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Temperature switchable Brønsted acid-promoted selective syntheses of spiro-indolenines and quinolines

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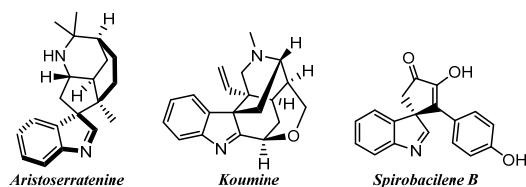
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A high-yielding, temperature switchable divergent approach towards the synthesis of either spiro-indolenines or quinolines is described, starting from easily available indolyl yrones. The application of TFA at rt promotes the dearomatization of the indole, resulting in the formation of the spiro-indolenine, while at higher temperature, rearrangement results in the formation of the quinoline.

In recent years spirocycles have attracted great attention in the chemical world due to their original stereostructure and challenging complexity of their synthesis.¹ The spiro-indolenine core is found in various natural products making this scaffold very attractive (Figure 1).² However, spiro-indolenines are known to be rather difficult to obtain, since the need of

Spiro-indolenines:



Quinolines:

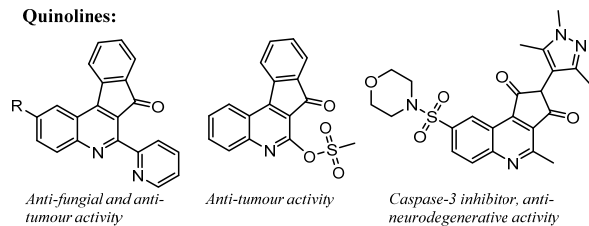
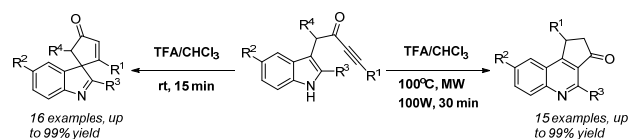


Fig. 1 Biologically active and natural spiro-indolenines and quinolines.



Scheme 1 Temperature switchable synthesis of spiro-indolenines and quinolines

indole dearomatization and further prevention of the spirocyclic structure from rearomatization.³

The spirocyclic core structure was for the first time reported by A. Pictet and T. Spengler in 1911⁴ as an intermediate, that rapidly underwent a 1,2-migration in order to restore aromaticity. The first report concerning the isolation of a spiro-indolenine dates from 2010 by S.-L. You applying an Ir catalyst.⁵ In 2012 our research group reported a protocol involving a gold-catalysed indole spirocyclization, resulting in a mixture of spiro- and rearomatized product.⁶ Recently, the research group of W. Unsworth reported a procedure comprising a concerted Michael addition/indole dearomatization.⁷ The same group reported a Lewis acid-catalysed quinoline synthesis from an indole in two steps.⁸ However, their conditions involved the need of a transition metal catalyst. Therefore, we were wondering if a simple Brønsted acid could be employed to perform the indole spirocyclization which should result in a convenient and greener protocol. Moreover, fine tuning of these conditions might result in a rearrangement resulting in the formation of the quinoline core. Quinolines are known to be valuable compounds⁹ which have been found to possess antimalarial, anti-bacterial, antifungal, antihelminthic, cardiotoxic, anticonvulsant, anti-inflammatory, and analgesic activity (Figure 1).¹⁰

We herein present a temperature switchable Brønsted acid-promoted selective syntheses of spiro-indolenines and 3,4-cyclopentan-quinoline-3-ones (Scheme 1). It might be clear that strategies allowing the selective formation of different scaffolds starting from a common starting material, by a simple switch of the conditions in metal-free environment, are highly desired.

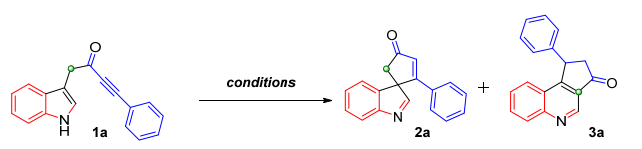
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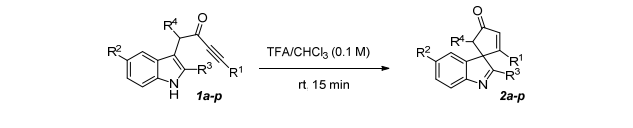
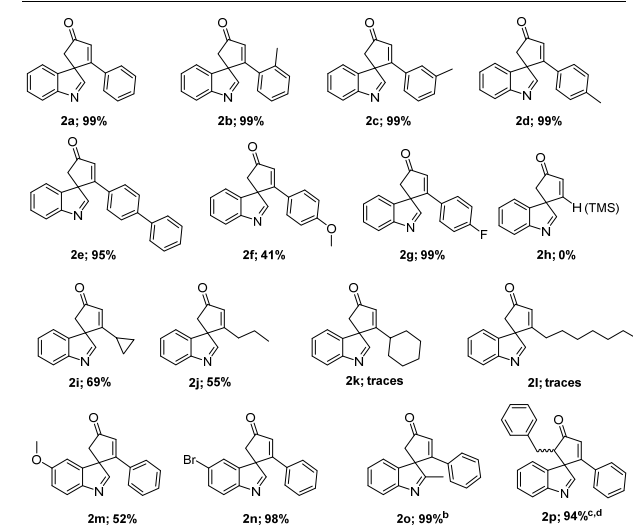
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Table 1 Optimization of the Brønsted acid-promoted cyclization^{a,b}


