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Synthesis of novel symmetrical 2-oxo-spiro[indole-3,4’-pyridines] by reaction of oxindoles with 1,2-diaza-1,3-dienes

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Abstract. A simple reaction of some oxindole derivatives with 1,2-diaza-1,3-dienes to produce 2-oxo-spiro[indole-3,4’-pyridines] in good yields is here described. This transformation represents a practical two steps approach to new and biologically interesting 2-oxo-spiro[indole-3,4’-pyridine] scaffolds by means of double Michael addition/cyclization sequence.

Oxindoles constitutes a prominent class of heterocycles that represent important building blocks found in a wide variety of many pharmaceuticals and natural compounds, such as alkaloids.[1] In particular, the synthesis of spiroxindoles is one of the most target for many organic chemists, as several natural products that exhibit significant bioactivity, possess this core in their structure.[2,3] For example, the spyrotryprostatins A and B, isolated from the fermentation broth of *Aspergillus fumigatus*, were found to completely inhibit the G2/M progression of cellular division in mammalian tsFT210 cells.[3] Strychnofoline, belonging to a class of natural products isolated from the leaves of *Strychnos usambarensis*,[4a] displays antimitotic activity against coltures of mouse melanoma and Ehrlich tumor cells.[4b] Surugatoxin, isolated from the Japanese ivory shell, antagonizes the depolarizing effect of carbachol on isolated rat superior cervical ganglia, depresses the orthodromic transmission, and is a ganglionic blocker of nicotinic acetylcholine receptors.[4c] In the field of the synthetic therapeutic agents containing a spiroxindole core, SOID-8, analogue of spyrotryprostatin B, has been described to have anticancer activity against Melanoma cells,[5] while NITD609 is a promising novel drug for the treatment of malaria[6] (Figure 1).

The common structural characteristic of these compounds is the spiro ring fusion at the 3-position of the oxindole nucleus with several five- or six-membered aza-heterocycles.

