and the α-thio-functionalized hydrazones **3 a,b** were purified by column chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 80 : 20 for compound **3 a** and cyclohexane : ethyl acetate, 65 : 35 for compound **3 b**. The pure products **3 a,b** were precipitated in ethyl acetate/petrol ether.

General procedure for the synthesis of 4-((1*H*-indol-2-yl)-thio)-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carboxylates 4 a-o.

To a solution of 1,2-diaza-1,3-dienes **1 a–d**[37] (1 mmol) in acetonitrile (6 mL) at room temperature, indoline-2-thiones **2 a–g**[38] (1 mmol) dissolved in acetonitrile (6 mL) were added and the reaction mixture was stirred at room temperature until the disappearance of the reagents (TLC monitoring, 0.1-0.5 h) as also evidenced by the colour change from red, typical of DDs, to pale yellow. Then, directly to the reaction mixture, sodium acetate (2 mmol) was added and the reaction was stand under magnetic stirring for 13–17 h until the disappearance of the hydrazone intermediates **3** (TLC monitoring). The sodium acetate was removed by filtration, the solvent evaporated under reduced pressure and compounds **4 a–o** were purified by chromatography on silica gel (elution mixture: cyclohexane: ethyl acetate, 20 : 80).

General procedure for the synthesis of 4-((6-chloro-1*H*-indol-2-yl)thio)-3-methyl-1*H*-pyrazol-5(4*H*)-one 4 p.

To a solution of methyl 4-((6-chloro-1*H*-indol-2-yl)thio)-3-methyl-5-oxo-4,5-dihydro-1*H*-pyrazole-1-carboxylate **4 i** (0.5 mmol) in acetonitrile (5 mL), sodium acetate (2 mmol) was added and the reaction was refluxed until the disappearance of the starting material (TLC monitoring, 8 h). Then, the sodium acetate was removed by filtration, the solvent evaporated under reduced pressure and compound **4 p** was purified by chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 30 : 70).

General procedure for the synthesis of 3,3-dimethyl-3′*H*-spiro-indoline-2,2′-thiazoles 5 a–e.

A solution of 1,2-diaza-1,3-dienes **1**[37] (0.5 mmol) and 3,3-dimethylindoline-2-thione **2 h**[38] (0.5 mmol) in chloroform (3 mL) was stirred at room temperature for DDs **1 a,f** (3.5 and 4.5 h respectively), or refluxed in the case of DDs **1 c,g,h** (3–4.5 h), until the disappearance of the reagents (TLC monitoring) and as also evidenced by the colour change from red, typical of DDs, to pale yellow. Then, the solvent was evaporated under reduced pressure and compounds **5 a-e** were purified by chromatography on silica gel (elution mixture: cyclohexane : ethyl acetate, 85 : 15).

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: Cyclization · Indole · Michael addition · Pyrazol-5-one · Thiazole

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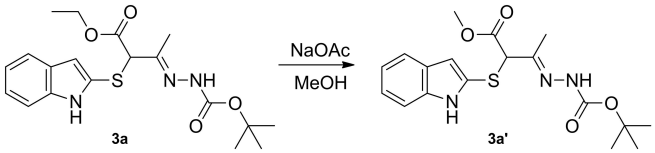
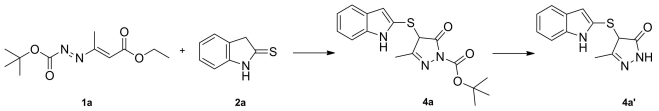
[30] The treatment of hydrazone **3a** with sodium acetate in MeOH provokes a concomitant transesterification that leads to the corresponding methyl-ester hydrazone **3a'**.



[31] At reflux, the cyclization reaction is followed by the hydrolysis of the carbamate function with consequent formation of the N(1) unprotected pyrazole **4a'**:



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