No	Acid	Equiv	Temp	Time	Solvent	Conversion	Yield of 2a ^c	Yield of 3a ^c
1	TFA	1	rt	3h	CHCl ₃	40	34	0
2	TFA	1	rt	18h	CHCl ₃	98	5	3
3	TFA	2	rt	18h	CHCl ₃	100	43	51
4	TFA	2	60°C	3h	CHCl ₃	100	2	15
5	TFA	2	60°C	18h	MeCN	100	0	28
6	TFA	2	60°C	18h	THF	33	0	0
7 ^c	TFA	2	100°C	1h	Toluene	98	0	50
8	AcOH	2.5	60°C	18h	CHCl ₃	7	0	0
9	TfOH	1.5	rt	1h	CHCl ₃	100	0	45
10	TFA	6	60°C	1.5h	CHCl ₃	100	31	60
11	TFA	10	60°C	1.5h	CHCl ₃	100	23	73
12	TFA	0.1M ^d	rt	15min	CHCl ₃	100	100 ^e	0
13	TFA	0.1M ^d	60°C	1h	CHCl ₃	100	16	84
14 ^f	TFA	0.1M ^d	100°C	30min	CHCl ₃	100	0	100 ^e

a) The reactions were run on 0.1 mmol scale of **1a**, in 1.0 mL of the indicated solvent; b) full optimization table can be found in the supporting information; c) the data were obtained via ¹H NMR using CH₂Br₂ as an internal standard; d) concentration of **1a** in TFA/CHCl₃ 1:1 mixture; e) the isolated yields are 99%; f) the reaction was performed under microwave irradiation at 100W.

To start our study, we examined the reaction of the easily available^{7,8} indolyl-ynone **1a** used as a model compound, with 1 equiv of TFA for 3 h (Table 1). This resulted in the formation of the spiro-indolenine **2a** in 34% yield with 40% conversion. While prolonged stirring for 18 h dramatically decreased the yield (entry 2), the application of 2 equiv of TFA for 18h at rt yielded a mixture of spiro-indolenine **2a** and quinolone **3a** in 43% and 51% respectively (entry 3), delivering a proof of our supposition. To the best of our knowledge, the rearrangement of a spiro-indolenine **2a** to a quinolone **3a** was reported only once in a two-steps synthesis.⁸ Inspired by the obtained results we continued our study by increasing the temperature to 60°C. However, this met with failure (entry 4). Variation of the solvent or the Brønsted acid was deleterious for the reaction (entries 6 and 8) or resulted in the selective formation of the rearranged compound, although with a meager yield (entries 5, 7 and 9). A further increase to 6 or 10 equiv of TFA resulted in the isolation of a mixture of both the spiro-indolenine **2a** and the quinolone **3a** (entries 10 and 11). Therefore, we decided to proceed with a 0.1 M solution of **1a** in TFA/CHCl₃ with ratio 1:1. To our great satisfaction upon stirring at rt for 15 min the spiro-indolenine **2a** was selectively and quantitatively obtained (entry 12), while upon heating at 100°C rearrangement took place, solely delivering the quinolone **3a** in quantitative yield (entry 14)! Apparently, a simple switch of the temperature resulted in the selective formation of two totally different scaffolds starting from the readily available indolyl ynone. To the best of our knowledge, this is the first report about the conservation of the

Table 2 TFA-promoted synthesis of spiro-indolenines^a



Yields for products **2a-p**:
2a: 99%
2b: 99%
2c: 99%
2d: 99%
2e: 95%
2f: 41%
2g: 99%
2h: 0%
2i: 69%
2j: 55%
2k: traces
2l: traces
2m: 52%
2n: 98%
2o: 99%^b
2p: 94%^{c,d}

a) The reactions were run on a 0.3 mmol scale of **1a-p**, employing the optimized conditions of Table 1, entry 12; b) the reaction time is 2.5 h; c) the reaction time is 1h d) dr=5:4.