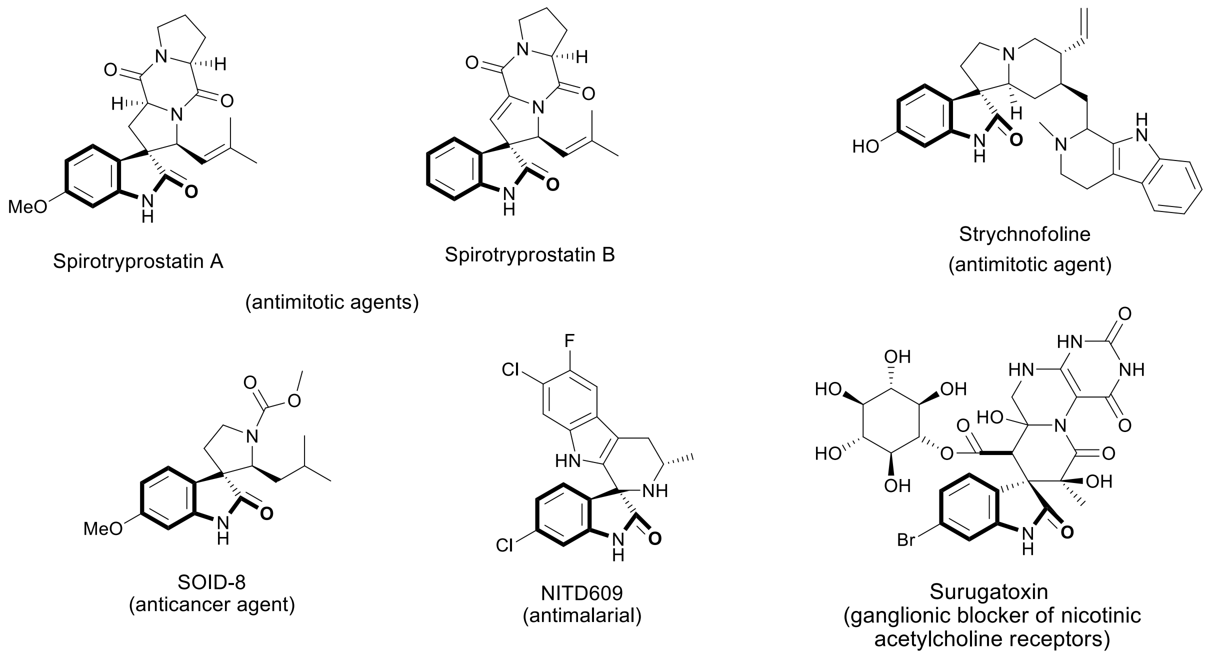


Figure 1. Examples of natural products and synthetic therapeutic agents containing a spiroxindole core.

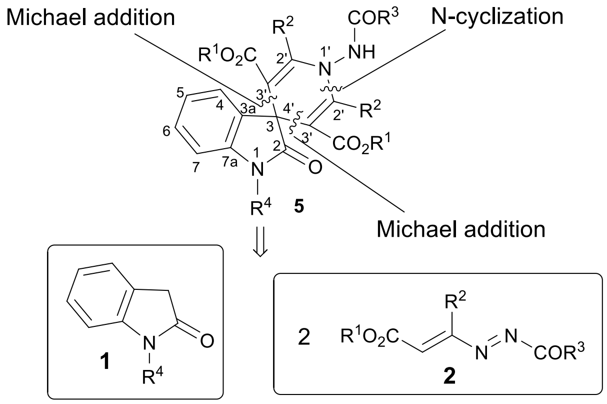
Among them, 1,4-dihydropyridines are of particular interest thanks to their biological and pharmacological actions. First of all, they represents one of the most important groups of calciul-channel modulating agents and they are used in the treatment of cardiovascular diseases. Besides, they also show antibacterial, anticancer, antileishmanial, anticoagulant, anticonvulsant, antitubercular, antioxidant, antiulcer, CFTR, antimalarials and neuroprotection properties, as well as HIV-1 protease inhibitors, and antifertility activities.[7]

So, taking into account the potential biological properties of the 2-oxo-spiro[indole-3,4'-pyridine] system, the construction of complex molecular frameworks containing this core is a very challenging goal. The main reported methods for the synthesis of spiroxindole-pyridines require the employ of isatins as one of the starting materials, in multicomponent approaches (MCRs).[4c]

For example, Alizadeh and Mokhtari described a four component route to obtain spiro[indoline-3,4'-pyridine]-3'-carboxylates from isatin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, amines and dicarbonyl compounds.[8a] Yan *et al.* reported the synthesis of spiro[oxindole-dihydropyridines] from isatins, arylamines and cyclopentane-1,3-dione.[8b] The same group described a $BF_3\cdot OEt_2$-catalyzed three component reaction of the same isatins, arylamines and acetylenedicarboxylate to obtain spiro[indoline-3,2'-pyridines] or spiro[indoline-3,4'-pyridines].[8c] Langer *et al.* prepared some spiro[indoline-3,4'-pyrrolo[2,3-*b*]pyridines] by a MCRs starting from Meldrum's acid, isatins and 5-amino-3-cyanopyrroles, in acetic acid/ammonium acetate.[8d] Another recent example includes acid-catalyzed one-pot sequential reactions of isatins, arylamines and methyl propiolate to give spiro[indoline-3,4'-pyridines].[8e]

An alternative elegant route to spirocyclic dihydropyridines through an electrophile-induced dearomatizing spirocyclization of *N*-arylisonicotinamides was also reported by Clayden and co-workers.[9]

