Synthesis of highly functionalised spiro-indoles by a halogen atom transfer radical cyclization†

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The halogen atom transfer radical cyclization (HATRC) has been evaluated on *N*-(indolylmethyl)trichloroacetamides under Cu(I)Cl catalysis using nitrogen containing ligands. The ring closure leads to the formation of 3,3-spiro-3H-indoles in moderate to good yields by a 5-*exo*-mechanism. Derivatives with an N-electron withdrawing substituent also lead to a 5-*exo-trig* and not to a 6-*endo-trig* cyclization.

Indoles are an extremely important class of compounds due to their frequent occurrence in nature and their wide range of biological activities. Therefore, there is a continuing search for synthetic methods to prepare new types of indoles for screening in medicinal and pharmaceutical programmes. Among the indole derivatives, the spiro-indoles and spiro-oxindoles occupy an important position because of their interaction with essential mechanisms in the cell. Spirotryptostatins A **1** and B *i.e.*, isolated from *Aspergillus fumigatus*, target the microtubules which induce M-phase specific inhibition and microtubule disassembly resulting in the blockade of cell growth.[1]

Horsfiline **2** and elacomine **3** are more straightforward derivatives of the natural occurring oxindole alkaloids with cell cycle inhibition activity[2] (Fig. 1).

Because of our interest in halogen atom transfer radical cyclization (Kharasch type ring closure) for the construction of lactams,[3,4] a program was started to use this methodology to develop new indole skeletons. This approach allows to create new spiro-indoles with a high degree of functionality which can be exploited for further synthetic transformations. There are two main cyclization procedures, the tin method on the one hand (which has been used to prepare benzocarbazoles from indoles[5] and cyanospiroindoles[6]) and the atom transfer method on the other hand.[7] Since no toxic and difficult to remove tin compounds are used, the latter method is safer and more environmentally friendly. Moreover, this method introduces versatile halogen atoms in the end product, suitable for further functionalisation. Our attention was focussed on the use of copper since it is cheap and easy to handle, compared to certain ruthenium catalysts.[8]

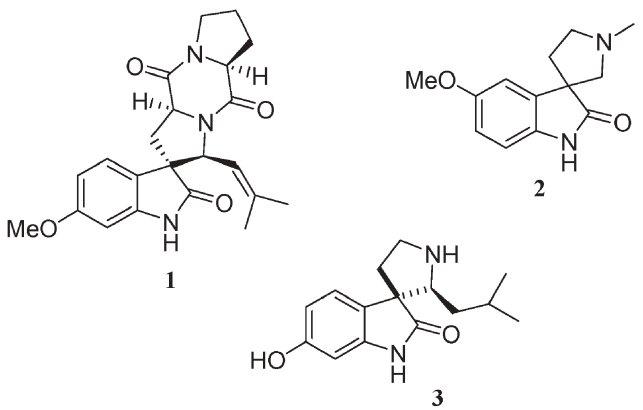

Fig. 1 Natural spiro-oxindoles.

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In order to prove the synthetic principle, the strategy was evaluated starting from 3-formylindole **4** which is commercially available. In the first step of the reductive amination, the formylindole was transformed into the corresponding imine **5** in almost quantitative yield (73–98%) upon treatment with an amine in the presence of magnesium sulfate in dichloromethane.