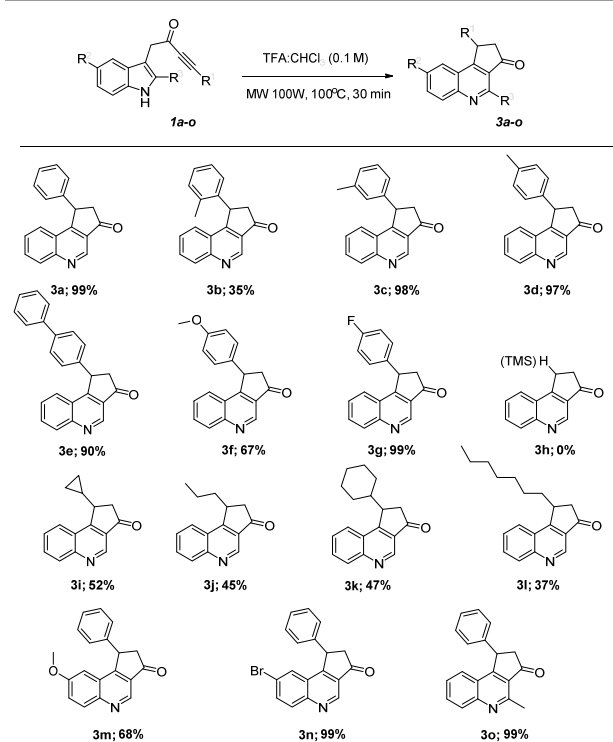
spiro-structure under acidic conditions without the subsequent occurrence of the 1,2-migration¹¹.

To explore the scope of both optimized protocols (Table 1 entries 12 and 14), variously substituted substrates **1a-p** were subjected to the conditions. First, the indole spirocyclization was investigated with an *ortho*-, *meta*- and *para*-tolyl or biphenyl R1-substituent, resulting in excellent yields of **2b-e**. Similarly, the product bearing an electron-deficient *p*-fluorophenyl substituent at the ynone position was cleanly converted into **2g**, while an electron-donating *p*-methoxyphenyl moiety resulted in a decreased 41% yield for **2f**. The trimethyl silyl substituted **1h** did not lead to formation of the desired spiro-indolenine due to its instability in acidic medium. Aliphatic substituents have shown to have a negative effect on the reaction giving decreased yields (**2i**, **2j**) or undergoing decomposition (**2k**, **2l**). A 5-methoxy-substituent on the indole core resulted in a moderate yield of 52% for **2m**, while with a 5-bromo substituent **2n** was obtained in an excellent yield 98%.

Replacing the C-2 hydrogen of the indole with methyl still lead to the formation of the desired product **2o** in 99% yield after an extended reaction time of 2.5h. Applying the protocol to the R4-benzyl-substituted **1p** resulted in the formation of an inseparable mixture of diastereomers **2p** in an excellent yield of 94% and a dr = 5:4.

Next, we investigated the scope of the quinoline formation at higher temperature (Table 3), employing the optimized conditions (Table 1, entry 14). A sterically hindering R1-*o*-tolyl substituent negatively influenced the yield of **3b** (35%). Contrary, *meta*- and *para*-tolyl substituents resulted in

quantitative formation of **3c** and **3d**. A biphenyl- as well as an electron-deficient *p*-fluorophenyl substituent resulted in the **Table 3** TFA-promoted synthesis of quinolines^a

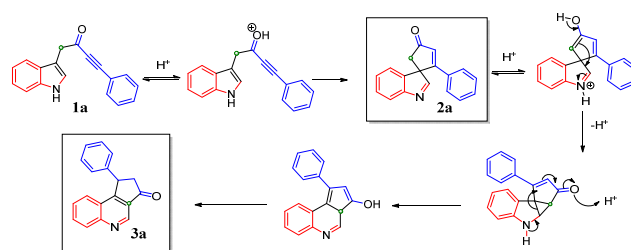


formation of **3e** and **3g** in excellent yields. However, an electron-donating *p*-methoxyphenyl moiety decreased the yield of **3f** to 67%. In contrast to the spiro-indolenine formation, aliphatic R1-substituents were better tolerated in this protocol, delivering the compounds **3i-3l** in moderate yields. A bromine at the C-5 of the indole core resulted in a smooth formation of the desired **3n**, while an electron-donating methoxy substituent disposed a negative influence on the process (**3m**).

A plausible mechanism is depicted in Scheme 2. First, a Brønsted acid-catalyzed intramolecular Michael addition¹² takes place at the C-3 carbon of the indole to the ynone, resulting in the formation of the spiro-indolenine **2a**. The activation energy for the formation of **3a** is significantly higher than the one for **2a**, as is proven by the higher temperature needed to perform the rearrangement. At elevated temperature, the second step is assumed to be a double-protonation of the spiro-indolenine, catalysing ketone tautomerization and creating an electrophilic iminium ion that is attacked by the enol. This is followed by a rearrangement with formation of a cyclopropane ring, leading to ring expansion and finally restoration of the aromaticity, resulting in the formation of the quinoline core.

To confirm the proposed mechanism, we performed transformation of the isolated spiro-indolenine **2a** into the quinoline **3a** using standard conditions applied in Table 3. The desired quinoline was successfully formed in 99% yield.

Scheme 2 Plausible mechanism



Conclusions

In summary, we have developed a metal-free temperature switchable Brønsted acid-promoted protocol for the synthesis of spiro-indolenines and quinolines. This convenient protocol is delivering the products in high yields starting from easily available materials.

Acknowledgements

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