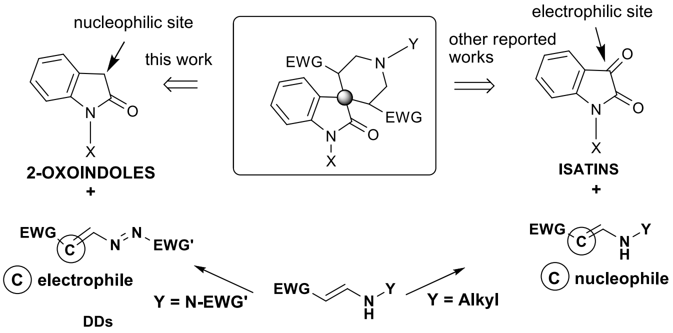
So, by exploiting our experience in the field of 1,2-diaza-1,3-dienes (DDs) for the syntheses of five- and six-membered azaheterocycles,[10] we have thought to focus a strategy that aims at developing a simple methodology for the synthesis of the target 2-oxo-spiro[indole-3,4'-pyridine]. Our retrosynthetic analysis emphasizes three strategic disconnections of the pyridine ring. The first one is along the nitrogen-carbon N(1')-C(2') bond obtainable from two hydrazonic residues, by means of a N-heterocyclization (Scheme 1).



Scheme 1. Retrosynthetic analysis to assemble 2-oxo-spiro[indole-3,4'-pyridines].

Two further disconnections can be envisaged between the spiro carbon C(3,4') and the two C(3') atoms. These can be connectable to the oxindoles **1** and two molecules of DDs **2**, through a double Michael addition (Scheme 1).

As reported above,[8a-e] the common building blocks for the preparation of the 2-oxo-spiro[indole-3,4'-pyridine] nucleus are represented by the isatins.[4c] In this case, the indole core participates with an electrophilic site in the construction of the spiro derivatives, as indicated in Scheme 2.



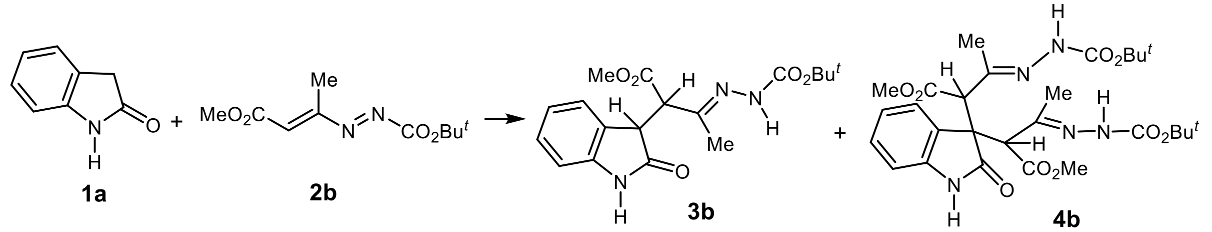
Scheme 2. Different reactivity of isatins and oxindole derivatives, in the construction of 2-oxo-spiro[indole-3,4’-pyridines].

Using 2-oxindoles, the generating spiro carbon atom acts as a nucleophilic centre reacting with two molecules of DDs (Scheme 2).

In fact, DDs **2** are good Michael acceptors, since these substrates undergo nucleophilic additions at the terminal carbon atom of the azo-ene system.[10] Therefore, the initial conjugate 1,4-addition of the carbon in position 3 of oxindoles **1** to two different molecules of DD **2** could permit the N(3’)-C(3,4’) junctions; the subsequent intramolecular cyclization could furnish connection N(1’)-C(2’).

To verify our hypothesis for the synthesis of 2-oxo-spiro[indole-3,4’-pyridines] **5**, we began our investigation by studying the reaction between oxindole **1a** and DD **2b** chosen as representative example. (Table 1).