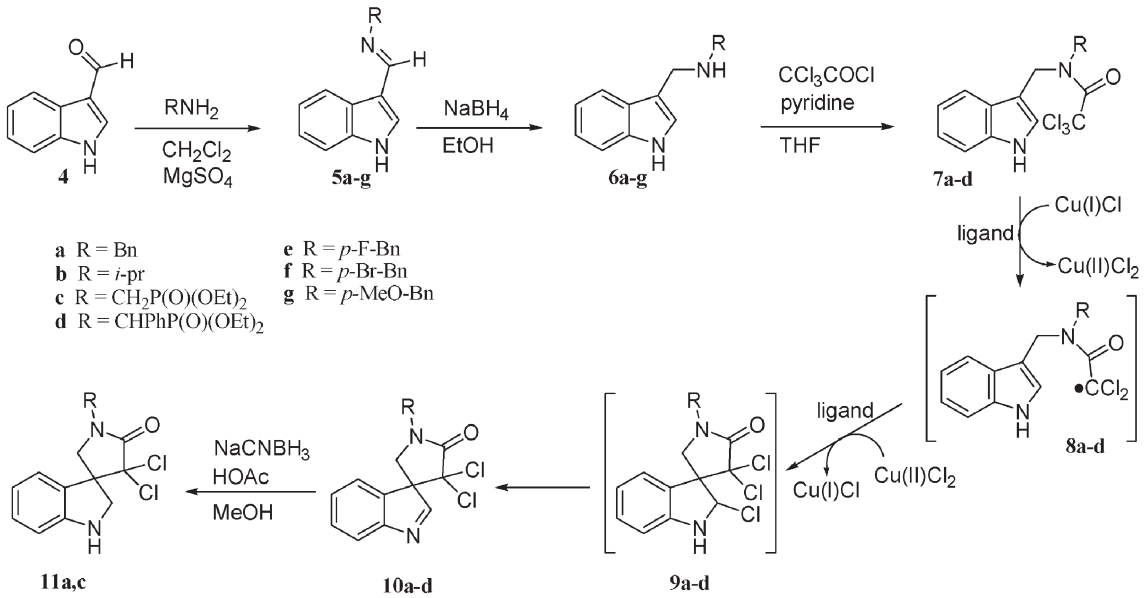
The imine **5** was then reduced to the amine (Scheme 1). For the reduction, several systems have been evaluated including sodium borohydride in methanol, sodium cyanoborohydride in methanol with varying amounts of acetic acid, sodium triacetoxy borohydride and the Wallach reduction. However, these reactions led to complex reaction mixtures or incomplete reductions even after the evaluation of many different time–temperature combinations. Although sodium borohydride in methanol did not lead to satisfying results, the choice of ethanol as solvent resulted in a smooth reduction of the imines (1 up to 3 equivalents of $NaBH_4$, during 1 to 3 days at rt depending on the type of imine).

The 3-aminomethylindoles **6** were then treated with trichloroacetyl chloride and pyridine in THF in order to acylate the N-atom. (Scheme 1).

Depending on the derivative **6**, different acylating conditions had to be utilized in order to obtain reasonable amounts of end product. One equivalent of base and acid chloride seemed insufficient. In Table 1 the optimal reaction conditions are reported for each derivative. However, the acylation of the compounds **6e–g** could not be performed in a reasonable yield so that the atom transfer methodology could not be performed on these derivatives.

The acylated indoles **7** appeared to be quite sensitive to light, leading to decomposition.

The chlorinated amides **7** were now evaluated as precursors for the atom transfer radical cyclization, upon treatment with Cu(I)Cl generating the reactive radical **8** (Scheme 1). Because of the nucleophilic nature of the 3-position of indoles, the ring closure of the electrophilic dichloro radical **8** was expected to lead to



Scheme 1

Table 1 Optimized reaction conditions for the acylation

Substrate	Pyridine (equiv.)	CCl_3COCl (equiv.)	Time/h	Yield (%)[a]
6a	4	4	48	94
6b	2	2	20	33
6c	1.3[b]	1.3	72	87
6d	2	2	6	63

[a] If necessary the end product was filtrated over 5 cm of silicagel (chromatography results in extensive loss of compound). [b] In this case Et_3N in dichloromethane was used.

spiro-indoles **9** *via* a *5-exo-trig* mechanism in relation to the double bond of the pyrrole ring of the indole nucleus. Indeed no traces of the annulated indoles which could be formed by a *6-endo-trig* mechanism were found. The indolines **9**, formed after the Kharasch ring closure, spontaneously lose hydrochloric acid with the formation of the 3,3-spiro-3H-indoles **10**.[9]

Since the Kharasch radical ring closure can be performed at lower temperature using amine ligands, which can solubilize the Cu catalyst,[10,11] several ligands were evaluated: bipyridine, TMEDA (tetramethylethylene diamine) and PMDETA (pentamethyldiethylene triamine) (Table 2).

The results show that it depends on the type of derivative whether TMEDA or PMDETA should be preferably used.