Table 1. Screening of different conditions in the reaction between oxindole **1a** and DD **2b**, for the synthesis of bis-hydrazone **4b**.[a]



entry	Solvent	Catalyst (**C**)	Molar ratio **1a/2b/C**	**3b** yield (%)[b]	**4b** yield (%)[b]	Time (h)
1	THF	K_2CO_3	1/2/0.5	45	10	2
2	CH_3CN	K_2CO_3	1/2.2/1.1	13	32	2
3	CH_2Cl_2	K_2CO_3	1/2.2/1.1	16	31	1
4	CH_2Cl_2	DBU	1/2/0.5	39	8	0.1
5	CH_3CN	DABCO	1/2/0.5	33	11	0.1
6	CH_2Cl_2	DMAP	1/2/0.5	26	13	0.1
7	THF	$CuCl_2\cdot 2H_2O$	1/2/0.5	38	5	0.1
8	Toluene	DIPEA	1/1/1	44	5	0.1
9	THF	DIPEA	1/2/0.5	29	18	0.1
10	Toluene	DIPEA	1/2.2/1.1	44	32	7
11	Toluene	DIPEA	1/3.3/2.2	18	55	5
12	CH_2Cl_2	DIPEA	1/3.3/2.2	10	61	48
13	**CH_2Cl_2**	**DIPEA**	**1/4.4/2.2**	**4**	**75**	**18**

[a] The reactions were performed at 0.5 mmol scale of oxindole **1a** in 3 mL of solvent. [b] Yields of isolated **3b** and **4b**, based on oxindole **1a**.

In the present screening, we have tested several solvents, such as dichloromethane, tetrahydrofuran, toluene, and acetonitrile. Furthermore, a series of catalysts were used, as K_2CO_3, DBU, DABCO, DMAP, $CuCl_2\cdot 2H_2O$ and DIPEA and different molar ratios between oxindole/DD/catalyst were employed. In all these cases, two different products were achieved, that were isolated and characterized as mono-hydrazonic adduct **3b**, resulting from the nucleophilic attack (Michael-type) of the oxindole **1a** to one equivalent of the DD **2b**, and bis-hydrazonic adduct **4b**, resulting from a double Michael-type addition of the oxindole **1a** to two equivalents of DD **2b**.

The structure of mono-adduct **3b** was unambiguously determined by ^{1}H-NMR spectrum, in which two doublets at 4.14 and 4.27 ppm, respectively are diagnostic peaks for the presence of CH–CH coupling.[11]

Though the reaction times with K_2CO_3, DBU, DABCO, DMAP, $CuCl_2\cdot 2H_2O$ (Table 1, entries 1–7) are lower, the use of the DIPEA enhances the global yield of the reactions (Table 1, entries 8–13). Besides, by increasing the molar ratio of DD **2b** from 1 to 4.4 equiv., the yield of the mono-adduct **3b** significantly decreased, while the one of bis-adduct **4b** drastically improved (Table 1, entries 8–13).

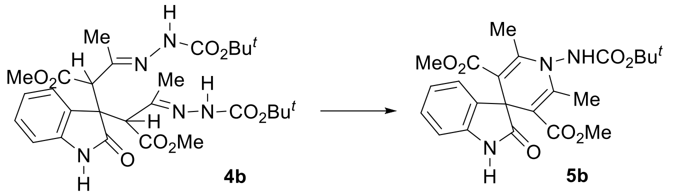
So, the best conditions we have found to obtain the highest yield of **4b** involve the use of 1 equiv. of the oxindole **1a**, 4.4 equiv. of DD **2b** and 2.2 equiv. of DIPEA as promoter, in dichloromethane as solvent (Table 1, entry 13).

Afterwards, we have optimized the reaction conditions for the cyclization of compound **4b** to tentatively obtain the corresponding 2-oxo-spiro[indole-3,4’-pyridines] **5b** (Table 2).

Acetonitrile and dichloromethane were tested as solvents and zinc(II) chloride, trifluoroacetic acid, ad Amberlyst 15H as catalysts, in different molar ratios. The best conditions found, both in terms of lower reaction times and of better yields of product **5b** (Table 2, entry 4), foresee the use of dichloromethane as solvent and of four drops of trifluoroacetic acid for one equiv. of **4b** as catalyst.

With these optimal conditions in hand, we explored the reactions of various oxindoles **1a–c** and DDs **2a–i** (Scheme 3, Table 3).

Table 2. Screening of different conditions for the cyclization of **4b** to **5b**.[a]

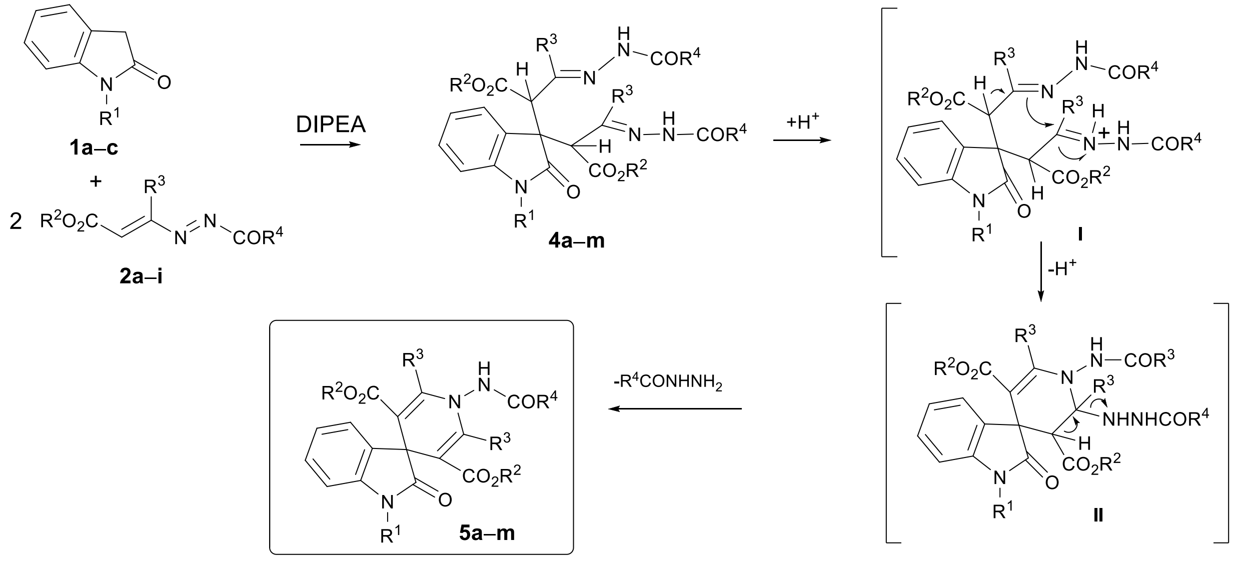


entry	Solvent	Cat.	Amount of Cat[b]	Temp	**5b** yield (%)[c]	Time (h)
1	CH_3CN	$ZnCl_2$	0.2 equiv.	25	55	24
2	CH_2Cl_2	$ZnCl_2$	0.2 equiv.	reflux	40	10
3	CH_2Cl_2	TFA[d]	3 drops	25	85	5.0
4	**CH_2Cl_2**	**TFA**[d]	**4 drops**	**25**	**91**	**3.5**
5	CH_2Cl_2	TFA[d]	4 drops	reflux	65	1.0
6	CH_2Cl_2	Amb.[e]	0.5 equiv.	25	35	8.0
7	CH_2Cl_2	Amb.[e]	1.0 equiv.	25	44	6.0

[a] The reactions were performed at a 0.5 mmol scale of bis-hydrazone **4b** in 3 mL of solvent. [b] Amount referred to 1 equiv. of **4b**. [c] Yields of isolated **5b** based on oxindole **4b**. [d] TFA as trifluoroacetic acid. [e] Amb. as Amberlist 15H

Bis-hydrazones **4a–m**[11] were obtained in good yields (65–75%) and the reactions were completed in 14.0–18.0 h. The final acidic treatment of compounds **4a–m**, under the conditions above described furnished the desired 2-oxo-spiro[indole-3,4'-pyridines] **5a–m**, in 3.0–5.0 h in good to excellent yields (64–92%).