Table 2 Optimized reaction conditions for the synthesis of spiroindolines **10**

Substrate	Ligand	Time/h	Temperature	Yield (%)
7a	TMEDA	6	reflux	81
7a	TMEDA	24	rt	79
7a	PMDETA	24	rt	35
7b	PMDETA	3	reflux	79
7c	TMEDA	24	rt	51
7c	PMDETA	24	rt	75
7c	bipy	24	rt	15
7d	TMEDA	24	rt	58
7d	TMEDA	4	reflux	57

Further on, also the temperature effect was evaluated. Reflux in dichloromethane results in shorter reaction times with comparable yields. These conditions are superior compared to the ones of the thermal catalysed Kharasch reaction (*e.g.* refluxing in xylenes, not shown in the table), where high temperatures can lead to partial breakdown of the reagents and products.

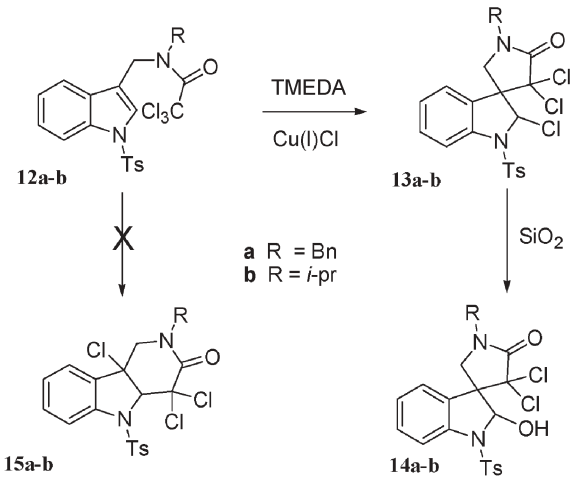
The purification of the compounds was problematic since column chromatography is associated with decomposition of the product. To remove all of the copper catalyst, the reaction mixture is washed three times with water.

Further, the imino function of the 3,3-spiro-3H-indoles **10** could be reduced easily to the corresponding saturated derivatives **11**, by treatment with sodium cyanoborohydride and glacial acetic acid in methanol in 65% yield, undoubtfully proving the disappearance of the imino function, so that the *5-exo-trig* mechanism of the cyclization could be deduced. (Scheme 1)

A second strategy consisted in the introduction of an electron withdrawing group on the indole nitrogen, in order to diminish the electron density on the 3-position. This was hoped to eventually lead to a *6-endo*-cyclisation in relation to the double bond of the pyrrole ring of the indole nucleus, resulting in the annulated indoles **15** which are also important from a medicinal point of view.[12] Therefore, the *N-t*-butoxycarbonyl indole derivative as well as the *N*-tosyl indole derivative **12** were synthesized and evaluated in the Cu-catalysed Kharasch reaction.

The ring closure of the *t*-Boc derivative however, did not lead to a clean product but rather to mixtures with some unidentified compounds. The cyclization of the *N*-tosyl derivative on the other hand, led to the isolation of the spiro-indole derivative **13** (**13a**: 64%; **13b**: 64%) and not to the six-membered ring analogue **15** (Scheme 2).

When the reaction is monitored carefully with TLC the chlorine atom was retained and no elimination took place. Longer reaction times however lead to elimination of the chlorine atom followed by expulsion of the tosyl-substituent, resulting in the 3,3-spiro-3H-indoles **10**. Shorter reaction times combined



Scheme 2

with reflux are preferred over longer reaction times at room temperature.

The *N*-tosyl derivative **13** could be isolated by crystallization in 64% yield after treatment of the amide **12** with 0.4 equivalents of Cu(I)Cl and 0.8 equivalents of TMEDA. Treatment of **13** with SiO_2 led to the isolation of the corresponding hydroxy derivative **14** by an elimination addition sequence in 61–80% yield.

The synthesis of this hemi-aminal **14** now also opens up the possibility towards the synthesis of the corresponding spiro-oxindoles which are certainly of interest due to the biological activity of some representatives of this class of compounds.

In summary, the synthesis of functionalized spiro-3H-indoles by a halogen atom transfer cyclization under copper/amine-ligand catalysis, is described. Precursors without a substituent on the indole-N result in 3,3-spiro-3H-indoles **10** *via* a *5-exo-trig* cyclization. Precursors having a tosyl substituent on nitrogen lead to the synthesis of the corresponding 2-chloro derivatives which can be transformed to the hydroxy derivatives upon stirring with silicagel. Further, work on the rearrangements and tandem cyclisations of these chlorinated indoles is currently under investigation.

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