The plausible mechanism of this reaction involves the preliminary double nucleophilic attack (Michael-type) of the carbon atom in 3 position of the oxindole **1** to the terminal carbon atom of the azo-ene system of two molecules of the DD **2**, with the formation of the bis-hydrazonic intermediate **4**. The intramolecular ring closure happens by means of nucleophilic attack of the sp^2 hydrazonic nitrogen to the other hydrazone moiety, activated by the acidic treatment, with the formation of the non-isolable intermediate **II** (Scheme 3). This process is promoted by the loss of the proton in the α position to the hydrazone acting as nucleophile. The final loss of the hydrazines furnishes the desired spiro[indole-3,4'-pyridines] **5a–m**.[11]



Scheme 3. Synthesis of bis-hydrazones **4a–m**, and of 2-oxo-spiro[indole-3,4'-pyridines] **5a–m**.

Table 3. Yields and reaction times for the synthesis of bis-hydrazones **4a–m** and 2-oxo-spiro[indole-3,4'-pyridines] **5a–m**. [a]

entry	**1**	R^1	**2**	R^2	R^3	R^4	**4**[b]	Yield (%)[b]	Time (h)	**5**	Yield (%)[c]	Time (h)
1	**1a**	H	**2a**	Me	Me	OEt	**4a**	72	14.0	**5a**	89	4.0
2	**1a**	H	**2b**	Me	Me	OBu*t*	**4b**	75	18.0	**5b**	91	3.5
3	**1a**	H	**2c**	Et	Me	OEt	**4c**	65	14.5	**5c**	88	5.0
4	**1a**	H	**2d**	Et	Me	OBu*t*	**4d**	71	16.0	**5d**	90	3.5
5	**1a**	H	**2e**	Et	Me	NHPh	**4e**	70	17.0	**5e**	52	3.0
6	**1a**	H	**2f**	*i*-Pr	Me	OBu*t*	**4f**	69	18.0	**5f**	88	3.0
7	**1b**	Me	**2b**	Me	Me	OBu*t*	**4g**	74	14.5	**5g**	75	4.0
8	**1b**	Me	**2g**	Me	Me	NHPh	**4h**	72	15.0	**5h**	92	4.5

9	**1c**	Ph	**2b**	Me	Me	OBu^t	**4i**	71	15.0	**5i**	87	4.5
10	**1c**	Ph	**2d**	Et	Me	OBu^t	**4j**	75	16.0	**5j**	73	5.0
11	**1c**	Ph	**2f**	*i*-Pr	Me	OBu^t	**4k**	69	17.5	**5k**	80	3.0
12	**1c**	Ph	**2h**	Me	Et	OBu^t	**4l**	68	16.0	**5l**	64	3.0
13	**1c**	Ph	**2i**	Allyl	Me	OBu^t	**4m**	73	17.5	**5m**	88	4.0

[a] Reagents and Conditions: **1a–c** (1.0 mmol), **2a–i** (4.4 mmol), DIPEA (2.2 mmol). [b] Yield of pure isolated bis-hydrazones **4** referred to **1a–c**. [c] Yield of pure isolated 2-oxo-spiro[indole-3,4'-pyridines] **5** referred to **4a–m**.

Conclusions

In conclusion, we report a pratical and very facile two-step methodology that leads to the formation of a set of 2-oxo-spiro[indole-3,4'-pyridines], starting from simple 2-oxindole derivatives and DDs. Further investigations are in progress to expand the utility of this procedure to other oxindole spiro-heterocycles, including non symmetrical 2-oxo-spiro[indole-3,4'-pyridines].

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Notes and references

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11) For the detailed spectral data, see Supporting Information.